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Low serum prealbumin levels on admission can independently predict in-hospital adverse cardiac events in patients with acute coronary syndrome

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Abstract

The aim of this study is to evaluate if low prealbumin levels on admission predict subsequent adverse cardiac events in patients hospitalized with acute coronary syndrome (ACS).

We designed a cohort study and enrolled 610 consecutive patients with ACS from whom venous blood for serum prealbumin measurement was drawn immediately upon hospital admission. Patients were classified in two groups according to prealbumin level: "normal" prealbumin levels (≥17 mg/dL, n=413) and "low" prealbumin (<17 mg/dL, n = 197). In-hospital adverse cardiac events were death, acute heart failure, reinfarction, and cardiogenic shock. Univariate and multivariable analyses were applied to evaluate the prediction value of low prealbumin.

The incidence of in hospital adverse cardiac events is 10.8%. The proportion of adverse cardiac events was significantly higher in low prealbumin group as compared with normal prealbumin group (20.8% versus 6.1%, $P < .001$). Univariate analysis indicates that low prealbumin levels can predict in hospital adverse cardiac events (odds ratio [OR]: 0.834, 95% confidence interval [CI]: 0.785–0.886, $P < .001$). Multivariable analysis shows that low prealbumin level was an independent predictor for in hospital adverse cardiac events (adjusted OR: 0.918, 95% CI: 0.848–0.993, $P = .033$). Other independent predictors were lower in average hemoglobin level and Killip class II-IV on admission.

Therefore, lower serum prealbumin levels on admission can independently predicts subsequent in hospital major adverse cardiac events in patients with ACS.

Abbreviations: 95% CI = 95% confidence interval, ACS = acute coronary syndrome, eGFR = estimated glomerular filtration rate, HDL = high density lipoproteins, hs-CRP = high sensitivity C-reactive protein, IL-6 = interleukin-6, TNF-α = tumor necrosis factor alpha, VEGF = vascular endothelial growth factor.

Keywords: acute coronary syndrome, adverse cardiac events, prealbumin

1. Introduction

Acute coronary syndrome (ACS) is one of the leading causes of cardiovascular disease-related death; therefore, identifying risk factors of ACS is urgent for prevention. Studies have shown a correlation between prealbumin levels and patient recovery and an increase in prealbumin levels is an early predictor of patient recovery. In high-risk patients, assessing prealbumin levels twice a week during hospitalization can remind the physician to prevent declining nutritional status, which shortens hospitalization and improves patient outcomes.[1] Prealbumin is mainly biosynthesized in the liver. Its half life is about 2 days while 20 days for albumin. It has been reported that blood albumin can be affected by multifactors, such as nourishment state and renal function.[2]

More and more studies have revealed that serum albumin levels were associated with coronary heart disease and mortality. Moreover, an increasing number of investigations have shown that prealbumin is closely associated with a variety of conditions, such as recurrence of malignant carcinoma,[3] postoperative complications,[4] hemorrhagic stroke,[5] ischemic stroke,[6] systemic sclerosis outpatients,[7] atherosclerotic vascular disease,[8] prognosis of heart failure,[9–11] and acute kidney injury.[12] In addition, one study showed that in coronary artery disease patients undergoing chronic hemodialysis have lower serum prealbumin levels.[13] Also, one other study reported that prealbumin was negatively correlated with angiographic severity in patients with ACS.[14] However, the association between prealbumin and adverse cardiac events of ACS has not been investigated in previous research.

Therefore, the aim of this research was to determine the association between low serum prealbumin level measured

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immediately on admission and in-hospital adverse cardiac events in patients with ACS. Furthermore, we combined this association with other variables to assess the value of prealbumin in predicting adverse outcomes.

2. Patients and methods

2.1. Patient population

The present study included patients with ACS who were admitted to the Department of Cardiology, Liaocheng People's Hospital and Clinical School of Taishan Medical University. We recruited the subjects consecutively between April 2017 and October 2017. The inclusion criteria of recruitment were patients diagnosed with ACS, which was based on clinical symptoms and some accessory examinations, and the diagnosis of ACS is based on criteria of ACS in ACCF/AHA guidelines,[15,16]patients with the onset of angina $\leq$24 hours, and patients agreed to participate by signing an informed consent. The exclusion criteria were patients previously diagnosed with chronic heart failure and NYHA class >II, patients had hepatic cirrhosis or malignancy, patients who had been already on regular dialysis or whose estimated glomerular filtration rate (eGFR) was <15 mL/kg/m^2, patients with known valvular heart disease, acute comorbidity such as acute stroke, acute infection and sepsis, and patients with known chronic inflammatory disease and venous thromboembolism. All procedures were approved by the Ethics Committee of Liaocheng People's Hospital and Clinical School of Taishan Medical University in accordance with principles of the Helsinki Declaration.

2.2. Data collection

The blood collection was drawn immediately upon hospital admission, before any reperfusion procedure or heparin therapy. Characteristic data were collected during hospitalization. Clinical presentation including heart rate and Killip class determination was assessed on admission by the attending physician. Medical history related to cardiovascular risk factors, that is, hypertension, diabetes mellitus, previous ischemic heart disease, and smoking status were noted. Biochemical profiles including prealbumin, albumin, total cholesterol, liver, and kidney function were recorded. The "normal" prealbumin values are variable depending on the different studies: >17 mg/dL, >15 mg/dL, and >13 mg/dL.[1,17,18] For the present study, we have used 17 mg/dL as cut-off point, as this value is the most used in literature. According to this, patients are divided into two groups: those with serum prealbumin <17 mg/dL were categorized as "low" serum prealbumin group and the others with serum prealbumin $\geq$17 mg/dL were categorized as "normal" serum prealbumin group.

2.3. Research outcome

From admission, the treatment strategy for the patients was made by attending cardiologists. The study outcome was in-hospital adverse cardiac events. The adverse outcomes were recorded and determined as in-hospital death, acute heart failure, reinfarction and cardiogenic shock. In-hospital death was determined as all cause of death during hospitalization. Acute heart failure was based on the presence of symptom of breathlessness and clinical signs of pulmonary congestion in physical examination, or intravenous loop diuretics to treat pulmonary congestion. Reinfarction was defined as newly or on-going developed pain, a repeated elevation of troponin I or recurrent ST-segment elevation following the event. Cardiogenic shock was diagnosed based on systolic blood pressure <90 mm Hg and low perfusion signs with subsequent use of vasopressors (dopamine or/and norepinephrine). The adverse outcomes were confirmed by attending cardiologists.

2.4. Statistical analysis

Statistical analysis was performed using SPSS 17.0 version (SPSS Inc, Chicago, IL). Continuous data was tested for normal distribution with Kolmogorov–Smirnov test, if applicable, with logarithmic transformation. The study population was divided based on the serum levels of serum prealbumin. Student *t*-test was applied to compare the normally distributed continuous data, while Mann–Whitney test was performed for not normally distributed continuous data. Comparison between categorical data was used with χ^2 test and Fisher exact test. Determine whether prealbumin level was an independent predictor for adverse cardiac events use univariate and multivariable analysis (logistic regression). Statistical significance level was when $P < .05$.

3. Results

3.1. Patient characteristics

A total of 610 patients admitted due to ACS were included in this research, 54.1% of them were men and the mean age was 65.1 years old. The low prealbumin group had 197 patients, with a mean prealbumin concentration of 13.5 $\pm$ 2.6 mg/dL; the rest 413 patients were in normal prealbumin group, with a mean prealbumin concentration of 20.8 $\pm$ 2.4 mg/dL. In low prealbumin group, the patients were older, faster heart rate, lower in average hemoglobin level, albumin, eGFR, and total cholesterol, while higher in high sensitivity C-reactive protein (hs-CRP) and Killip class II to IV on admission. Coronary angiography was done in 311 subjects, the advanced coronary artery disease (3 vessel disease) proportion tended to be higher in low prealbumin group (as shown in Table 1).

3.2. Incidence of adverse outcomes

In the present study, the incidence of in hospital major adverse cardiac events is 10.8% (66 of 610 patients). The in-hospital death rate is 0.8% (5 of 610 patients). Among non-fatal outcomes, the incidence of acute heart failure is 7.4% (45 of 610 patients), cardiogenic shock is 0.3% (2 of 610 patients), and reinfarction 2.3% (14 of 610 patients). The proportion of major adverse cardiac events was significantly higher in the low prealbumin group as compared with normal prealbumin group (20.8% vs 6.1%, $P < .001$). Furthermore, the incidence of non-fatal outcomes was also significantly higher in the low prealbumin group (19.8% vs 5.3%, $P < .001$), whereas the incidence of death was not significantly different between 2 groups (1.0% vs 0.7%, $P = 1.000$) (as shown in Table 2).

3.3. Univariate and multivariable analyses

Univariate analysis showed that low prealbumin was associated with in-hospital major adverse cardiovascular events (Table 3). Other covariates that also predicted in hospital adverse cardiovascular events were older age, faster heart rate, lower hemoglobin, albumin and eGFR level, and higher hs-CRP level and Killip class II to IV on admission. We performed

Table 1

Characteristics of patients according to serum prealbumin level.

	Prealbumin, <17 mg/dL n=197	Prealbumin, ≥17 mg/dL n=413	χ^2	P
Age, y	71.1±11.1	64.8±10.6		<.001
Male gender, n (%)	88 (44.7)	242 (58.6)	10.416*	.001
Current smoker, n (%)	49 (24.9)	125 (30.3)	1.903*	.168
Hypertension, n (%)	118 (60.0)	266 (64.4)	1.1621*	.281
Diabetes mellitus, n (%)	63 (32.0)	108 (26.2)	2.247*	.134
IHD, n (%)	35 (17.8)	55 (13.3)	2.099*	.147
Killip class II–IV, n (%)	21 (10.7)	24 (5.8)	4.589*	.032
Heart rate, bpm	81.0±10.6	74.4±10.2		<.001
Laboratory, mean±SD				
Hemoglobin, g/dL	12.4±1.8	13.5±1.6		<.001
Platelet, $\times10^3/\mu L$	216.9±72.0	226.9±54.9		.085
WBC count, $\times10^3/\mu L$	6.6 (3.2)	6.5 (2.4)		.938
eGFR, mL/min/1.73 m^2	77.3±30.2	89.7±32.1		<.001
Albumin, g/dL	3.7±0.4	4.0±0.3		<.001
Prealbumin, mg/dL	13.5±2.6	20.8±2.4		<.001
GPT, u/L	29.9±46.6	26.0±3.3		.283
GOT, u/L	34.4±38.5	32.0±39.9		.487
TC, mg/dL	174.0±44.6	187.1±46.5		.001
Hs-CRP, mg/dL	0.3 (1.6)	0.1 (0.2)		<.001
Angiography, n (%)	96 (48.7)	215 (52.1)	0.591*	.442
1 vessel disease	45 (22.8)	135 (32.7)		
2 vessel disease	28 (14.2)	60 (14.5)		
3 vessel disease	23 (11.7)	20 (4.8)		
Treatment, n (%)				
Anti-platelet	191 (97.0)	408 (98.8)	1.606†	.205
Beta-blocker	119 (60.4)	243 (58.8)	0.136*	.712
ACEI	52 (26.4)	103 (24.7)	0.149*	.699
ARB	43 (21.8)	83 (20.1)	0.244*	.622
Statin	83 (42.1)	197 (47.7)	1.665*	.197
LMWH	73 (37.1)	128 (31.0)	0.746*	.388

All continuous variables were normally distributed except for WBC count and Hs-CRP.

* Pearson χ^2.

† Continuity correction.

ACEI = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blockers, eGFR = estimated glomerular filtration rate, GPT = glutamate pyruvate transaminase, GOT = glutamate oxaloacetate transaminase, Hs-CRP = high sensitivity C-reactive protein, IHD = ischemic heart disease, LMWH = low molecular weight heparin, TC = total cholesterol, WBC = white blood cell.

multivariable analysis with logistic regression test to determine whether low prealbumin level was an independent predictor for in hospital major adverse cardiovascular events adjusted by variables in univariate analysis. The result showed that prealbumin independently predicted in hospital major adverse cardiovascular events in subjects with ACS (adjusted odds ratio [OR]: 0.918, 95% confidence interval [CI]: 0.848–0.993, $P=.033$). Other independent predictors were lower hemoglobin level and Killip class II to IV on admission (Table 4).

Table 2

In-hospital MACE according to serum prealbumin level.

	Prealbumin, <17 mg/dL n=197	Prealbumin, ≥17 mg/dL n=413	χ^2	P
Death, n (%)	2 (1.0)	3 (0.7)	0.000*	1.000
Acute heart failure, n (%)	26 (13.2)	19 (4.6)	14.429†	<.001
Shock cardiogenic, n (%)	2 (1.0)	0 (0)	‡	.104
Reinfarction, n (%)	11 (5.6)	3 (0.7)	11.951*	.001
Total MACE, n (%)	41 (20.8)	25 (6.1)	30.110†	<.001

* Continuity correction.

† Pearson χ^2.

‡ Fisher exact test.

MACE = major adverse cardiac events.

Table 3

Univariate analysis for predictors of in-hospital MACE.

Variables	Unadjusted OR	95% CI	P
Low prealbumin	0.834	0.785–0.886	<.001
Age	1.051	1.025–1.078	<.001
Heart rate	1.051	1.024–1.078	<.001
Hemoglobin	0.659	0.567–0.765	<.001
Hs-CRP	1.014	1.004–1.025	.008
Albumin	0.153	0.079–0,294	<.001
eGFR	0.988	0.979–0.997	.010
Killip class II-IV	7.181	3.690–13.972	<.001

MACE = major adverse cardiac events, OR = odds ratio, CI = confidence interval, Hs-CRP = high sensitivity C-reactive protein, eGFR = estimated glomerular filtration rate.

4. Discussion

Many studies have revealed that a lower level of serum prealbumin was associated with severities and prognosis of coronary heart diseases,[9–11] higher overall mortality in critically ill patients,[17] and negatively associated with angiographic severity in patients with ACS.[14] In accordance with these studies, we have found that low level of serum prealbumin (<17 mg/dL) is associated with in-hospital adverse cardiac events. Also, other studies have suggested that lower serum prealbumin was an early stage and long-term mortality predictor for patients with acute or chronic phase of heart failure.[9–11] However, the correlations between lower prealbumin and adverse cardiac events in ACS is unclear. In this research, we have found that low levels of serum prealbumin can independent predict in-hospital adverse cardiac events in ACS patients.

Our study show that the risk to develop in-hospital major adverse cardiac events increases 3-fold in low prealbumin patients group as compared with patients with normal prealbumin level. Among patients with low prealbumin, the occurrence of nonfatal in-hospital adverse outcomes, especially acute heart failure, is significantly higher than in patients with normal prealbumin ($P<.001$). In spite of a low serum prealbumin level was associated with in-hospital adverse cardiac events, the majority of the subjects survived. The occurrence of death was not significantly different between the groups. These study results suggest that a low serum prealbumin level has a deleterious impact during the acute phase of ACS, especially in the early presentation.

Table 4

Multivariable analysis for predictors of in-hospital MACE.

Variables	adjusted OR	95% CI	P
Low prealbumin	0.918	0.848–0.993	.033
Age	1.026	0.992–1.061	.132
Heart rate	1.029	1.000–1.059	.050
Hemoglobin	0.812	0.676–0.976	.026
Albumin	0.508	0.221–1.165	.110
Hs-CRP	1.003	0.992–1.014	.663
eGFR	1.005	0.995–1.015	.351
Killip class II-IV	5.857	2.818–12.174	<.001

MACE = major adverse cardiac events, OR = odds ratio, CI = confidence interval, Hs-CRP = high sensitivity C-reactive protein, eGFR = estimated glomerular filtration rate.

Prealbumin is synthesized in the liver. The prealbumin concentration level was reduced because of decreasing synthesis, extravascular distribution, higher catabolic rate, and exogenous loss.[19] Systemic inflammation and inadequate nutritional intake both affect the synthesis of prealbumin.[1,20] An inverse relationship between prealbumin and hs-CRP has been documented,[21] which has also demonstrated by our finding that patients located in the lower quartile of prealbumin had the higher level of hs-CRP. As a negative acute-phase protein, the synthesis of prealbumin is suppressed in the inflammatory settings in which cytokines, mainly tumor necrosis factor alpha (TNF-α), interleukin-1 (IL-1), and IL-6, resulting in elevated generation of hs-CRP and decreased synthesis of prealbumin by the liver.[1,22] This study found that the hemoglobin level is significantly lower in the low prealbumin group ($P < .001$). Anemia due to inflammation is common among hospitalized patients and may also be a sign of poor nutritional intake. Investigation showed that concentration of prealbumin is low in some instances of protein energy malnutrition.[19] Therefore, malnutrition and inflammatory are responsible for the low serum prealbumin in the ACS.

The underlying mechanism between low prealbumin and adverse cardiac events in patients with ACS is considered multifactorial. First, inflammation plays a pivotal role in the pathological process of arteriosclerosis,[23] may provide a bridge between low prealbumin and poorer prognosis in ACS patients. It is established that inflammatory state can reduce the rate of prealbumin synthesis,[24] thus decreasing serum prealbumin levels. Second, it has been shown that infected patients have low serum levels of prealbumin, high levels of TNF-α,[25,26] which induced vascular cell adhesion molecule-1 expression, monocyte adhesion, and nuclear factor-kappa B activation in human aortic endothelial cells,[27] suggesting that low levels of prealbumin may induce the atherosclerosis. Third, levels of prealbumin were inversely correlated with vascular endothelial growth factor (VEGF), which plays an important role in the maintenance of endothelial integrity and increases vascular permeability to serum proteins.[28,29] Increased VEGF expression could induced atherosclerosis.[30] Fourth, prealbumin is transported by high density lipoproteins (HDL), in association with Apolipoprotein AI, and it has been suggested that the absence of prealbumin affects the properties or stability of the HDL particles and reduce cardiovascular protection of HDL.[31] The above mechanisms may jointly lead to increase the risk of atherosclerosis and adverse outcome. However, the exact mechanism still needs further verification.

In patients with severe chronic kidney disease, the combined effects of inadequate protein and inflammation result in low serum prealbumin concentration, which was an independent risk factor for mortality in hemodialysis patients.[24] In this study, we exclude those with stage 5 of chronic kidney disease and those with dialysis dependence in order to eliminate the potential confounding effect. Our result demonstrated that albumin level was significantly lower in low serum prealbumin group and it was consistent with previous studies.[32,33] It was suggested that albumin, like prealbumin, represented as a risk marker indicating underlying inflammatory or nutritional status.

Our study has several limitations. First, nutritional status at admission may influence the levels of albumin and prealbumin, body mass index or total protein are need to be assessed at admission, more data is needed. Second, as we only include patients with ACS and our conclusions to other populations, such as patients with asymptomatic coronary atherosclerosis or stable angina pectoris, is unknown. Third, this study was designed as a hospital-based study, not community-based study and this design had potentially limitation. Fourth, the prognostic predictive ability of prealbumin was provided in our study just in hospitalization, further studies are currently underway to elucidate its long-term prognostic value.

In conclusion, the presence of a low serum prealbumin level (<17 mg/dL) immediately upon hospital admission in ACS independently predicts subsequent in hospital major adverse cardiac events. Measurement of serum prealbumin may aid in the risk stratification.

Author contributions

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Writing – original draft: Wei Wang.
Writing – review & editing: Heng-Chen Yao, Sheng-Jun Ma.

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