Independent and Combined Effects of Serum Albumin and C-Reactive Protein on Long-Term Outcomes of Patients Undergoing Percutaneous Coronary Intervention

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Background: Both inflammation and malnutrition have been reported to be closely linked to atherosclerosis, especially in patients with chronic kidney disease (CKD). The combined effects of serum albumin and C-reactive protein (CRP) on clinical outcomes after percutaneous coronary intervention (PCI) were investigated.

Methods and Results: A total of 2,164 all-comer patients with coronary artery disease who underwent their first PCI and had data available for preprocedural serum albumin and hs-CRP levels between 2000 and 2011 were studied. Patients were assigned to 4 groups according to their median serum albumin and CRP levels (4.1 g/dL and 0.10 mg/dL, respectively). The incidence of major adverse cardiac events (MACE), including all-cause death and non-fatal myocardial infarction (MI), was evaluated. During a median follow-up period of 7.5 years, 331 cases of MACE (15.3%), including 270 deaths and 61 non-fatal MIs, occurred. Kaplan-Meier curves showed that the rates of MACE differed significantly among the groups (log-rank P<0.0001), even stratified by with or without CKD (both log-rank P<0.0001). After adjustment for established cardiovascular risk factors, low serum albumin with high CRP levels was associated with adverse cardiac events (hazard ratio 2.55, 95% confidence interval 1.72–3.88, P<0.0001, high albumin/low CRP group as reference).

Conclusions: The presence of both low serum albumin and high CRP levels conferred a synergistic adverse effect on the risk for long-term MACE in patients undergoing PCI.

Key Words: Atherosclerosis; Coronary artery disease; Inflammation; Nutrition; Percutaneous coronary intervention
for long-term clinical outcomes was evaluated in CAD patients undergoing PCI.

**Methods**

**Study Population and Data Collection**
The present investigation was a single-center, observational, retrospective cohort study. Among consecutive patients with CAD who underwent their first PCI at Juntendo University Hospital between 2000 and 2011, only patients for whom preprocedural serum albumin and hs-CRP values were available were included. Patients with known malignancy and active inflammatory disease (hs-CRP >1.0 mg/dL) or without available preprocedural albumin and hs-CRP values were excluded. Median values of serum albumin (4.1 g/dL) and hs-CRP (0.10 mg/dL) were used as cutoff levels for allocating the patients to 4 groups: Group 1 included those with higher albumin and lower CRP levels; Group 4 included those with lower albumin and higher CRP levels; Groups 2 and 3 included patients with lower and higher levels of both components, respectively (Figure 1).

Demographic data, coronary risk factors, and medication use were collected from the institutional database. Blood samples were collected in the early morning after overnight fasting, and blood pressure (BP) was measured on admission. Patients with BP >140/90 mmHg or who were receiving antihypertensive drugs were regarded as hypertensive. Dyslipidemia was defined as low-density lipoprotein cholesterol (LDL-C) ≥140 mg/dL, high-density lipoprotein-cholesterol (HDL-C) ≤40 mg/dL, triglycerides (TG) ≥150 mg/dL, or current treatment with statins and/or other lipid-lowering agents. Diabetes mellitus was defined as either hemoglobin A1c (HbA1c) of 6.5% or medication with insulin or oral hypoglycemic drugs. The estimated HbA1c (%) was calculated as National Glycohemoglobin Standardization Program equivalent values (%) using the formula HbA1c (%)=1.02×HbA1c (JDS; %)+0.25%. CKD was defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m² calculated using the Modification of the Diet in Renal Disease equation modified with a Japanese coefficient using baseline serum creatinine. Levels of serum hs-CRP were measured using a validated immunoassay and an auto-analyzer. Other markers were determined by routine laboratory methods.

Written informed consent was given by all patients prior to PCI. This study was performed in accordance with the Declaration of Helsinki and with approval from the institutional review board.

**Primary Endpoints**
The primary outcome was major adverse cardiac events (MACE), defined as a composite of all-cause death and non-fatal myocardial infarction (MI). Clinical follow-up included a review of medical charts, telephone contact, and questionnaires sent to patients or their families. Mortality data were collected from the medical records of patients who died or who were treated at the institution, and the details and causes of death were obtained from other hospitals to which patients had been admitted. MI was defined as evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia.

**Statistical Analysis**
Quantitative data are presented as mean±standard deviation (SD) or median (interquartile range, IQR). Categorical variables are presented as frequencies. Continuous variables across groups were compared using one-way analysis of variance or the Kruskal-Wallis test. Categorical variables (presented as frequencies) were compared using the chi-squared test. Unadjusted cumulative event rates were estimated using Kaplan-Meier curves and compared across groups; patients were also stratified by the presence or absence of CKD in the Kaplan-Meier analysis. Cox proportional hazards models were used to assess univariate and multivariable covariates. Hazard ratios (HRs) and confidence intervals (CIs) were calculated for each factor by Cox proportional hazards analysis. Adjusted variables were acute coronary syndrome (ACS), age, body mass index (BMI), CKD, current smoker, diabetes, hypertension, left ventricular ejection fraction (LVEF), multivessel coronary disease and statin use on admission. Among these, only the variables showing P<0.05 on the univariate analyses were included in multivariate analyses. To assess whether internal correlation between serum albumin or hs-CRP levels and cardiac events was affected by any other covariates, we conducted a Cox proportional hazard regression with an interaction term between serum albumin and hs-CRP, and between serum albumin or hs-CRP and other covariates. To assess whether the accuracy of predicting adverse cardiac events would improve after adding serum albumin and hs-CRP levels to a baseline model.
Table 1. Clinical, Angiographic, and Procedural Characteristics of Patients Undergoing 1st PCI

<table>
<thead>
<tr>
<th>Albumin, g/dL</th>
<th>Overall (n=2,164)</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>hs-CRP, mg/dL</td>
<td>0.11 [0.05, 0.25]</td>
<td>0.04 [0.02, 0.06]</td>
<td>0.04 [0.03, 0.07]</td>
<td>0.20 [0.13, 0.35]</td>
<td>0.24 [0.15, 0.44]</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Baseline characteristics

- Age, years: 65.6±10.0, 63.8±9.6, 68.1±8.7, 62.8±9.5, 67.9±10.4, <0.0001
- Male, n (%): 1,789 (82.7), 442 (83.4), 334 (81.9), 482 (86.7), 531 (79.3), 0.006
- Hypertension, n (%): 1,557 (72.0), 373 (70.4), 291 (71.3), 392 (70.5), 501 (74.8), <0.0001
- Diabetes, n (%): 991 (48.5), 225 (42.5), 201 (49.3), 245 (44.1), 320 (47.8), 0.11
- Dyslipidemia, n (%): 1,567 (72.5), 410 (77.4), 275 (67.4), 437 (78.6), 445 (66.6), <0.0001
- Current smoker, n (%): 573 (26.5), 119 (22.5), 98 (24.0), 190 (34.2), 166 (24.8), <0.0001
- Family history, n (%): 612 (28.4), 162 (30.7), 112 (27.5), 156 (28.2), 182 (27.3), 0.57
- ACS presentation, n (%): 548 (25.3), 128 (23.4), 112 (27.5), 156 (28.2), 252 (37.6), <0.0001
- Multivessel, n (%): 1,227 (56.7), 292 (55.1), 241 (59.1), 299 (53.8), 395 (59.0), 0.19
- BMI, kg/m²: 24.3±3.3, 24.3±3.0, 23.8±3.2, 24.9±3.1, 24.0±3.8, <0.0001
- SBP, mmHg: 133.9±22.6, 133.4±22.0, 135.3±24.1, 133.2±21.2, 134.0±23.2, <0.0001
- DBP, mmHg: 72.4±13.1, 72.8±12.4, 72.2±13.5, 73.0±13.1, 71.8±13.7, 0.40
- TC, mg/dL: 184.9±38.2, 184.0±36.8, 177.2±33.3, 196.5±39.9, 180.8±38.6, <0.0001
- LDL-C, mg/dL: 112.1±32.8, 108.5±31.8, 106.4±28.5, 120.7±35.7, 113.3±32.2, <0.0001
- HDL-C, mg/dL: 45.1±13.3, 47.2±14.6, 45.2±12.6, 44.6±12.3, 43.9±13.2, 0.0002
- TG, mg/dL: 137.6±92.0, 142.3±96.0, 124.7±65.6, 156.4±89.3, 126.2±101.0, <0.0001
- FBG, mg/dL: 133.9±22.6, 134.4±22.0, 135.3±24.1, 133.2±21.3, 134.0±23.2, 0.51
- eGFR, mL/min/1.73 m²: 68.5±22.5, 72.8±17.1, 66.8±24.1, 70.8±20.4, 64.1±25.8, <0.0001
- CKD, n (%): 640 (29.6), 93 (17.6), 27 (6.6), 152 (27.3), 258 (38.5), <0.0001
- HD, n (%): 110 (5.1), 9 (1.7), 27 (6.6), 16 (2.9), 58 (8.7), <0.0001

Medications

- Aspirin, n (%): 2,027 (94.9), 499 (95.2), 387 (96.3), 523 (95.1), 618 (93.5), 0.23
- ACEI/ARB, n (%): 1,112 (52.0), 251 (47.9), 216 (53.7), 266 (48.4), 379 (57.3), 0.002
- β-blocker, n (%): 1,072 (50.2), 254 (48.5), 203 (50.5), 279 (50.7), 336 (50.8), 0.85
- OHA, n (%): 616 (28.9), 152 (29.0), 131 (32.6), 142 (25.9), 191 (28.9), 0.16
- Insulin, n (%): 235 (10.9), 38 (7.2), 75 (18.4), 36 (6.5), 86 (12.8), <0.0001
- Statin, n (%): 1,273 (59.6), 324 (51.3), 239 (59.0), 356 (64.7), 337 (51.1), <0.0001

Angiographic profile

- LAD culprit lesion, n (%): 1,008 (46.6), 250 (47.2), 193 (47.3), 266 (47.8), 299 (44.6), 0.67
- Reference lumen diameter, mm: 2.8 [2.5, 3.2], 2.7 [2.5, 3.1], 2.8 [2.5, 3.1], 2.9 [2.6, 3.3], 2.9 [2.6, 3.2], <0.0001
- Stent size, mm: 3.0 [2.75, 3.5], 3.0 [2.75, 3.5], 3.0 [2.75, 3.5], 3.0 [2.75, 3.5], 3.0 [2.75, 3.5], <0.0001
- LVEF, %: 62.5±11.9, 64.0±10.8, 62.9±10.4, 63.7±11.2, 59.0±13.9, <0.0001

with established risk factors (ACS, age, BMI, CKD, multivessel disease, and use of statins), the C-index, net reclassification improvement (NRI), and integrated discrimination improvement (IDI) were calculated. The C-index is defined as the area under the receiver-operating characteristic curves between individual predictive probabilities for events and the incidence of events, and it was compared for the baseline model and enriched models containing the established risk factors plus serum albumin and hs-CRP levels, either alone or both. The NRI indicates relatively how many patients improved their predicted probability for events, and the IDI represents the average improvement in predicted probability for events after adding variables to the baseline model. Differences were considered significant at P<0.05. Statistical analyses were carried out using JMP version 12.0 (SAS Institute, Cary, NC, USA) and R version 3.2.3 (http://www.R-project.org/; R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline and Procedural Characteristics

Of the 3,039 patients who underwent PCI, preprocedural serum albumin and hs-CRP data were available for 2,164 patients.
In total, 331 (frequency, 15.3%) cases of MACE were identified during follow-up, including 270 (12.5%) deaths and 61 (2.8%) non-fatal MIs. Figure 2 shows the Kaplan-Meier curves for MACE and all-cause death. The curves are significantly different (log-rank test, both \( P<0.0001 \)), and the cumulative incidences of these clinical events increase clearly in the low albumin/high CRP group. CRP, C-reactive protein; MACE, major adverse cardiac events.

Figure 2. Kaplan-Meier curves for (A) MACE and (B) all-cause death. The curves are significantly different (log-rank test, both \( P<0.0001 \)), and the cumulative incidences of these clinical events increase clearly in the low albumin/high CRP group. CRP, C-reactive protein; MACE, major adverse cardiac events.

Figure 3. Kaplan-Meier curves for MACE among patients (A) with CKD and (B) without CKD. Kaplan-Meier curves for MACE show significant differences in the incidence of events between the low albumin/high CRP group and other groups, even stratified by CKD (log-rank test, both \( P<0.0001 \)). CKD, chronic kidney disease; CRP, C-reactive protein; MACE, major adverse cardiac events.

Clinical Outcomes
The median follow-up period was 7.5 years (IQR, 4.7–10.0 years). In total, 331 (frequency, 15.3%) cases of MACE were identified during follow-up, including 270 (12.5%) deaths and 61 (2.8%) non-fatal MIs. Figure 2 shows the Kaplan-Meier curves for MACE and all-cause death for the groups. The curves of the groups differed significantly (log-rank test, both \( P<0.0001 \)), and the cumulative incidences of these clinical events increased clearly in the low albumin/high CRP group. Furthermore, Kaplan-Meier curves for MACE showed significant differences in the incidence of events between the low albumin/high CRP group and other groups, even stratified by CKD (Figure 3). Risk analyses using Cox proportional hazard models revealed significant interactions between serum albumin...
Discrimination and Reclassification of Serum Albumin and hs-CRP

Table 2. Cox Hazard Analyses for MACE and All-Cause Death of Study Patients Undergoing 1st PCI

<table>
<thead>
<tr>
<th></th>
<th>Univariate</th>
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<th>Multivariate</th>
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<tbody>
<tr>
<td></td>
<td>HR 95% CI P</td>
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<td>HR 95% CI P</td>
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<tr>
<td>MACE (all-cause death+non-fatal MI)</td>
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<tr>
<td>Serum albumin, 1 g/dL decrease</td>
<td>2.94 2.38–3.70 &lt;0.0001</td>
<td>1.75 1.35–2.33 &lt;0.0001</td>
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<tr>
<td>hs-CRP, 1 mg/dL increase</td>
<td>2.80 1.80–4.25 &lt;0.0001</td>
<td>1.85 1.15–2.99 0.01</td>
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<tr>
<td>ACS</td>
<td>1.57 1.25–1.96 &lt;0.0001</td>
<td>1.43 1.10–1.84 0.006</td>
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<tr>
<td>Age</td>
<td>1.05 1.04–1.06 &lt;0.0001</td>
<td>1.03 1.02–1.05 &lt;0.0001</td>
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<tr>
<td>BMI</td>
<td>0.91 0.88–0.94 &lt;0.0001</td>
<td>0.97 0.93–1.00 0.07</td>
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<tr>
<td>CKD</td>
<td>2.05 1.64–2.54 &lt;0.0001</td>
<td>1.62 1.28–2.06 &lt;0.0001</td>
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<tr>
<td>Current smoker</td>
<td>0.97 0.76–1.23 0.81</td>
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<tr>
<td>Diabetes</td>
<td>1.20 0.97–1.49 0.10</td>
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<tr>
<td>Hypertension</td>
<td>1.26 0.98–1.62 0.07</td>
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<tr>
<td>LVEF</td>
<td>0.98 0.97–0.99 &lt;0.0001</td>
<td>0.99 0.98–0.996 0.006</td>
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<tr>
<td>Multivessel disease</td>
<td>1.26 1.01–1.58 0.04</td>
<td>1.26 0.99–1.603 0.05</td>
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<tr>
<td>Statin use</td>
<td>0.54 0.43–0.67 &lt;0.0001</td>
<td>0.56 0.44–0.70 &lt;0.0001</td>
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<tr>
<td>All-cause death</td>
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<tr>
<td>Serum albumin, 1 g/dL decrease</td>
<td>3.23 2.50–4.17 &lt;0.0001</td>
<td>1.75 1.32–2.38 0.0002</td>
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<tr>
<td>hs-CRP, 1 mg/dL increase</td>
<td>3.42 2.14–5.37 &lt;0.0001</td>
<td>2.21 1.32–3.71 0.004</td>
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<tr>
<td>ACS</td>
<td>1.52 1.18–1.95 0.002</td>
<td>1.31 0.99–1.73 0.06</td>
<td></td>
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<tr>
<td>Age</td>
<td>1.07 1.05–1.09 &lt;0.0001</td>
<td>1.05 1.04–1.07 &lt;0.0001</td>
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<tr>
<td>BMI</td>
<td>0.89 0.85–0.92 &lt;0.0001</td>
<td>0.95 0.91–0.966 0.03</td>
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<tr>
<td>CKD</td>
<td>2.30 1.81–2.92 &lt;0.0001</td>
<td>1.65 1.27–2.15 0.0002</td>
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<tr>
<td>Current smoker</td>
<td>1.03 0.78–1.33 0.85</td>
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<tr>
<td>Diabetes</td>
<td>1.16 0.91–1.48 0.22</td>
<td>– – –</td>
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<tr>
<td>Hypertension</td>
<td>1.30 0.99–1.72 0.06</td>
<td>– – –</td>
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<tr>
<td>LVEF</td>
<td>0.98 0.97–0.99 &lt;0.0001</td>
<td>0.98 0.97–0.99 0.0006</td>
<td></td>
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<tr>
<td>Multivessel disease</td>
<td>1.26 0.99–1.61 0.06</td>
<td>– – –</td>
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<tr>
<td>Statin use</td>
<td>0.53 0.42–0.68 &lt;0.0001</td>
<td>0.56 0.43–0.72 &lt;0.0001</td>
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</table>

CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiac events; MI, myocardial infarction. Other abbreviations as in Table 1.

Table 3. Cox Proportional Hazards Models for MACE and All-Cause Death of Study Patients Undergoing 1st PCI

<table>
<thead>
<tr>
<th></th>
<th>Univariate</th>
<th></th>
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<th>Multivariate</th>
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<tbody>
<tr>
<td></td>
<td>HR 95% CI P</td>
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<td></td>
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<td></td>
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<tr>
<td>MACE</td>
<td></td>
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<tr>
<td>High albumin/low CRP</td>
<td>Ref. – – &lt;0.0001</td>
<td>Ref. – – &lt;0.0001</td>
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<tr>
<td>Low albumin/low CRP</td>
<td>2.33 1.54–3.57 &lt;0.0001</td>
<td>1.84 1.18–2.90 0.007</td>
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</tr>
<tr>
<td>High albumin/high CRP</td>
<td>1.80 1.21–2.72 0.003</td>
<td>1.82 1.20–2.83 0.005</td>
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<tr>
<td>Low albumin/high CRP</td>
<td>3.84 2.70–5.62 &lt;0.0001</td>
<td>2.55 1.72–3.88 &lt;0.0001</td>
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<tr>
<td>All-cause death</td>
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<tr>
<td>High albumin/low CRP</td>
<td>Ref. – – &lt;0.0001</td>
<td>Ref. – – 0.0005</td>
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<tr>
<td>Low albumin/low CRP</td>
<td>2.25 1.41–3.64 0.0006</td>
<td>1.76 1.07–2.95 0.03</td>
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<tr>
<td>High albumin/high CRP</td>
<td>1.61 1.02–2.57 0.04</td>
<td>1.66 1.03–2.76 0.04</td>
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<tr>
<td>Low albumin/high CRP</td>
<td>4.10 2.78–6.28 &lt;0.0001</td>
<td>2.51 1.62–4.06 &lt;0.0001</td>
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</tbody>
</table>

Adjusted-for variables were ACS, age, BMI, CKD, LVEF, multivessel disease, and use of statins. These covariates were added to this model only if identified as significant predictors of MACE and all-cause death (P<0.05). CRP, C-reactive protein. Other abbreviations as in Tables 1,2.

Table 2 shows the Cox proportional hazard analyses for MACE and all-cause death. After adjustment for other confounders, serum albumin and hs-CRP levels were independent predictors for MACE and all-cause death. In the analysis of serum albumin and CRP combined, patients in the low albumin/high CRP group had significantly higher MACE and mortality compared with the high albumin/low CRP group (HR 2.55, 95% CI 1.72–3.88, P<0.0001; HR 2.51, 95% CI 1.62–4.06, P<0.0001, respectively) (Table 3).
in the model with both serum albumin and hs-CRP, even compared with the models with serum albumin alone and with hs-CRP alone.

Discussion

The major findings of the present study were as follows: (1) patients with low serum albumin and high hs-CRP levels showed significantly higher incidences of MACE and all-cause death than other patients; (2) multivariate Cox hazard analysis showed that both decreased serum albumin and increased hs-CRP levels were independent predictors of adverse cardiac events in post-PCI patients; and (3) the combination of serum albumin and hs-CRP was more closely related to clinical outcomes than either variable alone.

The hs-CRP level is one of the most useful inflammatory biomarkers for predicting cardiovascular diseases or clinical outcomes. Preprocedural hs-CRP elevation in post-PCI patients has been shown to be associated with higher rates of adverse cardiac events. On the other hand, hypoalbuminemia is a common finding in patients with chronic disease or poor nutritional status, and it becomes more prevalent in older patients or those with CKD. Previous studies showed that hypoalbuminemia was associated with worse clinical outcomes among patients with heart failure, cancer, stroke, or various other diseases. Plakht et al demonstrated that the serum albumin level on admission of patients with acute MI is an independent prognostic marker for long-term death. Recently, the relationship between CRP and serum albumin (the ratio of CRP to albumin) has been reported as a prognostic marker in patients with various diseases such as severe sepsis, CKD, or cancer. Furthermore, Ishii et al showed that the combination of lower serum albumin and elevated hs-CRP levels could strongly predict increased risk of amputation and death after endovascular therapy in hemodialysis patients with peripheral artery disease. The present study showed that the serum albumin and hs-CRP levels were both significantly associated with long-term clinical outcomes, and that the combination of these markers was an even stronger predictor in CAD patients who underwent PCI using Cox hazard analysis and discrimination analysis. To the best of our knowledge, this is the first study to show the combined effects of serum albumin and CRP on long-term outcomes in patients following PCI. We also believe that our results point to a promising and simple risk stratification tool for these CAD patients.

Patients in the lower serum albumin and higher hs-CRP group tended to have poor clinical status, such as older age, CKD, or lower BMI in the present study. However, even after adjusting for these factors, multivariate Cox hazard analysis showed that patients in this group had significantly worse clinical outcomes than patients in the other groups. One possible explanation is the various properties of albumin. The albumin plasma level is influenced by many factors, such as albumin synthesis, clearance, and dilution. Albumin synthesis is regulated by stimuli that include nutrient intake, insulin level, and oncotic pressure. Hypoalbuminemia is therefore thought to result from malnutrition, inflammation, or cachexia. Indeed, a previous study showed a significant association between decreased serum albumin levels and elevation of several inflammatory markers in patients with acute MI. These relationships suggest synergistic effects of the serum albumin and hs-CRP levels for predicting long-term clinical outcomes in patients with atherosclerotic diseases. Moreover, serum albumin has been shown to have antioxidant activity related to its ligand-binding capacity. Serum albumin has also been reported to be a specific inhibitor of human endothelial apoptosis and a significant inhibitor of platelet activation and aggregation.

Malnutrition is a complex state involving reduction of protein reserves, caloric collapse, and weakening of immune defenses. The MIA syndrome describes the high correlation of 3 significant separate clinical entities, namely malnutrition, inflammation, and atherosclerosis, which coexist in patients with CKD, especially ESRD. The MIA syndrome is considered to be an important issue for clinical management because of its high mortality rate. Nakagomi et al also found that malnutrition correlated with inflammation and atherosclerosis in patients with chronic heart failure and was associated with worse clinical outcomes. In the present study, patients with low serum
albumin and high hs-CRP levels had a higher prevalence of cardiac events, even in the non-CKD population. We therefore believe that MIA should be evaluated not only in CKD patients, but also non-CKD patients.

**Study Limitations**
First, as a single-center, observational study of a small patient cohort, unknown confounding factors might have affected the outcomes, regardless of analytical adjustments. The relatively small number of events may also have contributed to the lack of statistically significant differences. Second, although variables showing P<0.05 in univariate analyses were included in multivariate analyses, it is possible that other parameters affect the occurrence of cardiac events. Third, in some patients, high hs-CRP might be affected by the underlying disease or undetected infection. Finally, we only collected the information about medications on admission. Thus, information was not available about medical therapy after PCI that may have affected the prognosis of these patients.

**Conclusions**
Low serum albumin levels with high CRP levels were independently associated with long-term outcomes in post-PCI patients. Serum albumin and hs-CRP values had a combined predictive effect in CAD patients.

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**Conflict of Interest / Funding**
None.

**References**