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ORIGINAL RESEARCH

Development and Validation of Risk Stratification for Heart Failure After Acute Coronary Syndrome Based on Dynamic S100A8/A9 Levels

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BACKGROUND: The early assessment of heart failure (HF) risk in patients with acute coronary syndrome (ACS) can help reduce mortality. S100A8/A9 is not only rapidly released after myocardial ischemia, but is also involved in reperfusion injury, which is an important predictor of HF after ACS. We attempted to construct a reliable HF risk stratification tool for evaluating patients with ACS after reperfusion therapy based on S100A8/A9 dynamic changes.

METHODS AND RESULTS: This prospective study included 3 independent cohorts of patients with ACS who received reperfusion therapy. The discovery cohort was divided into 2 subgroups: the longitudinal subgroup (n=264) with serum S100A8/A9 levels measured at admission and on days 1, 2, 3, and 4 postadmission, respectively, and the 2-point subgroup (n=798) with S100A8/A9 levels measured at admission and on day 1 postadmission, respectively. Validation cohorts 1 (n=1399) and 2 (n=1183) both had S100A8/A9 levels measured on day 1 postadmission. HF events included in-hospital HF events after the initial presentation and long-term HF events after discharge. The median follow-up for the discovery cohort, validation cohort 1, and validation cohort 2 was 4.2, 2.6, and 1.8 years, respectively. In the discovery cohort, S100A8/A9's predictive ability at day 1 surpassed other time points. Through the S100A8/A9-guided risk stratification, patients deemed high risk (>7900 ng/mL) exhibited a higher 1-year HF event rate (46% versus 2%, 38% versus 5%) than patients at low risk (<2100 ng/mL) in both validation cohorts. Among patients without left ventricular dysfunction after ACS, β-blocker therapy correlated with reduced 1-year HF events in intermediate-to- high-risk patients but not in low-risk patients.

CONCLUSIONS: S100A8/A9 levels on day 1 accurately classified patients at varying risks of HF, serving as a robust tool for HF risk prediction and treatment guidance.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT03752515.

Key Words: acute coronary syndrome ■ heart failure ■ S100A8/A9 ■ β-blocker

Heart failure (HF) is a significant cause of mortality after acute coronary syndrome (ACS).[1,2] The advancements in reperfusion therapies, such as percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG), have led to improved long-term survival rates post-ACS, potentially paralleled by an increase in the prevalence of HF over time.[3,4] The impact of hospitalization and postdischarge HF on

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CLINICAL PERSPECTIVE

What Is New?

- The predictive efficacy of S100A8/A9 was higher at 1 day than that of S100A8/A9 at admission in 264 patients with acute coronary syndrome based on the dynamic changes in S100A8/A9 levels at admission and at 1, 2, 3, and 4 days after admission.
- The heart failure (HF) risk stratification tool was developed based on S100A8/A9 at 1 day postadmission in the discovery cohort and validated in 2 independent acute coronary syndrome patient cohorts. Intermediate- and high-risk patients with HF, but not low-risk patients with HF identified by the new S100A8/A9 risk stratification tool, benefited from postdischarge β-blocker therapy.

What Are the Clinical Implications?

- The new S100A8/A9-based HF risk stratification tool may help in the early classification of patients with acute coronary syndrome with different HF risks.
- This could facilitate the implementation of differentiated HF prevention treatments for patients with different HF risks and improve patient prognosis.

Nonstandard Abbreviations and Acronyms

ARSGB-ACS	*A Registry Study on Genetics and Biomarkers of Acute Coronary Syndrome*
cTnI	cardiac troponin I
GRACE	Global Registry of Acute Coronary Events Risk
I/R	ischemia/reperfusion

the prognosis of ACS underscores the importance of accurately estimating individual HF risks.[5]

Myocardial ischemia and reperfusion injury are dynamic pathological processes wherein biomarker levels at different time points during disease progression may correlate differently with HF. Determining the optimal timing of biomarker measurements to predict HF after ACS based on longitudinal biomarker levels may be helpful in accurately identifying patients with ACS who are at risk for HF. S100A8/A9, a critical inflammatory alarmin, is rapidly released from the site of the ischemic injury and increases in coronary and systemic circulation in patients with ACS.[6,7] Pathological roles of S100A8/A9 in ischemic injury, ischemia/reperfusion (I/R) injury, and cardiac dysfunction have been established.[8,9] Building upon our previous study, which demonstrated a causal association between S100A8/A9 and post-myocardial infarction HF events,[10] we hypothesized that leveraging S100A8/A9 at the most pertinent time point for HF could be used to construct a highly sensitive and specific risk stratification tool for HF.

This study examined the temporal profile of S100A8/A9 in a longitudinal subset of the discovery cohort, comparing its association with HF events at different time points. Subsequently, we compared the predictive ability of S100A8/A9 at admission and on day 1 postadmission in the discovery cohort with a known risk scoring system and clinical biomarkers and developed a risk stratification tool for HF events based on S100A8/A9 levels on day 1 after admission. The accuracy of the risk stratification tool was validated in patients with ACS who underwent PCI or CABG. Furthermore, we conducted a comparative analysis of the efficacy of β-blockers, the primary pharmacological intervention for HF, in patients with different HF risks.

METHODS

This article adheres to the Transparency and Openness Promotion Guidelines implemented by the American Heart Association journals. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design

This study comprised 3 steps (Figure 1). First, we measured S100A8/A9 levels at admission and at 1, 2, 3, and 4 days after admission in the longitudinal subset (n=264) of the discovery cohort to determine the serum S100A8/A9 measurement time points most correlated with HF events. Subsequently, we measured the S100A8/A9 levels at admission and 1 day after admission in the 2-point subset of the discovery cohort. We combined 2 subsets of the discovery cohort to determine which of the early time points was more accurate in predicting HF events in patients with ACS in the entire discovery cohort (n=1062). S100A8/A9 at the optimal time point was used to construct a risk stratification tool for HF events. Finally, the tool's accuracy was validated in validation cohorts 1 (n=1399) and 2 (n=1183).

Study Population

Three independent cohorts of patients with ACS were examined. Informed consent was obtained from all the patients, and the respective institutional review boards approved the study protocols. All studies were conducted in accordance with the Declaration of Helsinki (ClinicalTrials.gov identifier: NCT03752515, *A Registry Study on Genetics and Biomarkers of Acute Coronary Syndrome (ARSGB-ACS)*). As previously published,

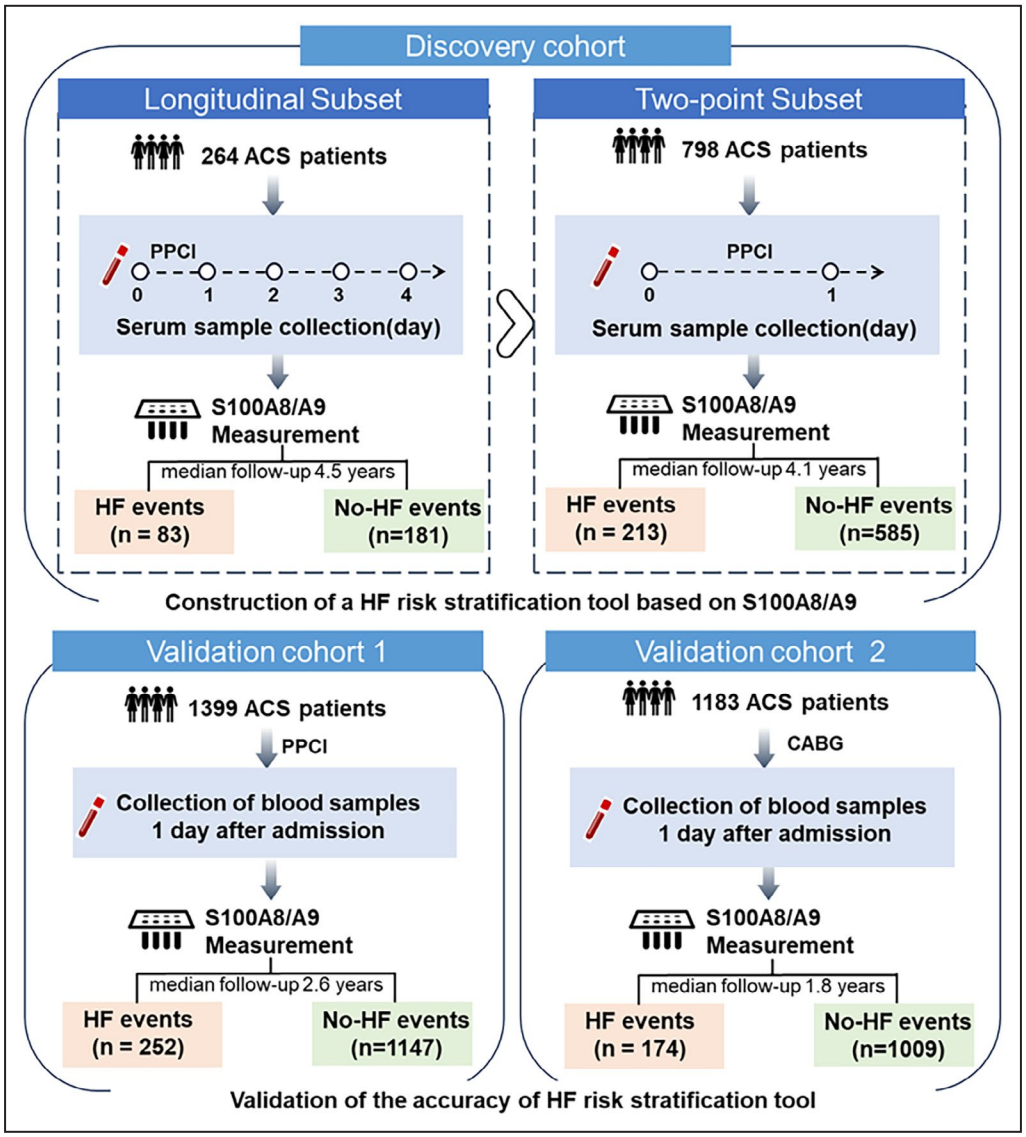

Figure 1. Study design.
ACS indicates acute coronary syndrome; CABG, coronary artery bypass grafting; HF, heart failure; and PPCI, primary percutaneous coronary intervention.

the discovery cohort (n=1062) comprised consecutive patients admitted to the Anzhen Hospital of Capital Medical University (Beijing, China) between August 2015 and November 2017.[10] This cohort included a longitudinal subset (n=264) and a 2-point subset (n=798). Using the same inclusion and exclusion criteria (Figure S1), 1399 patients with ACS treated with PCI between January 2018 and March 2019 were enrolled in validation cohort 1, and 1183 patients with ACS treated with CABG between January 2019 and December 2019 were included in validation cohort 2. Validation cohort 1 was a multicenter cohort that included 4 other hospitals in China: First Hospital of Jilin University (Jilin Province), First Affiliated Hospital of Dalian Medical University (Liaoning Province), Second Hospital of Dalian Medical University (Liaoning Province), and Beijing Luhe Hospital of Capital Medical University (Beijing). Validation cohort 2 was recruited from consecutive patients admitted to Anzhen Hospital, Capital Medical University (Beijing, China).

Study End Points and Follow-Up

The end points were the incidence of in-hospital and long-term postdischarge HF. In-hospital HF included new-onset HF (HF symptoms/signs after initial presentation and imaging evidence of pulmonary congestion), worsening HF (eg, Killip class II progressing to class III or IV, Killip class III progressing to class IV), diagnosis of cardiogenic shock, and in-hospital death due to HF or cardiogenic shock. Long-term HF included HF resulting in hospitalization or death due to HF after initial discharge. HF resulting in hospitalization required

all of the following criteria to be met: (1) hospitalization for at least 24 hours, (2) objective evidence of new or worsening HF (eg, orthopnea, jugular venous distention, pulmonary basilar crackles), and (3) intensification of HF therapy (eg, initiation of intravenous diuretics or inotropes).[10] The follow-up of the 3 cohorts ended on May 31, 2021. Median follow-up for the discovery cohort was 4.2 years (interquartile range [IQR], 1.7–5.1) and for the validation cohort 1 was 2.6 years (IQR, 2.3–3.1), and the median follow-up in validation cohort 2 was 1.8 years (IQR, 1.5–2.1). The discovery, validation cohort 1, and validation cohort 2 had 52, 35, and 17 patients, respectively, who missed visits.

Statistical Analysis

Data are presented as absolute numbers with percentages for categorical variables and as medians with IQRs (IQR: 25th–75th percentiles) for continuous variables. Categorical variables were analyzed using the χ^2 test or Fisher exact test, whereas continuous variables were compared using either the Student *t* test or the Mann-Whitney *U* test (for 2 groups, as appropriate).

The area under the curve (AUC) for S100A8/A9 over 5 days was calculated using the linear trapezoidal method based on S100A8/A9 levels measured at admission and at 1, 2, 3, and 4 days after admission. Univariate Cox proportional hazards regression models were used to assess the relationship between S100A8/A9 levels at admission, on days 1 to 4 postadmission, and the estimated AUC within the first 5 days, with HF events. The inverse probability of censoring weighting method was used to estimate and compare the time-dependent AUC of S100A8/A9 levels, GRACE (Global Registry of Acute Coronary Events Risk) score, and other biomarkers using the time ROC package to assess their prognostic accuracy. The added predictive ability of S100A8/A9 beyond that of a reference model in which the GRACE score plus 3 biomarkers was assessed using the Harrell C statistic calculated from a Cox proportional hazards regression model. Two conditions were used to select the optimal cutoff point of S100A8/A9 on day 1 postadmission for risk stratification. For low-risk patients, the cutoff value was at least 95% for both the negative predictive value and the sensitivity, and covered at least 10% of the patients, whereas for high-risk patients, it had a high positive predictive value and a specificity of at least 90%, covering at least 15% of the patients. Kaplan-Meier cumulative-event curves displayed outcomes of S100A8/A9-guided risk status, with group-wise comparisons by the log-rank test.

Efficacy Analysis of β-Blockers for Long-Term HF Events

Considering the existence of multiple confounding factors interfering with the efficacy of β-blockers, inverse probability of treatment weighting was used to adjust for the differences between the group with β-blockers at discharge and the group without β-blockers at discharge. The process was structured as follows:

1. Calculation of propensity scores: Propensity scores for each patient were calculated using a logistic regression model, with β-blocker use as the dependent variable and all baseline characteristics as independent variables, indicating the likelihood of receiving β-blocker therapy based on these characteristics.
2. Determination of weights: For patients receiving β-blocker therapy, the weights were set as the reciprocal of the propensity score:

$$\text{Weight}_{\text{treated}} = \frac{1}{\text{propensity score}}.$$

For patients not receiving β-blocker therapy, the weights were set as the reciprocal of (1–propensity score):

$$\text{Weight}_{\text{untreated}} = \frac{1}{1 - \text{propensity score}}$$

These weights were crucial in balancing the groups and minimizing the impact of confounding variables.

3. Assessment of covariate balance: The absolute standardized mean difference threshold of ≤10% was used to ensure group balance, thus validating the efficacy of our weighting approach.
4. Weighted Cox regression analysis: Cox regression models were used to assess the association between β-blocker therapy and HF events in low- and intermediate-high-risk patients based on S100A8/A9 risk stratification, with individual observations weighted for accurate treatment effect estimation.
5. Weighted Kaplan-Meier curve analysis: Kaplan-Meier curves were used to visualize the cumulative incidence of 1-year HF events over time in low- and intermediate-high-risk patients based on S100A8/A9 risk stratification. These curves were adjusted using inverse probability of treatment weighting to account for the risk disparity between β-blocker and non–β-blocker groups.

Statistical significance was set at $P<0.05$. Due to the explorative nature of the study, no corrections for multiple comparisons were made. Analyses were performed using the IBM SPSS software (version 26.0; IBM, Armonk, NY) or R (version 4.1.1; R Foundation for Statistical Computing, Vienna, Austria).

Blood sample collection, BNP (B-type natriuretic peptide), cTnI (cardiac troponin I), hs-CRP

(high-sensitivity C-reactive protein) measurements, and detailed statistical analyses are described in Data S1.

RESULTS

Patient Characteristics

A total of 1062 patients with ACS underwent PCI, 1399 patients with ACS underwent PCI, and 1183 patients with ACS underwent CABG, constituting the discovery, validation cohort 1, and validation cohort 2, respectively. The median follow-up times for discovery cohort, validation cohort 1, and validation cohort 2 were 4.2, 2.6, and 1.8 years, respectively. During this period, there were 118 (11%), 145 (10%), and 102 (9%) in-hospital HF events and 178 (17%), 107 (8%), and 72 (6%) long-term HF events in the discovery cohort and validation cohorts 1 and 2, respectively. In the discovery cohort and validation cohorts 1 and 2, patients with HF events had older age, higher levels of serum creatinine, fasting glucose, and biomarkers (BNP, hs-CRP, and hs-cTnI), and lower left ventricular ejection fraction (Table 1). In terms of multivessel lesions, the discovery cohort of patients with HF had more left main lesions, whereas the incidence of multivessel disease was similar between patients with and without HF in validation cohorts 1 and 2. Medications were similar in patients with and without HF of the discovery cohort, and aspirin was prescribed more often to patients without HF events than to those with HF events in validation cohorts 1 and 2. In addition, patients with HF events were more likely to be women and have lower blood pressure (systolic and diastolic) in the discovery cohort and validation cohort 1. Patients with HF in validation cohort 1 were less likely to be discharged on statin lipid-lowering medications (Table 1).

Longitudinal S100A8/A9 Levels Associated With HF Events

First, we analyzed the relationship between serial measurements of S100A8/A9 and HF events in a longitudinal subset (n=264) of the discovery cohort. The baseline characteristics of the longitudinal subset of the discovery cohort stratified by HF events are presented in Table S1. S100A8/A9 levels at all sampling points were significantly higher in patients who experienced HF events than in those who did not (Figure 2A). The temporal profile of S100A8/A9 in patients with HF showed a significant increase on day 1 after admission, followed by a subsequent decrease. A similar but weak trend in S100A8/A9 levels was observed in patients without HF. COX regression analysis demonstrated that the longitudinal S100A8/A9 levels were associated with HF (Figure 2B). S100A8/A9 levels at 1 day postadmission had the highest correlation with HF events (hazard ratio [HR], 3.60 [95% CI, 2.77–4.70]; $P<0.001$), followed by the AUC of S100A8/A9 within 5 days after admission (HR, 3.05 [95% CI, 2.30–4.04]; $P<0.001$). The S100A8/A9 levels at 1, 2, 3, and 4 days after admission and the AUC of S100A8/A9 within 5 days after admission were compared with the S100A8/A9 levels at admission to predict HF events (Figure 2C) accurately. Among the 4 time points, only the C statistic and AUC of S100A8/A9 at 1 day after admission were significantly higher values (ΔC statistic, 0.12 [95% CI, 0.07–0.17]; $P<0.001$; ΔAUC, 0.10 [95% CI, 0.05–0.16]; $P<0.001$) than those at admission.

S100A8/A9 Value 1 Day After Admission Was a Strong Predictor of HF Events

Early identification of HF events could help mitigate the risk; hence, we evaluated the predictive abilities of S100A8/A9 at admission and S100A8/A9 levels on day 1 postadmission in the discovery cohort (n=1062). The distribution of both measures in patients with and without HF is shown (Figure S2). As shown in Figure S3, S100A8/A9 at 1 day after admission (AUC, 0.84 [95% CI, 0.81–0.87]; C statistic, 0.76 [95% CI, 0.73–0.77]) was more accurate in predicting HF events than S100A8/A9 levels at admission (AUC, 0.74 [95% CI, 0.70–0.78]; C statistic, 0.65 [95% CI, 0.62–0.68]). Moreover, S100A8/A9 1 day after admission was more accurate in predicting HF events than the GRACE score and contemporaneous clinical biomarkers (Figure S3). After adjusting for age, sex, systolic blood pressure, fasting glucose, creatinine, left main artery disease, GRACE score, aspirin use, biomarkers (BNP, cTnI, hs-CRP) at the same period with S100A8/A9, and left ventricular ejection fraction at the same period with S100A8/A9, S100A8/A9 at admission (HR, 2.11 [95% CI, 1.84–2.43]; $P<0.001$), S100A8/A9 (HR, 2.30 [95% CI, 1.98–2.67]; $P<0.001$), BNP (HR, 1.77 [95% CI, 1.48–2.13]; $P<0.001$), hs-CRP (HR 1.22 [95% CI 1.07–1.39]; $P=0.003$) at 1 day after admission, and GRACE score (HR, 1.28 [95% CI, 1.08–1.52]; $P=0.006$) remained associated with HF events (Figure S3). The increase in C statistic when S100A8/A9 at 1 day after admission was added to the reference model (GRACE score+BNP, cTnI, hs-CRP) was greater than that when S100A8/A9 at admission was added to the reference model (ΔC statistic: S100A8/A9 at 1 day after admission, 0.10 [95% CI, 0.08–0.13]; S100A8/A9 at admission, 0.05 [95% CI, 0.03–0.07]) (Table S2). These results indicated that S100A8/A9 on day 1 postadmission was more predictive than baseline S100A8/A9 and CRP, BNP, and cTnI levels, as well as the GRACE score, and added significant discrimination/reclassification value to the established risk score and biomarkers.

Table 1. Baseline Clinical Characteristics According to HF Events in the Discovery and Validation Cohorts

Variables	Internal cohort (n=1062)		*P* value	Validation cohort 1 (n=1399)		*P* value	Validation cohort 2 (n=1183)		*P* value
	HF events (n=296)	No HF events (n=766)		HF events (n=252)	No HF events (n=1147)		HF events (n=174)	No HF events (n=1009)	
Demographics									
Age (y)	60.5 (53.0–70.0)	59.0 (50.0–66.0)	0.001*	61.0 (54.0–69.8)	59.0 (50.0–66.0)	<0.001*	65.0 (59.0–70.0)	62.0 (56.0–67.0)	0.002*
Male sex	225 (76.0)	626 (81.7)	0.037	186 (73.8)	915 (79.8)	0.036*	127 (73.0)	779 (77.2)	0.225
SBP, mm Hg	116.0 (103.3–134.0)	120.0 (110.0–136.0)	<0.001*	115.0 (104.0–130.0)	122.0 (112.0–134.0)	<0.001*	130.0 (120.0–140.0)	130.0 (116.0–140.0)	0.560
DBP, mm Hg	70.0 (63.3–80.0)	74.0 (70.0–82.0)	0.002*	70.0 (64.3–80.0)	73.0 (68.0–80.0)	0.003*	72.0 (61.8–80.0)	70.0 (62.0–80.0)	0.567
Current smoking	187 (63.2)	465 (60.7)	0.458	138 (54.8)	678 (59.1)	0.205	82 (47.1)	527 (52.2)	0.214
Medical history									
Hypertension	177 (59.8)	444 (58.0)	0.587	148 (58.7)	691 (60.2)	0.657	117 (67.2)	680 (67.4)	0.968
Hyperlipidemia	197 (66.6)	498 (65.0)	0.636	172 (68.3)	797 (69.5)	0.701	88 (50.6)	583 (57.8)	0.076
Diabetes	106 (35.8)	249 (32.5)	0.306	84 (33.3)	351 (30.6)	0.396	71 (40.8)	421 (41.7)	0.820
CAD	90 (30.4)	229 (29.9)	0.871	81 (32.1)	343 (29.9)	0.484	42 (24.1)	199 (19.7)	0.182
Biochemical									
HDL cholesterol, mmol/L	1.0 (0.9–1.2) †	1.0 (0.9–1.2) †	0.913	1.0 (0.9–1.2)	1.0 (0.9–1.2)	0.439	0.9 (0.8–1.1)	0.9 (0.8–1.1)	0.942
LDL cholesterol, mmol/L	2.9 (2.2–3.5) †	2.8 (2.3–3.5) †	0.647	2.7 (2.1–3.3)	2.7 (2.1–3.3)	0.752	2.3 (1.8–2.9)	2.2 (1.7–2.8)	0.274
Fasting glucose, mmol/L	7.1 (5.8–10.0)	6.6 (5.5–8.9)	0.001*	7.3 (5.9–9.8)	6.6 (5.5–8.7)	<0.001*	7.3 (5.9–11.1)	6.8 (5.6–9.5)	0.009*
Creatinine, μmol/L	76.4 (64.7–87.6)	71.9 (61.6–83.2)	0.001*	76.4 (64.0–94.9)	73.1 (63.2–83.6)	0.003*	71.7 (60.8–90.9)	68.0 (56.8–80.1)	0.001*
cTnI, ng/mL	64.5 (23.3–102.0)	36.2 (10.3–80.0)	0.001*	61.0 (24.4–98.0)	50.4 (20.0–78.0)		0.2 (0.1–0.7)	0.1 (0.1–0.3)	<0.001*
BNP, pg/mL	315.0 (177.0–600.0)	133.4 (62.5–289.9)	<0.001*	305.0 (119.0–594.3)	147.0 (63.0–324.0)		567.0 (262.0–1417.5)	269.0 (138.0–525.0)	<0.001*
hs-CRP, mg/L	12.0 (6.4–28.0)	8.5 (4.8–18.8)	0.002*	12.2 (5.1–28.0)	8.1 (4.5–18.4)		51.7 (12.9–100.9)	37.1 (4.5–82.0)	0.010*
Multivessel disease									
Left main artery disease	15 (5.1)	17 (2.2)	0.015*	6 (2.4)	31 (2.7)		32 (18.4)	171 (16.9)	0.641
2-vessel disease	86 (29.1)	225 (29.4)	0.918	77 (30.6)	349 (30.4)		9 (5.2)	35 (3.5)	0.273
3-vessel disease	43 (14.5)	94 (12.3)	0.326	44 (17.5)	147 (12.8)		158 (90.8)	911 (90.3)	0.831
Echocardiography									
1 day after admission LVEF (%)	45.0 (40.0–52.8)	56.0 (51.0–60.0)	<0.001*	45.0 (39.0–55.0)	58.0 (51.0–62.0)		48.0 (38.0–58.0)	58.0 (52.0–62.0)	<0.001*
Medication at discharge									
Aspirin	276 (93.2)	762 (99.5)	0.392	220 (87.3)	1129 (98.4)		138 (79.3)	884 (87.6)	0.035*
P2Y12 receptor inhibitor	279 (94.3)	766 (100.0)		232 (92.1)	1147 (100.0)		157 (90.2)	944 (93.6)	0.749
Statin	272 (91.9)	747 (97.5)	0.979	216 (85.7)	1102 (96.1)		138 (79.3)	817 (81.0)	0.833
ACEI or ARB	161 (54.4)	445 (58.1)	0.911	125 (49.6)	603 (52.6)		42 (24.1)	249 (24.7)	0.961
β-blockers	218 (73.6)	565 (73.8)	0.149	166 (65.9)	870 (75.9)		149 (85.6)	907 (89.9)	0.653

Data are presented as absolute number (percentage) or median (interquartile range). P2Y12 is an ADP receptor on platelet surfaces, part of the GPCR family, mediating platelet aggregation. P2Y12 inhibitors, including clopidogrel and ticagrelor, block this receptor to decrease platelet aggregation. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; BNP, B-type natriuretic peptide; CAD, coronary artery disease; cTnI, cardiac troponin I; DBP, diastolic blood pressure; HDL, high-density lipoprotein; HF, heart failure; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; and SBP, systolic blood pressure.

*$P<0.05$.

Derivation and Validation of S100A8/A9-Guided Risk Stratification

To facilitate the clinical usefulness of S100A8/A9 in risk stratification, optimal cutoff points for S100A8/A9 levels on day 1 postadmission should be developed and validated. In the discovery cohort, receiver operating characteristic analysis showed that the AUC for S100A8/A9 on day 1 postadmission was the best predictor of HF events (AUC, 0.84; $P<0.001$) (Figure S3). Two cutoff values of S100A8/A9 on day 1 postadmission were chosen to classify patients into low-risk (≤2100 ng/mL, 14% of patients) and high-risk (>7900 ng/mL, 15% of patients) groups through receiver operating characteristic

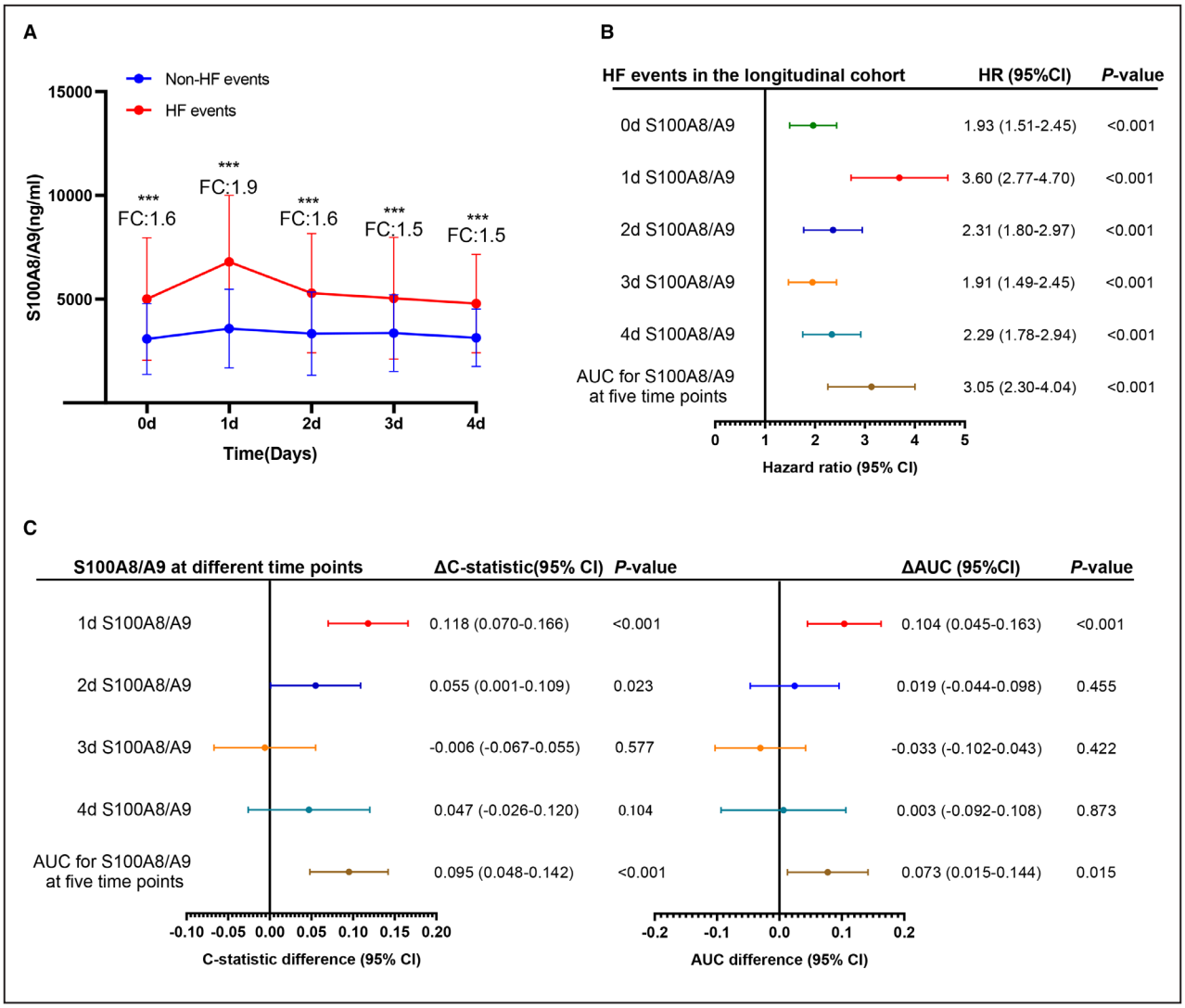

Figure 2. Association of longitudinal S100A8/A9 levels with HF events in the longitudinal subset of discovery cohort.
A, S100A8/A9 levels on admission and on days 1, 2, 3, and 4 after admission (following primary percutaneous coronary intervention). Data are presented as mean and mean±SD of patients who had HF event (red) and patients who did not have HF event (blue). Fold changes in S100A8/A9 between the 2 groups at each time are shown. **B**, Associations between the incidence of HF events and S100A8/A9 levels at different time points were calculated using univariate Cox proportional risk regression models. **C**, Predictive efficacy of the increase in S100A8/A9 levels at 1 to 4 days after admission and the area under the S100A8/A9 curve at 5 time points over the admission S100A8/A9 level was assessed using Harrell C statistic calculated from the Cox regression model and receiver operating characteristic. ***P<0.001. 0d S100A8/A9 indicates S100A8/A9 levels at admission; 1d S100A8/A9, S100A8/A9 levels at 1 day of admission; 2d S100A8/A9, S100A8/A9 levels at 2 days of admission; 3d S100A8/A9, S100A8/A9 levels at 3 days of admission; 4d S100A8/A9, S100A8/A9 levels at 4 days of admission; AUC indicates area under the curve; FC, fold change; HF, heart failure; and HR, hazard ratio.

curve analysis (Table 2, Figure 3, and Tables S3 and S4). In the Kaplan-Meier analysis, the S100A8/A9-based low- (≤2100 ng/mL), intermediate- (2100–7900 ng/mL), and high-risk (>7900 ng/mL) groups were effectively stratified in the discovery cohort (Figure 4A).

After that, we aimed to determine whether the strong prognostic value of S100A8/A9 levels on day 1 postadmission in patients with ACS receiving different reperfusion therapies could be replicated. In validation cohort 1 (an independent multicenter cohort of patients with ACS treated with PCI) and validation cohort 2 (an independent single-center cohort of patients with ACS treated with CABG), S100A8/A9 levels on day 1 postadmission were significantly higher among patients who experienced HF events (Table S5 and Figure S4), remained independently associated with an increased risk of HF events after adjustment (validation cohort 1: adjusted HR, 2.11 [95% CI, 1.79–2.48]; P<0.001; validation cohort 2: adjusted HR, 2.59 [95% CI, 2.15–3.13]; P<0.001), and indicated good predictive

Table 2. Performance of S100A8/A9-Guided Risk Stratification for Predicting the HF Events Risk in Discovery and Validation Cohorts

Cohort	Median follow-up time (y)	HF event rate (%)	Patients (%)	Risk stratification	NPV	PPV	Sensitivity	Specificity
Discovery	4.2	296 (27.9%)	147 (13.8%)	Low risk	95.2%	31.6%	97.6%	18.3%
			162 (15.3%)	High risk	79.7%	69.8%	38.2%	93.6%
Validation 1	2.6	252 (18.0%)	287 (20.5%)	Low risk	95.1%	21.4%	94.4%	23.8%
			204 (14.6%)	High risk	87.3%	49.0%	39.7%	90.9%
Validation 2	1.8	174 (14.7%)	454 (38.4%)	Low risk	94.5%	20.4%	85.6%	42.5%
			186 (15.7%)	High risk	90.4%	41.9%	44.8%	89.3%

HF indicates heart failure; NPV, negative predictive value; and PPV positive predictive value.

ability (Figure S5). The C statistic showed that S100A8/A9 on day 1 postadmission significantly improved the risk assessment of HF events when added to the GRACE score combined with the 3 biomarkers (Table S6). These cutoff values of S100A8/A9 on day 1 postadmission performed well in predicting HF events in validation cohorts 1 and 2 (Table 2). The S100A8/A9 cutoff concentration of ≤2100 ng/mL both had an negative predictive value of 95%, and that of >7900 ng/mL had specificities of 91% and 89% for predicting HF events in validation cohorts 1 and 2, respectively (Table 2, Tables S7 and S8). Kaplan-Meier analyses revealed a stepwise increase in HF events among the S100A8/A9-guided risk groups in validation cohorts 1 and 2 (Figure 4B and 4C). In addition, we assessed the association between ventricular arrhythmias and S100A8/A9 levels at 1 day of admission. The incidence of ventricular arrhythmias was 4.3% in the discovery cohort, 3.1% in the validation cohort 1, and 1.4% in the validation cohort 2. There was no significant association between S100A8/A9 levels on day 1 after admission and ventricular arrhythmias (Figure S6).

Impact of β-Blockers on HF Events Following S100A8/A9 Levels

β-blockers are among the main therapeutic agents for patients with HF post-ACS.[11] However, the use of

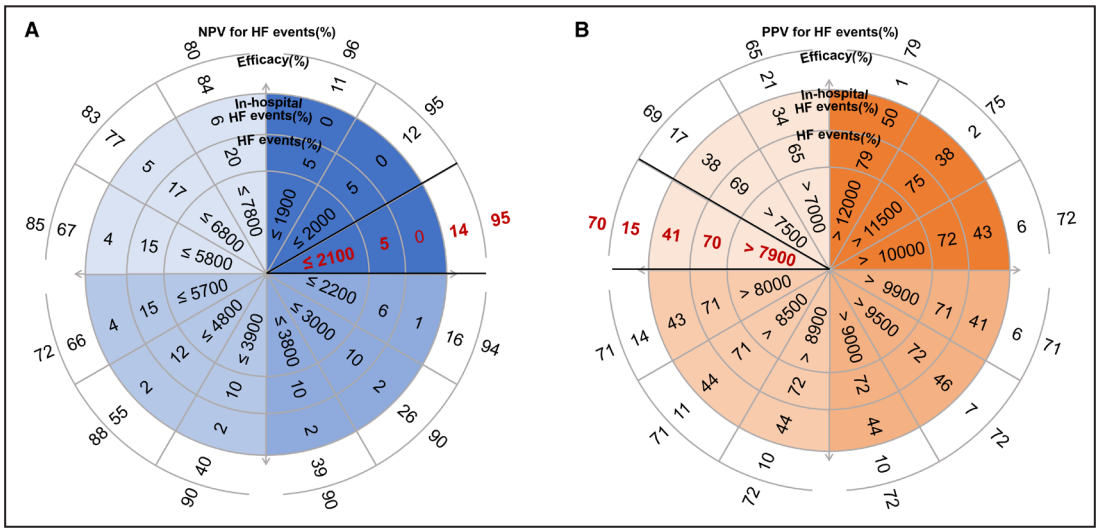

Figure 3. Risk-assessment tool for defining low- or high-risk clinical events using day 1 S100A8/A9 cutoff concentrations.

S100A8/A9 concentrations at 1 day after admission are shown for the entire discovery cohort (n=1062). The innermost circle shows the set low-risk threshold for S100A8/A9 levels at day 1 postadmission (in nanograms per milliliter). The second circle shows the rate of total HF events. The third circle shows the rate of in-hospital HF events. The fourth circle shows the proportion of patients designated as having low (**A**) or high (**B**) risk if either value is lower than or equal to the cutoff, and high risk if the value is greater than the cutoff. The outermost circle shows the NPV (**A**) or PPV (**B**) of S100A8/A9 on 1 day of admission. Based on the cutoff points of S100A8/A9, the corresponding NPV and PPV are indicated by bold black lines in (**A**) and (**B**), respectively. The darker the shade of blue, the lower the concentration of S100A8/A9, and the darker the shade of orange, the higher the concentration of S100A8/A9. HF indicates heart failure; NPV, negative predictive value; and PPV, positive predictive value.

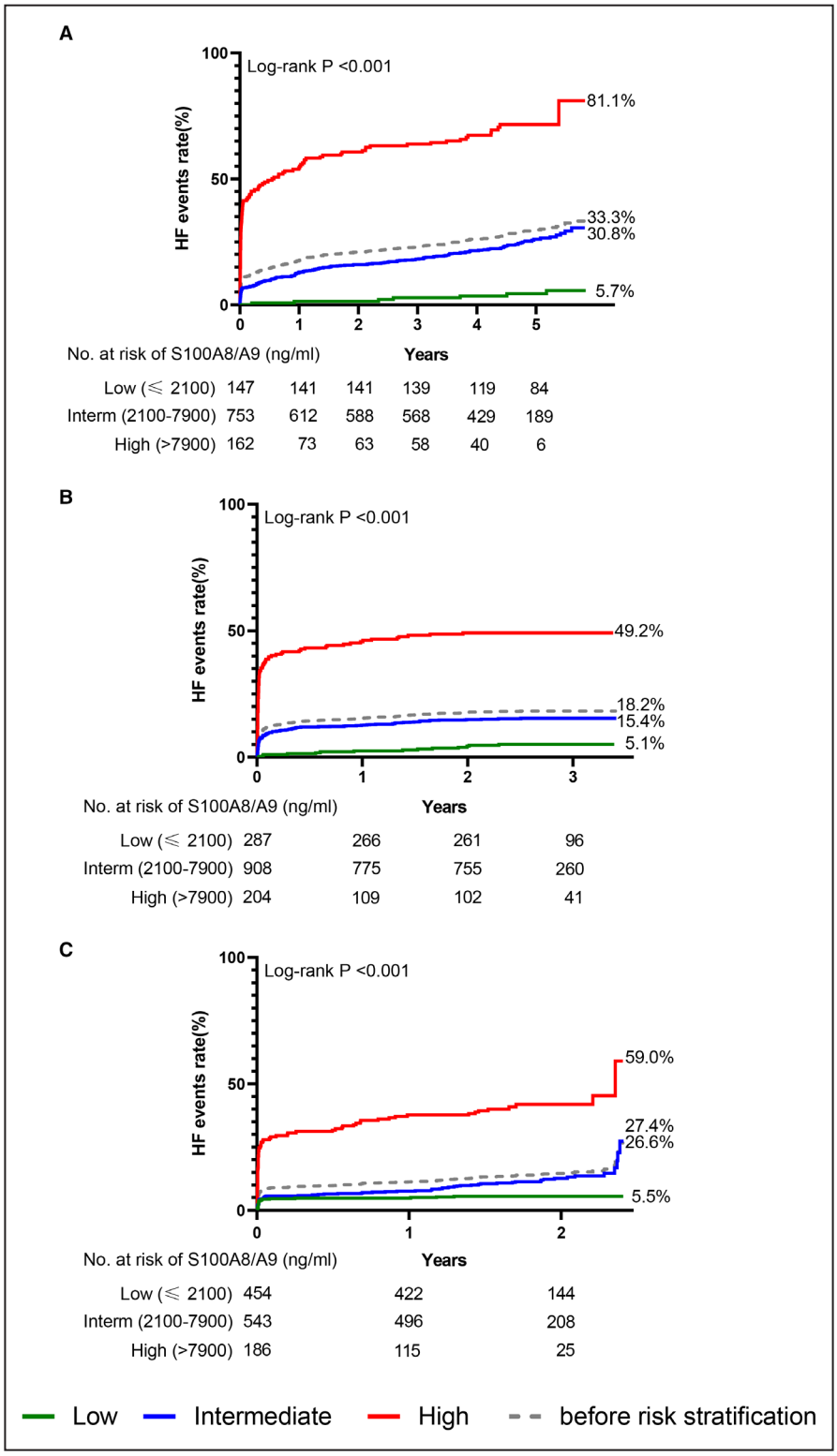

Figure 4. Incidence of HF events compared with the levels of day 1 S100A8/A9.
Kaplan-Meier curves illustrating the timing of HF events in the 3 risk strata of S100A8/A9 levels at 1 day of admission in the discovery cohort (**A**), validation cohort 1 (**B**), and validation cohort 2 (**C**). HF indicates heart failure; and Interm, intermediate.

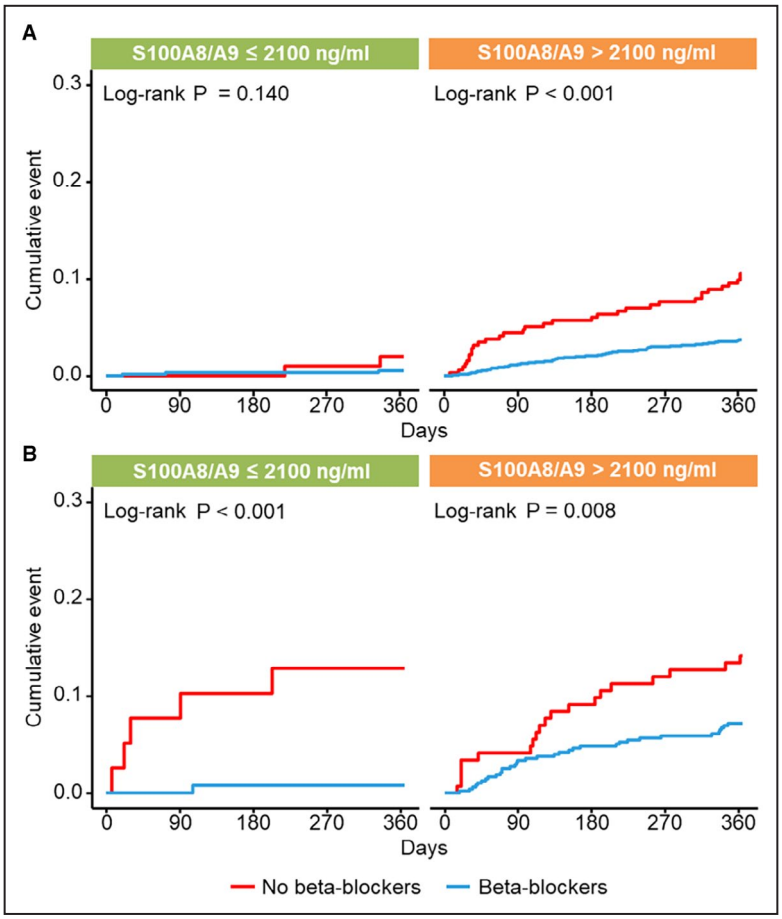

Figure 5. Prognostic impacts of β-blockers on 1-year HF events according to IPTW analysis in the low-risk group and the intermediate-high-risk group of HF events.
A, Patients with ACS without left ventricular dysfunction at discharge (n=2344). **B**, Patients with ACS with left ventricular dysfunction at discharge (n=864). ACS indicates acute coronary syndrome; HF, heart failure; and IPTW, inverse probability treatment weighting.

β-blockers in patients with ACS without HF has been long debated.[12–14] Early use of β-blockers may not be effective in patients with low HF risk but may be beneficial in intermediate- and high-HF-risk populations. In the combined cohort, patients without left ventricular dysfunction after ACS (n=2344) were divided into the low-risk group (≤2100 ng/mL) and intermediate-high-risk group (>2100 ng/mL) based on S100A8/A9 levels at 1 day after admission. In patients without left ventricular dysfunction, after adjustment for clinical variables, GRACE score, BNP, hs-CRP, and hs-cTnI (Figure S7), inverse probability of treatment weighting analyses showed that in the low-risk group (n=687, 29%), β-blocker use at discharge was not significantly associated with 1-year HF events (HR, 0.40 [95% CI, 0.05–3.00]; *P*=0.372) (Figure 5A and Table S9). However, in the intermediate-high-risk group (n=1657, 71%), β-blocker therapy at discharge was associated with a reduction of 1-year HF events (HR, 0.34 [95% CI, 0.21–0.56]; *P*<0.001) (Table S9 and Figure 5A). In patients with left ventricular dysfunction, the incidence of 1-year HF events after discharge was lower in patients taking β-blockers than in those not taking β-blockers in both the low- and intermediate-high-risk groups (Figure 5B).

DISCUSSION

Our study has 3 main findings. First, we demonstrated that S100A8/A9 measured 1 day after admission predicted HF events more accurately than S100A8/A9 at admission, as well as other clinical biomarkers and GRACE scores. Second, we developed and validated a risk stratification tool for HF events using S100A8/A9 levels measured 1 day after admission. Third, in low-risk patients without left ventricular dysfunction, discharge to β-blocker therapy was not significantly associated

with 1-year HF events, but intermediate-high-risk patients benefited from discharge to β-blocker therapy. In conclusion, S100A8/A9 levels measured 1 day after admission represent a simple and effective tool to identify patients with low-, intermediate-, or high-risk HF events occurring following ACS, guiding clinicians in selecting appropriate therapies for patients at different risk stratifications.

Prognostic Importance of Longitudinal S100A8/A9 in ACS

This study elucidated the prognostic value of measuring S100A8/A9 levels at admission and 1, 2, 3, and 4 days after admission. Neutrophil-derived S100A8/A9 is rapidly released into the circulation after myocardial ischemia[15] and changes dynamically with the severity of myocardial ischemia and I/R injury. Most current studies on the role of S100A8/A9 in ACS prognosis have measured S100A8/A9 levels at a single time point,[9,10] and few studies have investigated the potential of longitudinal S100A8/A9 levels for ACS prognosis.[16] In this study, we observed a significant increase in S100A8/A9 levels after PCI, peaking 1 day following admission. This trend closely reflected the progression of the I/R injury process, aligning with previous observations of dynamic S100A8/A9 levels in the myocardium of an I/R injury animal model.[8] Our study demonstrated that longitudinal S100A8/A9 levels were significantly associated with HF events, with the AUC of serum S100A8/A9 for predicting HF events on admission and 1, 2, 3, and 4 days after admission being 0.72, 0.82, 0.73, 0.68, and 0.72, respectively. In a clinical setting, early and accurate assessment of HF risk may help identify high-risk patients before the onset of clinical symptoms and provide a time window to prevent HF through therapeutic intervention. Hence, we focused on the prognostic value of S100A8/A9 levels on admission and 1 day after admission. Importantly, our study is the first to demonstrate the following: (1) The prognostic power of S100A8/A9 1 day after admission was better than that of S100A8/A9 on admission. (2) S100A8/A9 1 day after admission improved risk stratification when added to the established predictors (GRACE and biomarkers). Hence, S100A8/A9 1 day after admission is a powerful biomarker for predicting HF after ACS.

It is possible that S100A8/A9 1 day after admission is more predictive than S100A8/A9 at admission in patients with ACS receiving reperfusion therapy. The ischemic time and final infarct size are the main determinants of post-myocardial infarction HF. In patients with myocardial infarction, timely reperfusion minimizes ischemic time and limits myocardial ischemia and infarct size.[17] However, restoration of coronary blood flow after an ischemic episode can cause I/R injury, which accounts for up to 50% of the final infarct size.[18] Thus, both ischemic and I/R injury contribute to final infarct size in patients with ACS. In addition to the relatively longer duration of myocardial ischemia 1 day after admission compared with that at admission, I/R injury is more important. High levels of S100A8/A9 play an important role in I/R injuries. S100A8/A9 is a key initiator of cardiomyocyte death in the early stages of myocardial I/R injury by downregulating mitochondrial complex I activity,[8] exerting potent proinflammatory effects by activating pattern recognition receptors (such as Toll-like receptor 4),[19,20] and promoting oxidative stress by interacting with the nicotinamide adenine dinucleotide phosphate oxidase complex by binding to p67phox and Rac in neutrophils.[21] Overall, S100A8A9 1 day after admission was higher than S100A8/A9 at admission and more strongly association with the risk of HF events.

Clinical Implications

Current guidelines recommend that patients undergo early risk assessment after ACS to facilitate appropriate treatment.[22] However, reliable and responsive tools for predicting post-ACS HF to help clinical interventions prevent progression are lacking.[22] Although several clinical biomarkers, including BNP,[23] cTnI,[24] and hs-CRP,[25] have been reported to be associated with HF after ACS, the optimal measurement time and appropriate cutoff value for predicting HF events using these biomarkers have not been recommended. Based on S100A8/A9 levels 1 day postadmission, we established a new risk stratification tool to identify patients with high, intermediate, or low risk of HF events, guiding treatment decisions. S100A8/A9 levels at 1 day after admission were ≤2100 ng/mL in 14% of patients, with a negative predictive value of 95% and a sensitivity of 98%, indicating that this measure may be valuable as a screening tool for ruling out patients at risk of HF events. In addition to well-established anticoagulation, antiplatelet, and lipid-lowering therapies, β-blockers are widely prescribed at discharge; however, a prospective, observational cohort study reported that β-blocker therapy was not associated with a reduction in all-cause mortality in patients with acute myocardial infarction without HF or systolic dysfunction.[13] Similarly, a meta-analysis of 10 observational studies suggested a lack of evidence to support the routine use of β-blockers in all patients with acute myocardial infarction who received primary PCI.[26] A multicenter randomized controlled trial of β-blockers also showed that, among patients with acute myocardial infarction who had undergone coronary angiography and had a left ventricular ejection fraction of at least 50%, the rates of readmission for HF and cardiac death were similar between the group treated with β-blockers and the group that did not receive treatment at the time of

discharge.[27] These studies suggested that not all patients with acute myocardial infarction benefited from β-blocker therapy. In our study, we observed similar incidences of 1-year HF events among patients without left ventricular dysfunction and at low risk for HF regardless of β-blocker use. Our S100A8/A9-based HF risk stratification tool can aid clinicians in identifying patients who need β-blockers and filter out those at low risk of HF, helping to avoid medication overuse and reduce health care costs.

Limitations

Certain aspects of this study warrant further investigation. First, this cohort study was performed within a Chinese population, necessitating further research to validate these findings in other populations across diverse genetic backgrounds. However, the consistent prognostic value of S100A8/A9 for HF events in our 3 cohorts implies its potential as a reliable, predictive biomarker. Second, this study indicated that S100A8/A9-based risk stratification could aid in the early identification of patients with high-risk of HF, which may help prevent progression to HF by promptly initiating intensive clinical management strategies. However, the effects of these strategies remain speculative. Although we retrospectively analyzed the efficacy of the HF β-blocker drugs at different HF risks levels and found no significant reduction in HF events in the low-risk group, further evidence of convincing experimental data from randomized controlled trials is required to validate the clinical use of this risk stratification tool. Last, this study did not determine the optimum time point for S100A8/A9 within 24 hours of admission, because this would have required multiple measurements within a short time interval.

CONCLUSIONS

This study clearly demonstrated that S100A8/A9 levels 1 day after admission were strong and independent predictors of HF events. Using S100A8/A9 levels for HF risk stratification proves to be a highly sensitive and specific predictive tool, offering a convenient and effective means of identifying both patients at low and high risk of HF and guiding appropriate preventive interventions.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Data S1
Tables S1–S9
Figures S1–S7
Reference [28]

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