

Prognostic impact of follow-up serum albumin after acute myocardial infarction

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Abstract

Aims Previous studies have suggested that low serum albumin (LSA) at admission for acute myocardial infarction (AMI) is associated with adverse in-hospital outcomes. The aim of this study was to investigate whether LSA in the remote phase after AMI is prognostic for long-term outcomes.

Methods and results This was a single-centre, retrospective study of consecutive patients admitted for AMI from 2008 to 2016. Serum albumin concentrations were measured serially at admission and 1 year after discharge in Japanese patients. Occurrence of a composite of hospitalization for heart failure and cardiovascular death was the primary endpoint. The prognostic impact of remote LSA, defined as a serum albumin level < 3.8 g/dL at 1 year after discharge, was investigated with a multivariate-adjusted Cox model. Among 1424 subjects analysed, 289 (20.3%) had LSA at admission, and 165 (11.6%) had LSA at 1 year after discharge. During follow-up (median: 4.1 years), the primary endpoint occurred in 31/165 (18.8%) patients with remote LSA and 42/1259 (3.3%) patients without it [adjusted hazard ratio (aHR), 2.76; 95% confidence interval (CI), 1.32 to 5.72; $P = 0.007$]. The all-cause death rate was 29.7% (49/165) in patients with remote LSA and 4.3% (54/1259) in patients without it (aHR, 4.02; 95% CI, 2.36 to 6.87; $P < 0.001$). The prognostic impact of remote LSA was consistent across albumin status in the acute phase of AMI.

Conclusions Regardless of albumin status in the acute phase of AMI, LSA in the remote phase after AMI was significantly associated with long-term adverse outcomes.

Keywords Acute myocardial infarction; Nutritional status; Albumin; Heart failure

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Introduction

Technological advances in primary reperfusion therapy for acute myocardial infarction (AMI) have reduced short-term mortality after infarction.¹ Especially in the era of primary percutaneous coronary intervention (PCI), the in-hospital mortality rate has improved in patients with AMI. However, post myocardial infarction death after discharge and heart failure (HF) as a remote phase event after AMI are still important issues. Hence, risk stratification for their prevention should be carried out in the early phase.^{2–5} Previous studies showed that the following were important risk factors: patient background, electrocardiographic features, and factors

of reperfusion therapy, including onset-to-balloon time, ventricular dysfunction, and frailty.^{6–8}

Serum albumin is one of the most essential nutritional indicators and is also a simple indicator that has been widely used as a quantitative measure of nutritional or inflammatory status.⁹ We previously reported that low serum albumin (LSA) in the acute phase of AMI was an independent predictor of adverse outcomes in patients with AMI.¹⁰ However, the serum albumin level can fluctuate according to the immediate inflammatory response and systemic conditions in the acute phase of AMI and can change chronically during the course of care after discharge. Nonetheless, the clinical significance of measuring the albumin level and LSA in patients in

the remote phase of AMI remains uncertain. We therefore investigated the long-term prognostic impact of remote LSA in patients 1 year after discharge for AMI.

Methods

Design and population

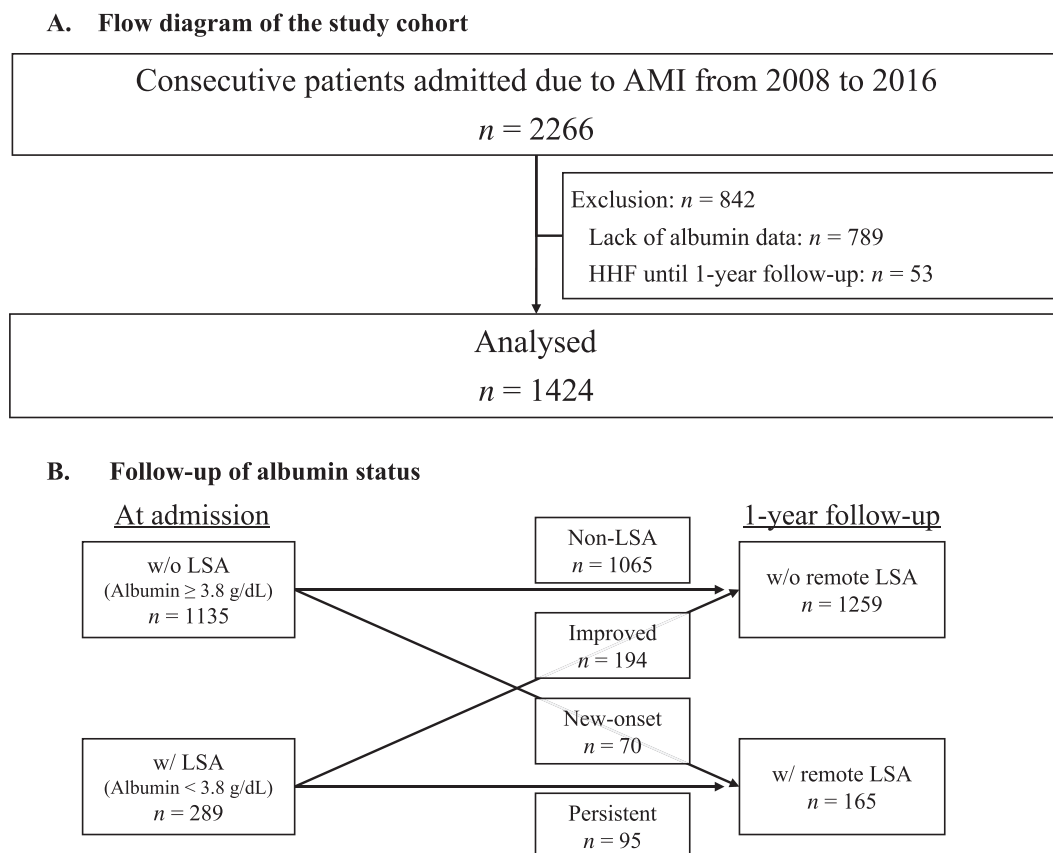
This was a single-centre, non-randomized, retrospective study performed in Miyazaki Medical Association Hospital, Japan. Of 2266 consecutive patients with either ST-segment elevation myocardial infarction (STEMI) or non-ST-segment elevation myocardial infarction (NSTEMI) from February 2008 to January 2016, 789 patients who were lacking data on albumin and 53 patients who were hospitalized due to HF until the 1 year follow-up were excluded. In total, 1424 patients who provided serum albumin data at both admission and 1 year follow-up were analysed (Figure 1A). According to the level of serum albumin, patients were first stratified into two subgroups of (i) with LSA, defined as <3.8 g/dL,¹⁰ and (ii) without LSA (Figure 1B). In addition, according to the

presence or absence of LSA at admission and 1 year follow-up, patients were further classified into the following four groups: non-LSA, improved LSA, new-onset LSA, and persistent LSA (Figure 1B). All procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later revisions. All patients provided informed consent for both the procedure and the subsequent data collection and analysis for research purposes. Ethics approval was obtained from the Institutional Review Board of Miyazaki Medical Association Hospital.

Definition and diagnosis of STEMI and NSTEMI

Diagnosis of STEMI and NSTEMI, based on the 2007 universal definitions,⁹ was made by each cardiologist. STEMI and NSTEMI were defined as follows: for STEMI, patients had to have chest symptoms, ST-segment elevation in two contiguous leads or left bundle branch block, and an elevated biochemical marker of myocardial necrosis [high-sensitivity troponin T > 0.032 ng/mL or creatine phosphokinase (CPK)

Figure 1 Study cohort and follow-up. Flow diagram of the study cohort (A). Follow-up of albumin status (B). AMI, acute myocardial infarction; HHF, hospitalization for heart failure; LSA, low serum albumin



at least two-fold the upper limit of normal], whereas for NSTEMI, patients had to have chest symptoms, ST-segment depression or T-wave inversion in two contiguous leads, and an elevated biochemical marker of myocardial necrosis. The therapeutic strategies for AMI treatment depended on the practice of each individual cardiologist, but all patients' treatments followed the guidelines set forth by the Japanese Circulation Society and the American College of Cardiology/American Heart Association for the diagnosis and treatment of AMI.³

Data collection and endpoints

The following types of data were collected: baseline demographics and clinical characteristics of the study patients, including medical history, presenting signs and symptoms, results of blood tests, transthoracic echocardiography, electrocardiography, cardiac procedures, and clinical outcomes. Transthoracic echocardiography was carried out for all patients immediately after admission and left ventricular ejection fraction (LVEF) was estimated by the standard bi-plane Simpson method. In addition, all blood biomarkers were measured within 24 h after admission as acute phase data. Clinical follow-up was carried out through clinic visits, telephone calls, and records from hospital admissions. Serum albumin data at 1 year were collected between 10 and 12 months after AMI as chronic phase data.

The primary endpoint was a composite of hospitalization for HF or cardiovascular death. The diagnosis of HF was made based on the guidelines, in which HF is diagnosed by the presence of at least one sign (rales, peripheral oedema, ascites, or radiographic evidence of pulmonary congestion) and one symptom (dyspnoea, orthopnoea, or oedema), regardless of ejection fraction.¹¹ The secondary endpoint was all-cause death.

Statistics

For continuous variables, normally distributed data are reported as the mean \pm standard deviation; non-parametric data are reported as the median and interquartile range. For categorical variables, data are presented as count and percentage. Comparisons of continuous variables between groups were performed with the Student's *t*-test, Mann-Whitney *U* test, or Kruskal-Wallis tests, as appropriate. Comparisons of categorical variables were assessed with the chi-square or Fisher's exact test, as appropriate. The cumulative incidence of each endpoint was calculated according to the Kaplan-Meier method. The effects of remote LSA and its course on primary and secondary endpoints were determined with a multivariate Cox proportional hazards regression model adjusting for confounding baseline factors [age; sex; body mass index and

conventional coronary risk factors; onset-to-admission time; pre-TIMI grade; PCI; max CPK; length of hospital stay; medication use at discharge including antiplatelet agents, statins, β -blockers, angiotensin-converting enzyme inhibitors (ACE-I), angiotensin II receptor blockers (ARB), mineralocorticoid receptor antagonists (MRA), and diuretics; LVEF; cardiogenic shock; high-sensitivity troponin T level; C-reactive protein; estimated glomerular filtration rate (eGFR); brain natriuretic peptide (BNP); alanine aminotransferase; and Killip \geq III]. Logistic regression analyses were performed to identify baseline factors associated with each subgroup stratified by the course of albumin status. A two-sided *P* value < 0.05 was considered statistically significant. All statistical analyses were performed with JMP[®] 14 (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics and treatment details during hospitalization

Patient clinical characteristics and treatments during the acute phase are summarized in *Table 1*. The mean patient age was 67.6 ± 11.6 years, with 75.8% being male. Electrocardiography revealed that 71.0% were STEMI and 29.0% were NSTEMI. Almost all patients (95.2%) received primary revascularization, such as PCI and coronary artery bypass grafting. The overall level of serum albumin increased from 4.1 ± 0.5 g/dL at admission to 4.2 ± 0.4 g/dL at 1 year after AMI (paired sample *t*-test, *P* < 0.001). LSA was observed in 289/1424 (20.3%) patients at admission and 165/1424 (11.6%) patients at 1 year after AMI (*Figure 1B*). The subgroup with LSA at 1 year after discharge (remote LSA) was older and more likely to have lower body mass index, lower systolic blood pressure, and more frequent smoking habits and histories of prior myocardial infarction compared with the subgroup without remote LSA. The subgroup with remote LSA also had lower levels of haemoglobin, eGFR, lipid parameters, and LVEF, and higher levels of high-sensitivity C-reactive protein, high-sensitivity troponin T, BNP, and Killip grade at admission. Regarding medications at discharge, the prevalence of ACE-I and statin prescriptions was lower in the subgroup with remote LSA relative to the subgroup without remote LSA. In contrast, the prescription rates of diuretics and MRA were higher in the subgroup with remote LSA than those in the subgroup without remote LSA.

Clinical endpoints

The median duration of follow-up was 4.1 (interquartile range, 2.2–6.1) years. Overall, the primary composite

Table 1 Baseline demographics and clinical characteristics

| Variable | Albumin status at 1 year after discharge | | | P |
|-------------------------------------------------------------------|------------------------------------------|------------------------------|---------------------------|--------|
| | Total (n = 1424) | w/o remote LSA (n = 1259) | w/remote LSA (n = 165) | |
| Male | 1079 (75.8) | 969 (76.9) | 110 (66.7) | <0.001 |
| Age (years) | 67.6 ± 11.6 | 66.5 ± 11.3 | 74.8 ± 10.5 | <0.001 |
| Body mass index (kg/m ²) | 24.1 ± 3.7 | 24.3 ± 3.6 | 22.7 ± 3.6 | <0.001 |
| Heart rate (/min) | 78.1 ± 20.0 | 77.6 ± 19.2 | 77.9 ± 22.0 | 0.847 |
| Systolic blood pressure (mmHg) | 141 ± 29 | 141 ± 29 | 136 ± 29 | 0.050 |
| Medical history | | | | |
| Hypertension | 978 (68.7) | 850 (67.5) | 128 (77.6) | <0.001 |
| Dyslipidaemia | 720 (50.6) | 659 (52.3) | 61 (37.0) | <0.001 |
| Diabetes mellitus | 472 (33.2) | 409 (32.5) | 63 (38.2) | 0.148 |
| Smoking | 686 (48.1) | 624 (49.6) | 62 (37.6) | 0.004 |
| Family history of cardiovascular disease | 138 (9.7) | 126 (10.0) | 12 (7.3) | 0.247 |
| Myocardial infarction | 53 (3.7) | 40 (3.2) | 13 (7.9) | <0.001 |
| Malignancy | 48 (3.4) | 42 (3.4) | 6 (3.6) | 0.861 |
| Serum albumin at admission (g/dL) | 4.1 ± 0.5 | 4.1 ± 0.4 | 3.6 ± 0.5 | <0.001 |
| Serum albumin at 1 year after AMI (g/dL) | 4.2 ± 0.4 | 4.3 ± 0.3 | 3.4 ± 0.3 | <0.001 |
| WBC (×10 ³ /mL) | 90 (70–120) | 91 (70–120) | 92 (70–122) | 0.989 |
| Haemoglobin, g/dL | 13.7 ± 2.1 | 14.0 ± 2.0 | 12.0 ± 2.1 | <0.001 |
| eGFR (mL/min/1.73 m ²) | 65.7 ± 21.8 | 68.7 ± 20.6 | 53.0 ± 24.5 | <0.001 |
| Triglycerides (mg/dL) | 114 (79–171) | 117 (81–181) | 95 (68–135) | <0.001 |
| Total cholesterol (mg/dL) | 198.9 ± 47.8 | 200.2 ± 47.6 | 187.6 ± 48.1 | <0.001 |
| LDL-cholesterol (mg/dL) | 124.1 ± 37.8 | 125.4 ± 37.4 | 111.9 ± 37.5 | <0.001 |
| HDL-cholesterol (mg/dL) | 47.1 ± 13.2 | 46.8 ± 12.7 | 49.0 ± 17.3 | 0.051 |
| High-sensitivity CRP (mg/dL) | 0.15 (0.06–0.51) | 0.13 (0.06–0.45) | 0.38 (0.13–1.43) | <0.001 |
| High-sensitivity troponin T, ng/mL (upper limit of normal: 0.032) | 0.23 (0.04–1.90) | 0.21 (0.03–1.79) | 0.34 (0.10–2.00) | 0.943 |
| Brain natriuretic peptide, pg/mL (upper limit of normal: 18.4) | 55.9 (19.4–169.4) | 47.6 (17.2–132.7) | 185 (47.8–572.7) | <0.001 |
| STEMI | 1011 (71.0) | 893 (70.9) | 118 (71.5) | 0.876 |
| NSTEMI | 413 (29.0) | 366 (29.1) | 47 (28.5) | |
| Onset-to-admission time (min) | 180 (120–480) | 180 (60–480) | 180 (90–420) | 0.192 |
| Delayed arrival (≥48 h after onset) | 42 (3.4) | 40 (3.1) | 2 (1.2) | 0.153 |
| Killip class ≥ 3 | 91 (6.6) | 65 (5.3) | 26 (16.2) | <0.001 |
| LVEF (%) | 57 ± 11.2 | 57.9 ± 10.7 | 54.8 ± 12.1 | <0.001 |
| Pre TIMI grade 0.1 | 786 (58.9) | 700 (59.3) | 86 (55.5) | 0.362 |
| Peak CPK (IU/L) | 1592 (549–3389) | 1575 (547–3352) | 1385 (485–3365) | 0.790 |
| Revascularization | 1356 (95.2) | 1200 (95.3) | 156 (94.5) | 0.676 |
| PCI | 1312 (92.1) | 1160 (92.0) | 152 (92.1) | 0.995 |
| CABG | 44 (3.1) | 40 (3.1) | 4 (2.4) | 0.481 |
| IABP | 131 (9.1) | 105 (8.3) | 26 (15.8) | 0.021 |
| ECMO | 11 (0.8) | 8 (0.6) | 3 (1.8) | 0.154 |
| Length of hospital stay (days) | 15 (13–20) | 15 (12–19) | 18 (14–25) | <0.001 |
| Medication at discharge | | | | |
| Antiplatelet | 1393 (97.8) | 1235 (98.1) | 158 (95.8) | 0.081 |
| Statin | 1222 (85.9) | 1098 (87.2) | 124 (75.6) | <0.001 |
| β-Blocker | 657 (46.1) | 585 (46.5) | 72 (43.9) | 0.535 |
| ACE-I | 401 (28.2) | 368 (29.2) | 33 (20.1) | 0.012 |
| ARB | 586 (41.2) | 520 (41.3) | 66 (40.2) | 0.795 |
| MRA | 144 (10.1) | 122 (9.7) | 22 (13.4) | 0.252 |
| Diuretic | 259 (18.2) | 204 (16.2) | 55 (33.5) | <0.001 |

Data for categorical variables given as number (%); data for continuous variables given as mean ± standard deviation for normal distribution or median (interquartile range) for skewed distribution. Clinical data at 1 year was collected only for serum albumin level.

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CABG, coronary artery bypass grafting; CPK, creatine phosphokinase; CRP, C-reactive protein; ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; IABP, intra-aortic balloon pumping; LDL, low-density lipoprotein; LSA, low serum albumin; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; MVD, multi-vessel disease; NSTEMI, non-ST elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction; WBC, white blood cell.

endpoint of hospitalization for HF or cardiovascular death occurred in 73/1424 (5.1%) patients; individual components of the primary composite endpoint occurred in 53 (3.7%) patients for hospitalization for HF and 29 (2.0%) patients for cardiovascular death (Table 2). The receiver operating

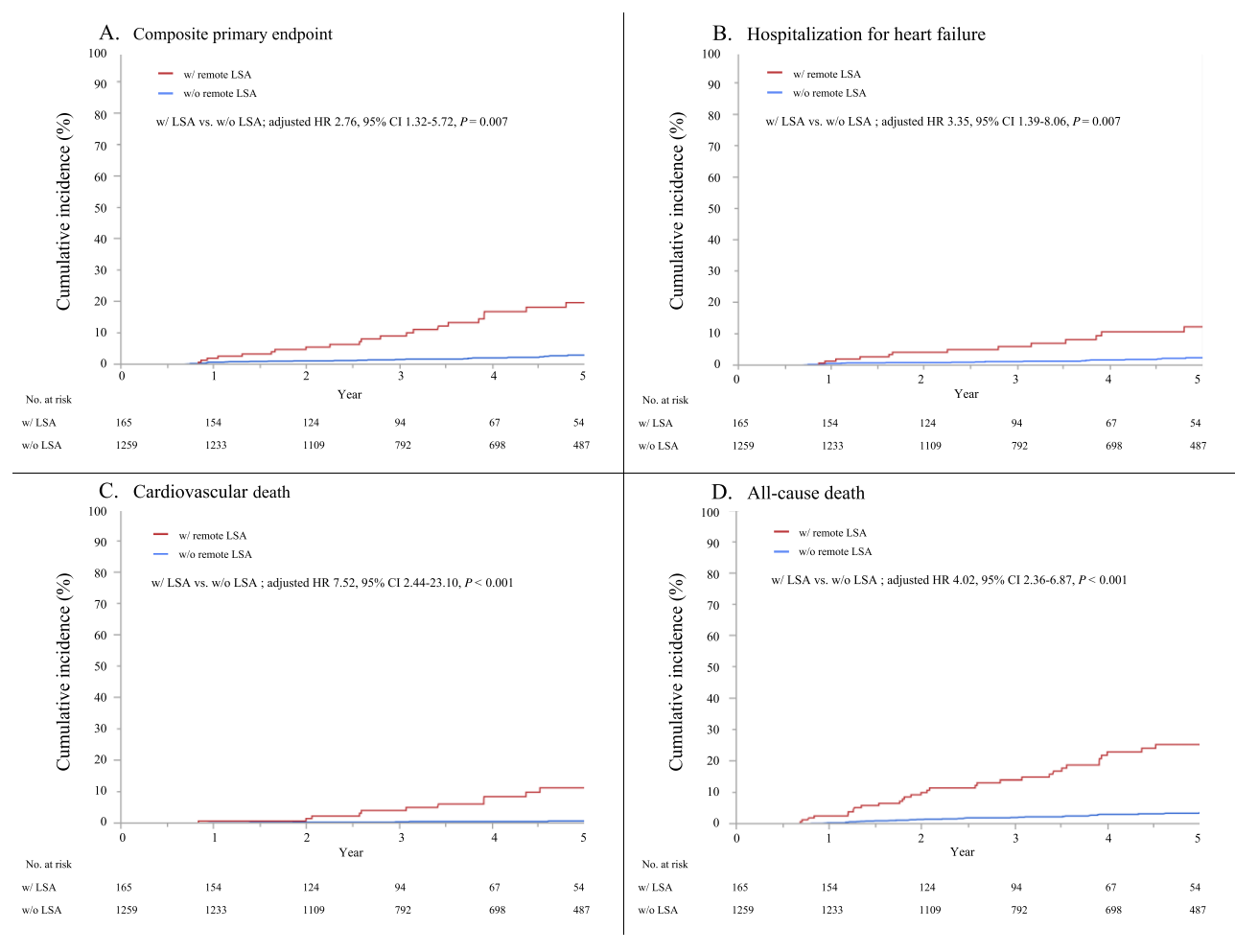
characteristic curve of serum albumin level for the primary composite outcome showed that the cut-off value was 3.8 g/dL (Supporting Information, Figure S1).

The primary composite endpoint was observed in 31/165 (18.8%) patients in the subgroup with remote LSA and 42/

Table 2 Primary and secondary outcomes in subgroups stratified by LSA at 1 year after discharge and course of serum albumin level

| Variable | Albumin status at 1 year after discharge | | | | | | |
|-----------------------------------|------------------------------------------|---------------------------------|------------------------------|-----------------------|------------------------------|------------------------------|-------------------------------|
| | Total (n = 1424) | w/o remote LSA (n = 1259) | w/remote LSA (n = 165) | Non-LSA (n = 1065) | Improved LSA (n = 194) | New-onset LSA (n = 70) | Persistent LSA (n = 95) |
| Composite primary endpoint, n (%) | 73 (5.1) | 42 (3.3) | 31 (18.8) | 30 (2.8) | 12 (6.2) | 15 (21.4) | 16 (16.8) |
| Hospitalization for heart failure | 53 (3.7) | 33 (2.6) | 20 (12.1) | 23 (2.1) | 10 (5.2) | 8 (11.4) | 12 (12.6) |
| Cardiovascular death | 29 (2.0) | 13 (1.0) | 16 (9.7) | 10 (0.9) | 3 (1.6) | 9 (12.9) | 7 (7.4) |
| Secondary endpoint, n (%) | | | | | | | |
| All-cause death | 103 (7.2) | 54 (4.3) | 49 (29.7) | 34 (3.2) | 20 (10.3) | 22 (31.4) | 27 (28.4) |

LSA, low serum albumin.

Figure 2 Primary and secondary outcomes stratified by LSA at 1 year after discharge. Kaplan–Meier curves show the cumulative incidence and adjusted hazard ratios of the composite primary endpoint (A), hospitalization for heart failure (B), cardiovascular death (C), and all-cause death (D). CI, confidence interval; HR, hazard ratio; LSA, low serum albumin

1259 (3.3%) patients in the subgroup without remote LSA [adjusted hazard ratio (HR), 2.76; 95% confidence interval (CI), 1.32 to 5.72; $P = 0.007$] (Figure 2A). The individual adjusted HRs for hospitalization for HF and cardiovascular death were 3.35 (95% CI, 1.39 to 8.06; $P = 0.007$, Figure 2B) and 7.52

(95% CI, 2.44 to 23.10; $P < 0.001$, Figure 2C), respectively. The secondary endpoint of all-cause death occurred in 49/165 (29.7%) patients in the subgroup with remote LSA and 54/1259 (4.3%) patients in the subgroup without remote LSA (adjusted HR, 4.02; 95% CI, 2.36 to 6.87; $P < 0.001$, Figure 2D).

Stratified subgroups according to course of albumin level

Among 1135 patients with albumin ≥ 3.8 g/dL at admission, LSA was newly developed in 70 patients (6.2%) remotely, and 1065 patients remained as non-LSA at 1 year after discharge. Among 289 patients with LSA at admission, the albumin level was improved remotely in 194 patients (67.1%), and 95 patients showed persistent LSA. Detailed baseline clinical characteristics of those subgroups are shown in *Table S1*. The logistic regression analysis showed that younger age, PCI, and lower max CPK were independent predictors of non-LSA (*Table 3*). Similarly, younger age, preserved eGFR, male, MRA use at discharge, and ACE-I or ARB use at discharge were independent predictors of improved LSA. In contrast, no use of statins at discharge, reduced eGFR, and older age were independent predictors of new-onset LSA, and no use of MRA at discharge was an independent predictor of persistent LSA.

The numbers and frequencies of patients reaching the primary and secondary endpoints in each subgroup are shown in *Table 2*. The subgroups with remote LSA (new-onset LSA and persistent LSA) had numerically higher incidences of the composite primary and secondary endpoints relative to the subgroups without remote LSA (non-LSA and improved LSA), irrespective of LSA in the acute phase. In particular, the persistent LSA subgroup was associated with higher incidences of those endpoints compared with the other three

subgroups (*Figure 3A* and *3B*). The occurrence of the composite primary endpoint was also significantly more frequent in the new-onset LSA subgroup compared with the improved and non-LSA subgroups (*Figure 3A*). Furthermore, the incidence of all-cause death was more common in the new-onset LSA subgroup compared with the non-LSA subgroup (*Figure 3B*). Thus, the prognostic impact of remote LSA was consistent across albumin status in the acute phase of AMI.

Discussion

This is the first clinical study that serially examined the incidence and clinical impact of remote LSA on long-term prognosis after discharge for AMI. The results clearly demonstrated that the serum albumin level changed dynamically from the acute to chronic phases after AMI. The major clinical implication of our study is that remote LSA is significantly associated with long-term adverse outcomes. Notably, even in patients without LSA in the acute phase of AMI, newly developed LSA in the remote phase of AMI was associated with worse outcomes compared with those in patients without remote LSA. These findings suggest that LSA in the remote phase of AMI, irrespective of albumin status in the acute phase of AMI, is a useful indicator to predict long-term adverse outcomes in patients with AMI. Thus, even

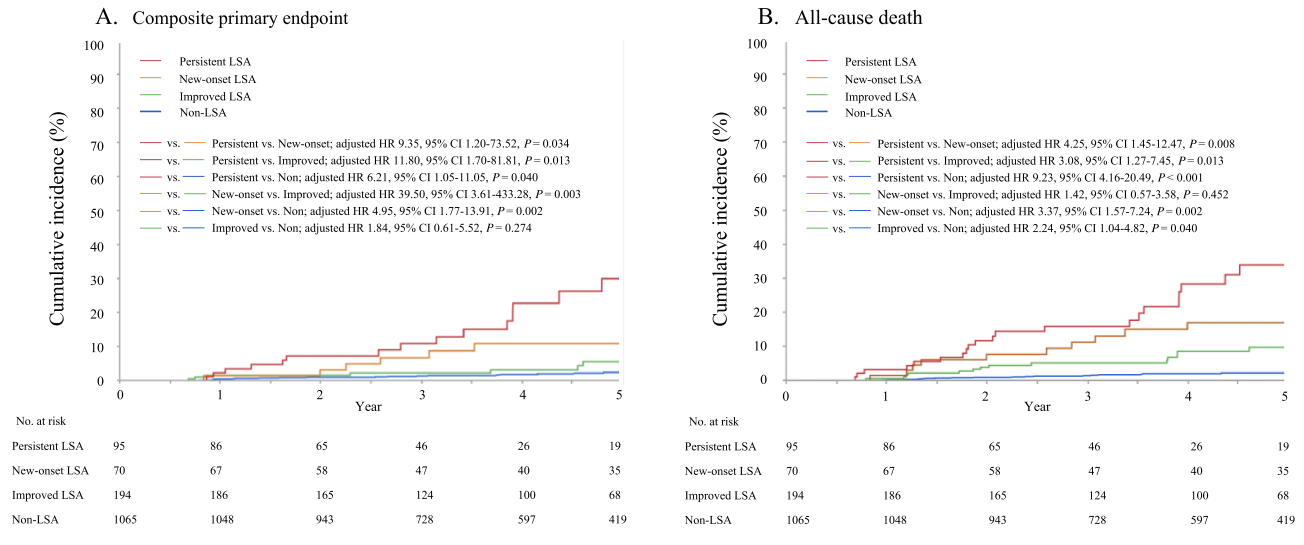
Table 3 Logistic regression analyses to identify baseline factors associated with each subgroup stratified by course of albumin level

| | Odds ratio | 95% confidence interval | P value |
|------------------------------------|------------|-------------------------|---------|
| Non-LSA | | | |
| Age (years) | 0.97 | 0.96–0.99 | <0.001 |
| Percutaneous coronary intervention | 1.94 | 1.12–3.35 | 0.018 |
| Peak CPK (IU/L) | 1.00 | 1.00–1.00 | 0.044 |
| Improved LSA | | | |
| Age (years) | 0.95 | 0.92–0.98 | <0.001 |
| eGFR (mL/min/1.73 m ²) | 1.02 | 1.01–1.03 | 0.001 |
| Male | 2.20 | 1.20–4.06 | 0.010 |
| MRA | 2.28 | 1.18–4.44 | 0.015 |
| ACE-I or ARB at discharge | 1.85 | 1.06–3.19 | 0.028 |
| New-onset LSA | | | |
| Statin at discharge | 0.28 | 0.14–0.58 | <0.001 |
| eGFR (mL/min/1.73 m ²) | 0.98 | 0.97–0.99 | 0.024 |
| Age (years) | 1.04 | 1.00–1.07 | 0.034 |
| Persistent LSA | | | |
| MRA | 0.33 | 0.13–0.85 | 0.021 |

Adjusted for age, sex, body mass index, coronary risk factors (hypertension, dyslipidaemia, diabetes mellitus, smoking, and family history of cardiovascular disease), history of malignant tumour, onset-to-admission time, pre-TIMI grade, percutaneous coronary intervention, max creatine phosphokinase, eGFR, length of hospital stay, statin use at discharge, beta-blocker use at discharge, angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker use at discharge, mineralocorticoid receptor antagonist use at discharge, left ventricular ejection fraction at acute phase, cardiogenic shock, acute myocardial infarction due to left anterior descending artery lesion, and acute myocardial infarction due to left main trunk.

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CABG, coronary artery bypass grafting; CPK, creatine phosphokinase; CRP, C-reactive protein; ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; IABP, intra-aortic balloon pumping; LDL, low-density lipoprotein; LSA, low serum albumin; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; MVD, multi-vessel disease; NSTEMI, non-ST elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction; WBC, white blood cell.

Figure 3 Primary and secondary outcomes stratified by course of serum albumin level. Kaplan–Meier curves show the cumulative incidence and adjusted hazard ratios of the composite primary endpoint (A) and secondary endpoint (B). CI, confidence interval; HR, hazard ratio; LSA, low serum albumin



in patients who survived the acute phase of AMI, measuring the serum albumin level in the remote phase can be prognostic, and careful follow-up is therefore needed, especially in patients with remote LSA after AMI.

Previous studies have shown that several risk factors, including advanced age, prior MI, female sex, Killip class 3 or 4, LAD involvement, complete occlusion of the infarcted vessel at baseline, severely reduced LVEF, frailty, and nutritional status in the acute phase, were associated with increased mortality in patients with AMI.^{12–14} Among several nutritional indicators, serum albumin, the most essential protein in plasma, is the major determinant of plasma oncotic pressure and the modulator of fluid distribution.⁹ In daily clinical practice, the serum albumin level is recognized as an important nutritional and liver functional marker and is often used to monitor the systemic condition during the course of disease care.^{9,15,16} However, serum albumin levels may be affected by systemic conditions resulting from other diseases, such as malignancy, inflammatory disease, and acute cardiovascular diseases including HF.¹⁷ Hence, it remained unclear whether LSA in the acute phase of AMI resulted from persistent malnutrition or represented a temporary decline from a hemodynamic and biochemical effect. In addition, the clinical implications of the serum albumin level in the remote phase were also uncertain. We therefore investigated changes in serum albumin and the prognostic impact of LSA in the chronic phase.

Several studies have reported that LSA was associated with prognosis in patients with cardiovascular disease, including acute and chronic HF, regardless of the aetiology of HF.^{18–20} In those studies, the negative impact of LSA was thought to result from malnutrition, decreased hepatic

synthesis, increased vascular permeability, and/or renal failure. In patients with coronary artery disease, LSA at admission can predict adverse events, including all-cause death, stroke, and myocardial infarction during long-term follow-up.^{21,22} The relationship between LSA and prognosis after AMI was recently reported,^{23,24} and LSA was also associated with new-onset HF during AMI hospitalization and resultant poor prognosis after AMI.¹⁰ LSA may facilitate increased peripheral oedema and pulmonary congestion, even at lower left atrial pressures, acting as an aggravating factor of HF.²⁵ Furthermore, previous reports showed an association between LSA and LV remodelling through activation of cardiac inflammation.^{10,26} Pathophysiological analysis also showed that excess inflammation contributes to LV remodelling associated with newly developing HF.²⁷ However, inflammation is accelerated in the acute phase of AMI, which could also cause a temporary decrease in the albumin level.⁹ However, few reports have focused on albumin levels in the remote phase of AMI, and the clinical impact on adverse outcomes in AMI survivors remained uncertain.

In this study, among patients without LSA in the acute phase, 6.2% developed new LSA in the remote phase, and this course of albumin change was associated with a higher incidence of adverse outcomes relative to the subgroups without remote LSA (improved LSA and non-LSA). These findings suggest that LSA in the remote phase of AMI, irrespective of the presence or absence of LSA in the acute phase of AMI, is an independent predictor of long-term adverse outcomes after discharge for AMI. In addition, this enhances the clinical significance of monitoring serum albumin levels in the remote phase of AMI.

The present study revealed several potential clinical factors, such as anaemia, kidney function, and biomarkers, associated with the variable course of albumin level from the acute to the remote phases of AMI. Anaemia has already been reported as having an important relationship with LSA through systemic inflammation in hospitalized patients.²⁸ LSA is a frequent feature of chronic kidney disease and depends on many factors, not only albuminuria and inflammation but also albumin homeostasis. Especially in patients with end-stage renal disease, LSA is also the result of decreased synthesis and increased degradation of protein.²⁹ Furthermore, LSA in chronic kidney disease has been reported as a predictor of poor clinical outcomes.^{30,31} Previous studies have demonstrated that serum albumin is an independent determinant factor of troponin T and BNP.^{32,33} These results indicate that the adverse effects of LSA could occur through inflammatory and/or unknown pathways.

In addition to those risk factors for LSA, our study demonstrated that statin and renin-angiotensin-aldosterone system inhibitor use at discharge may affect serum albumin positively. Previous studies have shown that statins reduced the levels of high-sensitivity CRP and increased serum albumin concentrations in patients on dialysis.³⁴ Several studies also reported that ACE-I or ARB have favourable effects on albuminuria.^{35,36} Although the detailed pathophysiological mechanisms underlying the improvement of serum albumin levels are still uncertain, these drugs may have a comprehensive protective effect for both cardiovascular and non-cardiovascular organs, partly via improvement of chronic inflammation and malnutrition. Thus, the present study supposed that multidisciplinary management including optimal medical therapy is important to preserve the albumin status and improve the clinical outcomes of AMI survivors.

Some limitations must be taken into account to interpret the present results. First, this was a retrospective, observational study carried out in a relatively small number of subjects at a single Japanese centre. Participants in this study were recruited between 2008 and 2016, so differences in treatment strategies over this time period might have affected the outcomes. In addition, although revascularization therapy, including PCI and coronary artery bypass grafting, and oral medication delivery was performed based on local treatment guidelines, national or international data could be of great value in assessing the generalizability of our findings. Second, because the study cohort included only survivors at 1 year after AMI to collect remote data on serum albumin level, selection bias should be noted. In addition, because the population of our study cohort also presented with various clinical features at the acute phase of AMI (e.g. with/without primary revascularization or cardiogenic shock), further studies focusing on those specific clinical characteristics are required to assess the clinical impact of LSA in such patient populations. Third, decision-making regarding hospitalization for HF was the choice of the treating physician, and

therefore, relevant endpoints were partly based on physicians' subjective judgement. In this context, hospitalization for HF was defined on the basis of one sign and one symptom, but not on the use of intravenous diuretics or increases in oral diuretic dose, resulting in uncertainty with respect to its ascertainment. Fourth, the optimal pharmacological therapies after AMI were also not completely achieved in the present study cohort, with statins used for 85.9%, ACE-I or ARB used for 69.4%, and β -blockers used for 46.1% at discharge, which might affect the outcomes in the remote phase after AMI. In particular, a relatively small percentage of the present cohort was treated with β -blockers, due mainly to tolerability. Fifth, we did not collect detailed follow-up data on drugs and clinical measures except for albumin after discharge. Specifically, we have no clinical information at the remote phase of AMI on physical functioning and other relevant laboratory markers, such as BNP, haemoglobin, and eGFR, which are prognostic after AMI. Furthermore, classification using cardiovascular imaging tests, such as stress scintigraphy, echocardiography, and cardiac magnetic resonance, in the chronic phase was also not performed in the present study. Thus, further study is needed to assess the prognostic relationships between LSA and other clinical findings at the remote phase of AMI and to reveal an additional clinical feature of the serum albumin level. Finally, questions remain as to whether LSA mechanistically facilitates worsening of HF and excess mortality or is merely a biomarker.

In conclusion, regardless of albumin status in the acute phase of AMI, LSA in the remote phase after AMI was significantly associated with long-term adverse outcomes. Even after a patient survives the acute phase of AMI, careful monitoring should be performed, especially in patients with LSA in the chronic phase of AMI.

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Conflict of interest

The authors have no conflicts of interest to declare.

Author contributions

GY and AT designed the research (project conception, development of overall research plan, and study oversight) and wrote the manuscript; GY, KN, NW, and YS conducted the research (hands-on conduct of the experiments and data collection); GY, AT, and AK analysed the data or performed

statistical analysis; MN and KN revised the manuscript; GY and AT had primary responsibility for the final content; and all authors read and approved the final manuscript.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Baseline demographics and clinical characteristics in subgroups stratified by course of serum albumin level.

Figure S1. Receiver operating characteristic curve of albumin at 1 year for the primary composite outcome.

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