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Association between serum S100A1 level and Global Registry of Acute Coronary Events score in patients with non-ST-segment elevation acute coronary syndrome

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Abstract

Objective: Acute coronary syndrome (ACS) is associated with several clinical syndromes, one of which is acute non-ST-segment ACS (NSTE-ACS). S100A1 is a calcium-dependent regulator of heart contraction and relaxation. We investigated the association between the serum S100A1 level and the Global Registry of Acute Coronary Events (GRACE) risk score in patients with NSTE-ACS and the potential of using the serum S100A1 level to predict the 30-day prognosis of NSTE-ACS.

Methods: The clinical characteristics of 162 patients with NSTE-ACS were analyzed to determine the GRACE score. The serum S100A1 concentration was determined using fasting antecubital venous blood. The patients were divided into different groups according to the serum S100A1 level, and the 30-day NSTE-ACS prognosis was evaluated using Kaplan–Meier analysis.

Results: The serum S100A1 levels differed significantly among the groups. Correlation analysis showed that the serum S100A1 level was positively correlated with the GRACE score. Kaplan–Meier analysis revealed that the number of 30-day cardiac events was significantly higher in patients with an S100A1 level of >3.41 ng/mL.

Conclusions: S100A1 is a potential biomarker that can predict the progression of NSTE-ACS and aid in its early risk stratification and prognosis.

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Introduction

Acute coronary syndrome (ACS) comprises a series of clinical syndromes caused by vascular endothelial injury and atherosclerotic plaque rupture, which induce platelet activation, adhesion, and aggregation that lead to acute myocardial ischemia.[1] The main syndromes under ACS are acute ST-segment elevation infarction, acute non-ST-segment elevation myocardial infarction, and unstable angina, the latter two of which are forms of non-ST-segment elevation ACS (NSTE-ACS). The clinical manifestations of NSTE-ACS differ based on the severity of coronary artery disease and hemodynamic changes; more severe coronary artery disease and hemodynamic changes increase the risk of mortality and result in varied prognoses.[2] The risk factors for NSTE-ACS include sex, age, smoking, hypertension, diabetes mellitus, and dyslipidemia. Risk assessment plays an important role in early determination of the short-term prognosis in patients with NSTE-ACS and therefore has important clinical value.[3,4]

The calcium (Ca^{2+})-binding protein S100A1 is a Ca^{2+}-dependent regulator of myocardial contractility.[5] As one of the most important regulatory factors of heart contraction and relaxation, S100A1 regulates the release, uptake, and transport of Ca^{2+} in cardiomyocytes by monitoring the levels of sarcoplasmic reticulum Ca^{2+}-ATP enzyme and ryanodine receptor.[6] Some researchers have suggested that increasing S100A1 expression by regulating the transport of myocardial Ca^{2+}, inhibiting ventricular remodeling, reducing cardiomyocyte apoptosis, and restoring the myocardial energy supply can strengthen cardiac contractility.[7,8] Therefore, myocardial S100A1 has the potential to be used as an intervention target to treat cardiovascular disease.

Recent studies have shown that the serum level of S100A1 is closely related to cardiac function and is significantly increased in patients with heart failure.[9] However, only a few studies have focused on the association between the serum S100A1 level and the severity of coronary artery lesions and short-term prognosis in patients with NSTE-ACS. Therefore, the present study was performed to investigate the association of the serum S100A1 level with the Global Registry of Acute Coronary Events (GRACE) score and short-term prognosis in patients with NSTE-ACS.

Methods

Study population

Men and women who were diagnosed with NSTE-ACS at our department from January 2009 to June 2012 were enrolled. All patients were included in compliance with the European Society of Cardiology Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation,[1]

and NSTE-ACS was confirmed by coronary angiography.

The exclusion criteria were acute infection, severe hepatic or renal failure, malignant tumors, severe valvular or congenital heart disease, and acute cerebrovascular accident. A study flow chart is shown in Figure 1.

Methods

After admission, all patients underwent collection of clinical data (blood pressure, heart rate, age, sex, presence of hypertension, tobacco use, and alcohol consumption) and biochemical tests (white blood cells, red blood cells, blood glucose, total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and high-sensitivity C-reactive protein [hs-CRP]). The left ventricular end-systolic dimension and left ventricular end-diastolic dimension of all patients were measured by performing echocardiography and calculating the left ventricular mass index. Fasting venous blood samples were obtained from both groups the next morning, and approximately 5 mL of blood was placed in an EDTA tube and centrifuged at $8000 \times g$ for 10 minutes. The plasma was separated at 4°C for analysis. The concentration of the serum Ca^{2+}-binding protein S100A1 was measured using an enzyme-linked immunosorbent assay kit from LifeSpan BioSciences (Seattle, WA, USA) according to the manufacturer's instructions.

This was an observational study only, and no intervention was performed on the

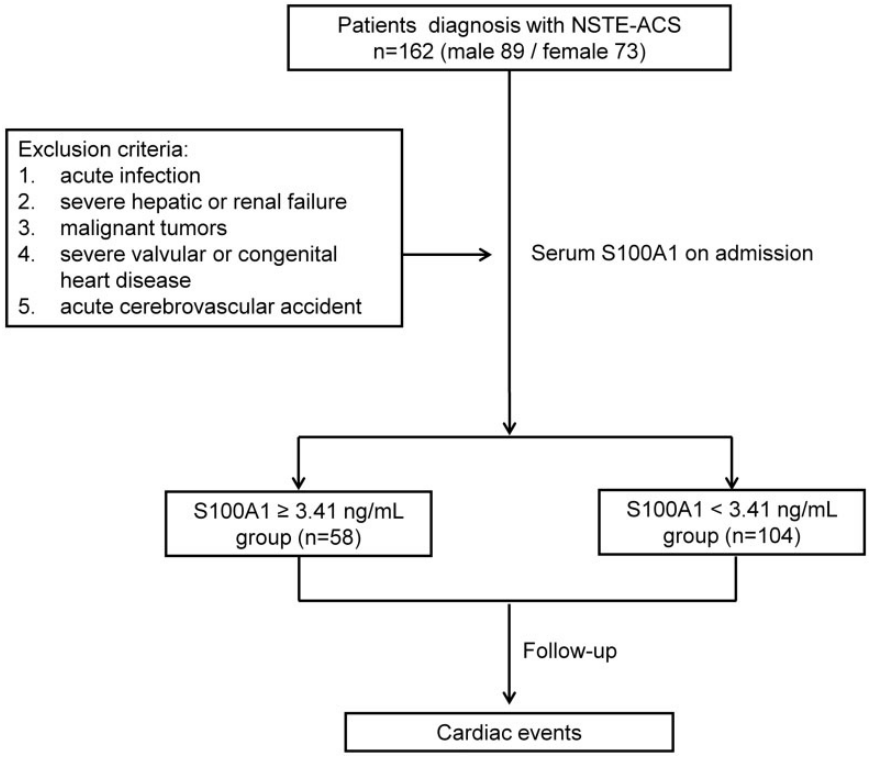

Figure 1. Study flow chart. This study included 162 patients with non-ST-segment acute coronary syndrome (NSTE-ACS) and followed short-term cardiac events.

patients. The study was approved by the hospital ethics committee, and all patients provided informed written consent.

GRACE scores

Eight indexes were recorded: age, heart rate at admission, systolic blood pressure, creatinine concentration, Killip grade, prehospital cardiac arrest, ST-segment deviation on electrocardiography, and myocardial markers. Dedicated software (http://www.outcome.org/grace) was used to calculate the GRACE score. The patients were divided into three groups based on the GRACE score: the low-risk group ($\leq$126 points), intermediate-risk group (127–147 points), and high-risk group (>147 points).

Cardiac function assessment

The Vivid 7 diagnostic ultrasound system (GE Healthcare, Chicago, IL, USA) was used to obtain the standard long-axis section, short-axis section, apical two-chamber view, and four-chamber view. The left ventricular ejection fraction (normal range, 55%–75%) was measured using the Simpson method.

Follow-up

Follow-up assessments were performed by means of telephone and/or face-to-face interviews 30 days after discharge. Cardiovascular death and events (including non-fatal recurrent myocardial infarction; non-fatal stroke; rehospitalization due to heart failure, angina, and arrhythmia; and revascularization procedures such as percutaneous coronary intervention and coronary artery bypass grafting) were recorded during the follow-up assessments.

Statistical analysis

SPSS Statistics, version 17.0 software (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. The measurement data are presented as mean $\pm$ standard deviation, and the t-test was used for comparison. Linear regression was used for correlation analysis. Differences were considered statistically significant at $p < 0.05$.

Results

Baseline characteristics

This study included 162 patients (89 men and 73 women) aged 53 to 77 years (mean, 65.2 ± 9.2 years). The biochemical indexes and clinical data of the patients in the different groups are shown in Table 1. When compared with patients in the low-risk and intermediate-risk groups, the patients in the high-risk group were older, had significantly higher cardiac troponin T (cTNT) and hs-CRP levels, and had a greater incidence of hypertension, diabetes mellitus, and coronary artery disease ($p < 0.05$). The presence of a smoking history and the body mass index were also significantly higher in the high- than intermediate-risk group ($p < 0.05$). Age, smoking history, hypertension, the body mass index, and the cTNT and hs-CRP levels were significantly higher in the intermediate- than low-risk group, and the difference was statistically significant ($p < 0.05$) (Table 1).

S100A1 cut-off value

The serum cTNT concentration was used as a diagnostic test for patients with NSTE-ACS. NSTE-ACS was set as 1, and non-NSTE-ACS was set as 0. The receiver operating characteristic curve was drawn with sensitivity as the ordinate and $1 -$ specificity as the abscissa. The area under the curve was 0.823, and the 95% confidence interval was 0.75–0.93. Both the sensitivity and specificity of S100A1 were higher when 3.41 ng/mL was used as the threshold (68.4% and 98.1%, respectively).

Table 1. Baseline characteristics of patients with different GRACE scores

	Low-risk group (n = 75)	Intermediate-risk group (n = 62)	High-risk group (n = 25)
GRACE score	99.1 ± 16.2	109.5 ± 20.1	133.4 ± 37.4
Sex (men/women)	40/35	36/26	13/12
Age (years)	52.3 ± 9.6	62.8 ± 7.4[a]	68.9 ± 7.7[a,b]
Smoking history	49 (65.3)	32 (51.6)[a]	28 (65.1)[b]
Hypertension	40 (53.3)	38 (61.3)[a]	29 (67.4)[a,b]
Diabetes mellitus	27 (36.0)	22 (35.5)	26 (60.5)[a,b]
CAD history	18 (24.0)	16 (25.8)	7 (16.3)[a,b]
cTNT (ng/mL)	1.74 ± 0.63	1.23 ± 1.05[a]	2.47 ± 1.70[a,b]
BMI (kg/m^2)	25.2 ± 2.1	26.3 ± 3.2[a]	24.8 ± 2.2[b]
FBG (mmol/L)	5.81 ± 2.0	5.92 ± 1.7	5.56 ± 1.8
HbA1C (%)	6.1 ± 1.1	6.2 ± 1.2	6.4 ± 1.2
TC (mmol/L)	4.45 ± 1.14	4.70 ± 1.19	4.56 ± 1.43
TG (mmol/L)	1.82 ± 1.26	2.05 ± 0.98	1.96 ± 1.30
HDL-C (mmol/L)	1.02 ± 0.26	1.22 ± 0.38	1.13 ± 0.32
LDL-C (mmol/L)	2.96 ± 1.02	3.14 ± 0.89	2.86 ± 1.13
Hcy (mmol/L)	11.87 ± 4.23	13.61 ± 6.27	12.98 ± 5.54
hs-CRP (mg/dL)	8.59 ± 3.44	12.78 ± 2.78[a]	14.65 ± 4.70[a,b]

Data are presented as mean ± standard deviation or n (%).
GRACE, Global Registry of Acute Coronary Events; CAD, coronary artery disease; cTNT, cardiac troponin T; BMI, body mass index; FBG, fasting blood glucose; HbA1C, hemoglobin A1c; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Hcy, homocysteine; hs-CRP, hypersensitive C-reactive protein.
[a]$p < 0.05$ compared with low-risk group.
[b]$p < 0.05$ compared with intermediate-risk group.

Therefore, the patients were divided into two groups based on this threshold: ≥3.41 ng/mL (n = 58; men/women, 35/23) and <3.41 ng/mL (n = 104; men/women, 70/34).

Comparison of serum S100A1 levels in patients with NSTE-ACS with different GRACE scores

The mean S100A1 level in the low-, intermediate-, and high-risk groups was 3.56 ± 1.04, 5.64 ± 0.78, and 8.38 ± 1.28 ng/mL, respectively. The high-risk group had a higher serum S100A1 level than the intermediate- and low-risk groups, and the difference was statistically significant ($p < 0.05$). The serum S100A1 level differed significantly between the low- and intermediate-risk groups ($p < 0.05$); thus, as the GRACE risk score increased, the S100A1 level also increased (Figure 2).

Correlation between serum S100A1 level and GRACE score

Linear regression analysis, performed with the Pearson rank correlation coefficient, showed that the serum S100A1 level was positively correlated with the GRACE risk score ($r = 0.546$, $p < 0.01$) (Figure 3).

Follow-up findings and Kaplan–Meier survival analysis

The mean follow-up duration was 25.8 ± 7.7 days. Twelve patients in the ≥3.41-ng/mL group but only five patients in the <3.41-ng/mL group experienced major cardiovascular events. The difference between

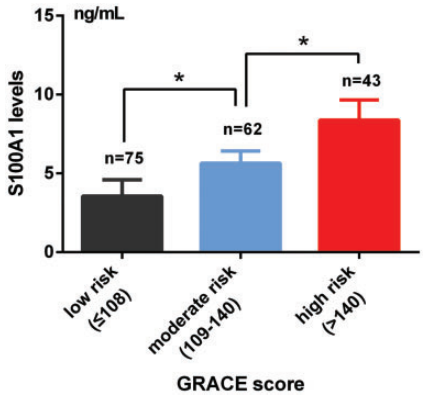

Figure 2. Serum S100A1 levels in the groups of patients with different Global Registry of Acute Coronary Events (GRACE) scores. The mean S100A1 level in the low-risk, intermediate-risk, and high-risk groups was 3.56 ± 1.04, 5.64 ± 0.78, and 8.38 ± 1.28 ng/mL, respectively. The S100A1 level was higher in the high-risk group than in the other groups. *$p < 0.05$ between the two groups.

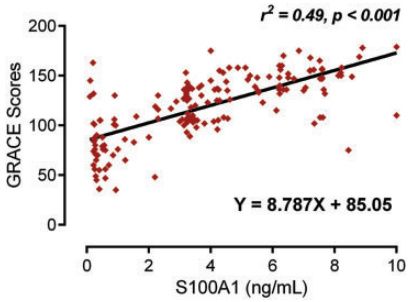

Figure 3. Correlation between the S100A1 level and Global Registry of Acute Coronary Events (GRACE) score. The S100A1 level was positively correlated with the GRACE score in patients with non-ST-segment acute coronary syndrome; $p < 0.01$.

the two groups was significant ($p < 0.01$) (Figure 4).

Discussion

The cardiovascular disease epidemiology statistics reported by the American Heart Association[10] showed that one of every three deaths in the United States in 2013 was associated with cardiovascular disease. Nearly 801,000 Americans died of cardiovascular disease, among whom 370,000 died of heart disease. Globally, cardiovascular disease accounts for 31% of deaths. Cardiovascular disease is a serious threat to human health.[11–13] Patients with NSTE-ACS, a common cardiovascular emergency, account for 75% of patients with ACS. The main pathological mechanism underlying NSTE-ACS involves rupture of a coronary artery plaque, which triggers activation of the coagulation system, promotes platelet aggregation and thrombosis concurrent with coronary artery spasms and microvascular emboli, and aggravates myocardial ischemia and hypoxia.[14] In the present study, we investigated the potential of using the serum S100A1 level in assessing the risk and prognosis in patients with NSTE-ACS. This study revealed a correlation between the S100A1 level and the GRACE score, and the incidence of short-term cardiovascular events was higher in patients with elevated S100A1 levels.

The GRACE score is an integrated scoring system and plays an important role in assessment of the in-hospital mortality and prognosis of patients with NSTE-ACS. The latest NSTE-ACS guidelines published by the European Society of Cardiology in 2015 emphasize that risk stratification should be performed before deciding on the strategy and timing of invasive management in patients with NSTE-ACS. An early invasive strategy (<24 h) is recommended for patients with a GRACE score of >140. For patients with a GRACE score of >108 or <140, the invasive strategy can be delayed; however, the intervention should not be delayed beyond 72 h from the time of admission. Risk stratification

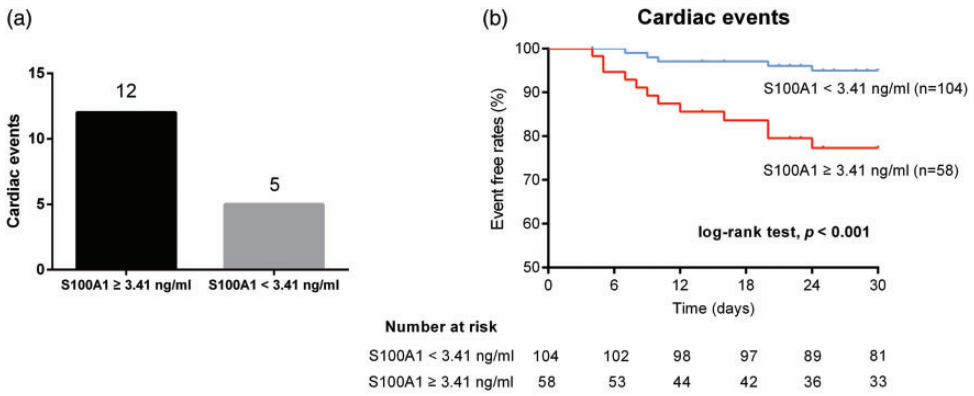

Figure 4. Cardiac events and Kaplan–Meier survival analysis. (a) Twelve patients in the ≥3.41-ng/mL group experienced major cardiovascular events, while only five patients in the <3.41-ng/mL group experienced major cardiovascular events. (b) Kaplan–Meier survival analysis revealed a significant difference between the two groups ($p < 0.01$).

will allow high-risk patients with NSTE-ACS to receive immediate and effective treatment intervention, thereby preserving a maximum number of ischemic cardiomyocytes.[1] Studies have shown that the use of the GRACE score can lead to early and effective interventional therapy, thereby improving myocardial ischemia and hypoxia, reducing ventricular remodeling, improving cardiac function, lowering rehospitalization rates within 6 months, and prolonging patient survival.[15]

In 1965, Moore et al. first isolated and characterized the Ca^{2+}-binding protein S100, which belongs to the multi-gene EF-hand Ca^{2+}-binding protein family.[5] Since then, 21 types have been isolated and characterized.[5] The human S100A1 gene is located at 1q21 and has a length of about 1.6 Mbp. The S100A1 protein is a homodyne, consisting of two subunits, and its relative molecular mass is about 10 to 11 kD; the hydrophobic C-terminal is an important functional group.[6] With co-immunoprecipitation, S100A1, SERCA2a, and RyR2 have been proven to coexist in cardiomyocytes, and S100A1 is regarded as a novel inhibitory modulator of RyR2 function at diastolic Ca^{2+} concentrations in cardiomyocytes.[16] The expression of the S100A1 protein is highly tissue-specific and cell-specific; it is rarely expressed in skeletal muscle, whereas it is abundantly expressed in healthy myocardial cells, with expression being highest in the left ventricle and lower in the right ventricle and the atria. The expression of S100A1 is down-regulated in heart failure and up-regulated in cardiac hypertrophy.[9] In addition, studies have shown that S100A1 is independent of the β-adrenergic receptor effect and does not increase the heart rate. Cardiac function can still be improved with the use of β-receptor antagonists, and S100A1 will not contribute to cardiac hypertrophy, arrhythmia, and myocardial fibrosis. Thus, S100A1 can be used as a novel target or biomarker for the treatment of heart failure.[17–19] Some researchers have studied whether the S100A1 level can be used to diagnose acute myocardial ischemia, and they found that a longer duration of myocardial ischemia was associated with a higher level of serum S100A1.[20,21] Jungi et al.[22] reported that S100A1 could exert a cardioprotective effect on global ischemia-

reperfusion injury. The present study showed that the serum concentration of S100A1 was significantly increased in patients with NSTE-ACS and was closely related to the short-term prognosis. These results indicate that the serum S100A1 level can aid in the diagnosis of ACS; further, the level can be used for risk stratification and assessment of the short-term prognosis in patients with NSTE-ACS.

This study has two main limitations. First, it was a single-center, observational study with a relatively small sample size. Therefore, our findings should be confirmed in larger studies. Second, the follow-up period of this study was short, and long-term follow-up could not be completed.

Conclusions

In summary, the serum level of S100A1, a novel biomarker, is greatly elevated in patients with NSTE-ACS and is significantly correlated with the GRACE score. Thus, S100A1 has the potential to be used for risk stratification and assessment of short-term prognosis in patients with NSTE-ACS.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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