



High-sensitivity C-reactive protein/albumin ratio as a predictor of in-hospital mortality in older adults admitted to the emergency department

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Objective The objective of this study was to test the hypothesis that an elevated high-sensitivity C-reactive protein (hs-CRP)/albumin ratio at admission increases the risk of mortality in older patients admitted to the hospital via the emergency department (ED).

Methods We performed a retrospective analysis of patients admitted to the ED with any medical problem between May 2013 and October 2013 who were older than 65 years. The hs-CRP and albumin levels were measured at the time of admission to the ED. The primary outcome was all-cause in-hospital mortality. Multivariate logistic analysis was performed.

Results A total of 811 patients were finally included in this study. The mean age was 76±7 years, and 438 subjects (54%) were male. The in-hospital mortality rate was 9.0% (73 patients). The hs-CRP/albumin ratio was higher in nonsurvivors than in survivors (34.2±37.6 vs. 16.2±25.5, P<0.001). Multivariate logistic analysis showed that the hs-CRP/albumin ratio was associated with all-cause in-hospital mortality after adjusting for other confounding factors (odds ratio, 1.011; 95% confidence interval [CI], 1.003 to 1.020). The prognostic value of the hs-CRP/albumin ratio for predicting mortality (area under the curve, 0.728; 95% CI, 0.696 to 0.758) was greater than that of hs-CRP alone (area under the curve, 0.706; 95% CI, 0.674 to 0.738; P<0.001).

Conclusion The hs-CRP/albumin ratio at admission to the ED is associated with all-cause in-hospital mortality among patients older than 65 years. The hs-CRP/albumin ratio may serve as a surrogate marker of disease severity.

Keywords Mortality; Aged; C-reactive protein; Albumins

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Capsule Summary

What is already known

The high-sensitivity C-reactive protein (hs-CRP)/albumin ratio has recently been tested as a prognostic marker for mortality in sepsis and acute kidney injury. The hs-CRP/albumin ratio has more value than either test alone for predicting prognoses in various clinical settings.

What is new in the current study

The hs-CRP/albumin ratio at admission to the emergency department is associated with all-cause in-hospital mortality among patients older than 65 years. A high hs-CRP/albumin ratio at initial presentation to the emergency department among older patients may provide evidence to aid the decision-making process regarding admission to the hospital regardless of etiology.

INTRODUCTION

The global population is aging worldwide, and this has been a major issue in healthcare.¹ The aging of the population in Korea is projected to be the fastest in the Organization for Economic Co-operation and Development countries.² Older adults visit the emergency department (ED) more frequently than younger adults.^{3,4} Accurate diagnosis and treatment of older adults is more complex because they tend to have atypical signs and symptoms with multiple comorbidities.^{5,6} Moreover, they are at a high risk of hospitalization, intensive care unit admission, and death.⁷ However, the association between risk factors and in-hospital mortality in older adults admitted to the ED has rarely been investigated.

High-sensitivity C-reactive protein (hs-CRP) is an acute-phase reactant and a marker of acute and chronic inflammation.⁸ The hs-CRP level is a marker for predicting the risk or prognosis of various diseases such as coronary artery disease (CAD), ischemic stroke, sepsis, and cancer.⁹⁻¹⁴ Albumin is an indicator of malnutrition, and hypoalbuminemia is a prognostic factor in hospitalized elderly patients.^{15,16} For this reason, the combination of these two parameters, namely the ratio of hs-CRP to albumin, may have more value than either of them individually for predicting prognoses in various clinical settings, and this ratio has recently been tested as a prognostic marker for mortality in sepsis and acute kidney injury.^{17,18} Moreover, older patients are susceptible to infectious disease, and nutritional status is an important prognostic factor in various geriatric clinical settings.

We tested the hypothesis that an elevated hs-CRP/albumin ratio at admission increases the risk of mortality in older patients admitted to the hospital via the ED. We assessed the association between the hs-CRP/albumin ratio at admission and in-hospital mortality in older patients admitted to the hospital via the ED.

METHODS

Study design and setting

This retrospective study was conducted in the Department of Emergency Medicine of Seoul St. Mary's Hospital, a tertiary educational hospital. This study was approved by our institutional review board, and a requirement for consent was waived owing to its retrospective design. Patients were included if they were older than 65 years and admitted to our hospital via the ED with any medical problem between May 2013 and October 2013. Patients were excluded if they had a trauma-related injury or were discharged from the ED.

Laboratory measurements

Blood samples for a complete blood count and serum chemistry including serum albumin and hs-CRP levels were obtained when admitted to the ED as part of the routine testing in all adult patients with any medical problem. The hs-CRP level was measured using a turbidimetric immunoassay (Wako Chemicals, Osaka, Japan) on a Hitachi 7600 chemistry analyzer (Hitachi, Tokyo, Japan). The analytical sensitivity of the assay was 0.2 mg/L, and the intra-assay coefficient of variation was < 5%.

Data collection

Demographic and clinical data were collected from electronic medical records. All comorbidities such as cancer, diabetes, hypertension, CAD, cerebrovascular accident, congestive heart failure, chronic kidney disease, and chronic pulmonary disease were also collected and defined according to the International Classification of Diseases, 10th revision.¹⁹ Laboratory parameters such as blood urea nitrogen, creatinine, hemoglobin, sodium, and CRP were also included. A Sequential Organ Failure Assessment (SOFA) score was calculated at the time of ED admission. The primary outcome was all-cause in-hospital mortality. Survival to hospital discharge was defined as discharge from the hospital alive to home or to another healthcare facility including a rehabilitation hospital.

Statistical analysis

Data are expressed as means \pm standard deviations for continuous variables and percentages for categorical variables. Student's *t*-test for continuous variables and Fisher's exact test and the χ^2 test for categorical variables were used. To find the factors associated with in-hospital mortality, univariate analyses were performed first followed by multivariate logistic regression analysis. Variables with *P*-values < 0.05 on univariate analysis were entered into the multivariate logistic regression model. To evaluate the association of the hs-CRP/albumin ratio with mortality outcomes, hs-CRP/albumin ratio values were divided into four categories using the following cutoff values: < 0.59, 0.59–5.03, 5.05–25.07, and > 25.07. Odds ratios and 95% confidence intervals (CIs) were calculated with the lowest quartile as the reference. The hs-CRP/albumin ratio was also examined as a continuous variable. To determine the best cutoff values for the albumin and hs-CRP levels and hs-CRP/albumin ratio, a receiver operating characteristic curve was generated and Youden's index was calculated; sensitivities, specificities, positive and negative predictive values, and their 95% CIs were also calculated. We determined predictive performance using receiver operating characteristic curves with logistic regression models to compare and assess for equality of the area under the curve using the DeLong test. Statistical

analyses were performed using IBM SPSS ver. 20.0 (IBM Corp., Armonk, NY, USA) and MedCalc ver. 15.2.2 (MedCalc Software, Mariakerke, Belgium), and P-values ≤ 0.05 were considered statistically significant.

RESULTS

Characteristics of the subjects

A total of 5,166 patients older than 65 years were admitted to our ED during the study period. Of those, 4,355 patients were excluded because they had a trauma-related injury ($n = 621$), were transferred from another hospital ($n = 723$), were dead on arrival ($n = 129$), or visited the ED for irrelevant medical treatment ($n = 52$) and did not admitted to our hospital ($n = 2,830$). The remaining 811 patients were finally included in this study. The mean age was 76 ± 7 years, and 438 patients (54%) were male. Seventy-three patients (9.0%) died during their hospital stay. Hypertension was the most common comorbidity. Men were more common in the nonsurvivor group. A history of cancer was more common among nonsurvivors, whereas hypertension was more common among survivors. Baseline characteristics and laboratory data are shown in Table 1.

Table 1. Baseline characteristics of patients with or without in-hospital mortality

	Survivors (n = 738)	Nonsurvivors (n = 73)	P-value
Age (yr)	75.6 \pm 7.3	75.0 \pm 7.6	0.514
Sex, male	390 (52.8)	48 (65.8)	0.035
Cancer	213 (28.9)	46 (63.0)	< 0.001
Diabetes mellitus	257 (34.8)	18 (24.7)	0.080
Hypertension	473 (64.1)	33 (45.2)	0.001
CAD	124 (16.8)	5 (6.8)	0.027
CVA	103 (14.0)	6 (8.2)	0.170
CHF	35 (4.7)	5 (6.8)	0.428
CKD	77 (10.4)	8 (11.0)	0.889
Lung disease	134 (18.2)	17 (23.3)	0.283
BUN (mg/dL)	27.1 \pm 21.6	34.3 \pm 20.8	0.007
Creatinine (mg/dL)	1.5 \pm 1.9	1.5 \pm 1.0	0.930
Hemoglobin (g/dL)	12.2 \pm 2.5	11.2 \pm 2.3	0.002
Albumin (g/dL)	3.7 \pm 0.6	3.0 \pm 0.6	< 0.001
Sodium (mEq/L)	137.2 \pm 6.1	135.5 \pm 7.5	0.024
hs-CRP (mg/dL)	5.2 \pm 7.7	9.1 \pm 8.2	< 0.001
SOFA score	2.4 \pm 1.7	4.4 \pm 2.8	< 0.001
hs-CRP/albumin ratio	16.2 \pm 25.5	34.2 \pm 37.6	< 0.001

Values are presented as mean \pm standard deviation or number (%).

CAD, coronary artery disease; CVA, cerebrovascular disease; CHF, congestive heart failure; CKD, chronic kidney disease; BUN, blood urea nitrogen; hs-CRP, high-sensitivity C-reactive protein; SOFA, Sequential Organ Failure Assessment.

Table 2. ORs for all-cause in-hospital mortality events according to the hs-CRP/albumin ratio as a categorical variable

Variable	Univariate			Multivariate		
	OR	95% CI	P-value	OR	95% CI	P-value
Age	0.989	0.956–1.023	0.514	–	–	–
Sex, male	1.713	1.034–2.838	0.036	1.631	0.922–2.885	0.093
Cancer	4.199	2.544–6.931	< 0.001	3.153	1.754–5.668	< 0.001
Diabetes mellitus	0.613	0.352–1.065	0.083	–	–	–
Hypertension	0.462	0.285–0.751	0.002	0.641	0.365–1.128	0.123
CAD	0.364	0.144–0.921	0.033	0.487	0.178–1.330	0.160
CVA	0.552	0.233–1.306	0.176	–	–	–
CHF	1.477	0.560–3.894	0.431	–	–	–
CKD	1.057	0.489–2.285	0.889	–	–	–
Lung disease	1.368	0.771–2.430	0.284	–	–	–
BUN (mg/dL)	1.012	1.003–1.021	0.009	1.003	0.990–1.017	0.618
Creatinine (mg/dL)	0.994	0.871–1.134	0.930	–	–	–
Hemoglobin (g/dL)	0.864	0.787–0.949	0.002	0.972	0.866–1.091	0.630
Albumin (g/dL)	0.185	0.123–0.279	< 0.001	–	–	–
Sodium (mEq/L)	0.962	0.931–0.995	0.025	1.000	0.957–1.044	0.989
hs-CRP (mg/dL)	1.049	1.024–1.076	< 0.001	–	–	–
SOFA score	1.488	1.338–1.655	< 0.001	1.412	1.235–1.614	< 0.001
hs-CRP/albumin ratio						
Quartile 1	REF	REF	REF	REF	REF	REF
Quartile 2	2.393	0.610–9.388	0.211	1.700	0.422–6.845	0.456
Quartile 3	12.016	3.610–39.992	< 0.001	5.599	1.622–19.328	0.006
Quartile 4	12.476	3.754–41.459	< 0.001	5.940	1.708–20.655	0.005

OR, odds ratio; hs-CRP, high-sensitivity C-reactive protein; CI, confidence interval; CAD, coronary artery disease; CVA, cerebrovascular disease; CHF, congestive heart failure; CKD, chronic kidney disease; BUN, blood urea nitrogen; SOFA, Sequential Organ Failure Assessment; REF, reference.

Table 3. ORs for all-cause in-hospital mortality events according to hs-CRP/albumin ratio as a continuous variable

Variable	Univariate			Multivariate		
	OR	95% CI	P-value	OR	95% CI	P-value
Age	0.989	0.956–1.023	0.514	–	–	–
Sex, male	1.713	1.034–2.838	0.036	1.664	0.941–2.940	0.080
Cancer	4.199	2.544–6.931	<0.001	3.531	1.971–6.327	<0.001
Diabetes mellitus	0.613	0.352–1.065	0.083	–	–	–
Hypertension	0.462	0.285–0.751	0.002	0.575	0.329–1.005	0.052
CAD	0.364	0.144–0.921	0.033	0.486	0.180–1.313	0.155
CVA	0.552	0.233–1.306	0.176	–	–	–
CHF	1.477	0.560–3.894	0.431	–	–	–
CKD	1.057	0.489–2.285	0.889	–	–	–
Lung disease	1.368	0.771–2.430	0.284	–	–	–
BUN (mg/dL)	1.012	1.003–1.021	0.009	1.003	0.990–1.016	0.616
Creatinine (mg/dL)	0.994	0.871–1.134	0.930	–	–	–
Hemoglobin (g/dL)	0.864	0.787–0.949	0.002	0.962	0.859–1.078	0.506
Albumin (g/dL)	0.185	0.123–0.279	<0.001	–	–	–
Sodium (mEq/L)	0.962	0.931–0.995	0.025	0.992	0.951–1.035	0.710
hs-CRP (mg/dL)	1.049	1.024–1.076	<0.001	–	–	–
SOFA score	1.488	1.338–1.655	<0.001	1.430	1.254–1.631	<0.001
hs-CRP/albumin ratio	1.017	1.010–1.024	<0.001	1.011	1.003–1.020	0.005

OR, odds ratio; hs-CRP, high-sensitivity C-reactive protein; CI, confidence interval; CAD, coronary artery disease; CVA, cerebrovascular disease; CHF, congestive heart failure; CKD, chronic kidney disease; BUN, blood urea nitrogen; SOFA, Sequential Organ Failure Assessment.

Table 4. Sensitivity, specificity, positive predictive value, and negative predictive value of albumin, hs-CRP, and hs-CRP/albumin ratio

	Cutoff	Sensitivity	Specificity	PPV	NPV
Albumin (g/dL)	≤ 3.4	78.1 (66.9–86.9)	68.7 (65.2–72.0)	19.8 (15.3–24.9)	96.9 (95.1–98.2)
hs-CRP (mg/dL)	> 1.58	89.0 (79.5–95.1)	51.4 (47.7–55.0)	15.3 (12.0–19.1)	97.9 (96.0–99.1)
hs-CRP/albumin ratio	> 6.44	86.3 (76.2–93.2)	56.78 (53.1–60.4)	16.5 (12.9–20.6)	97.7 (95.7–98.9)

Parenthesis is 95% confidence interval.

hs-CRP, high-sensitivity C-reactive protein; PPV, positive predictive value; NPV, negative predictive value.

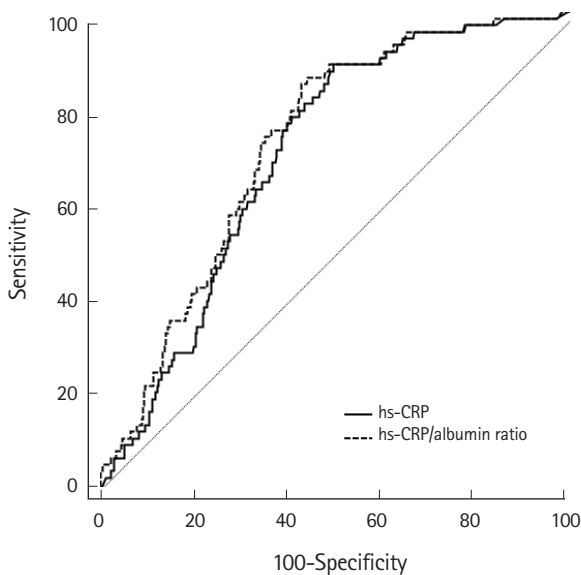


Fig. 1. Receiver operating characteristics curve of high-sensitivity C-reactive protein (hs-CRP) and hs-CRP/albumin ratio to predict in-hospital mortality. The area under the curve of the hs-CRP/albumin ratio and hs-CRP is 0.728 (95% confidence interval, 0.696 to 0.758) and 0.706 (95% confidence interval, 0.674 to 0.738), respectively (P<0.001).

Logistic regression analysis

The hs-CRP/albumin ratio ranged from 0.04 to 179.47 (17.9 ± 27.3). The hs-CRP/albumin ratio was higher in nonsurvivors than in survivors (34.2 ± 37.6 vs. 16.2 ± 25.5, P<0.001). In the univariate analyses, male sex, history of cancer, hypertension, CAD, blood urea nitrogen, hemoglobin, albumin, sodium, hs-CRP, and SOFA values showed statistically significant associations with all-cause in-hospital mortality.

After adjusting for these variables, the hs-CRP/albumin ratio still showed an association with all-cause in-hospital mortality. Patients in the fourth quartile were 5.94 times more likely to die compared with those in the lowest quartile of the hs-CRP/albumin ratio (Table 2). When the hs-CRP/albumin ratio was examined as a continuous variable, it still showed an association with all-cause in-hospital mortality (odds ratio, 1.011; 95% CI, 1.003 to 1.020) (Table 3).

Prognostic value of the hs-CRP/albumin ratio

Table 4 shows the sensitivity, specificity, and positive and negative predictive values of the albumin and hs-CRP levels and the

Table 5. Cause of death

Cause of death	Number
Cancer	29
Sepsis	20
Respiratory failure	16
Heart failure	4
Neurologic disorder	2
Pancreatitis	1
Pulmonary thromboembolism	1

hs-CRP/albumin ratio. The best cutoff value of the hs-CRP/albumin ratio is 6.44, with 86.3% sensitivity and 56.8% specificity. The area under the curve of the hs-CRP/albumin ratio (0.728; 95% CI, 0.696 to 0.758) was greater than that of hs-CRP alone (0.706; 95% CI, 0.674 to 0.738; $P < 0.001$) (Fig. 1). Table 5 shows the cause of death of individual patients.

DISCUSSION

The main finding of this study was that the hs-CRP/albumin ratio at admission was an independent predictor of all-cause in-hospital mortality among patients older than 65 years. To the best of our knowledge, this is the first report describing the association between the hs-CRP/albumin ratio and in-hospital mortality among older patients. After adjusting for multiple confounding factors, the all-cause in-hospital mortality rate was increased by 1.1% for each whole-number increase in the hs-CRP/albumin ratio. Furthermore, the prognostic value of the hs-CRP/albumin ratio for predicting mortality was greater than that of hs-CRP alone. If a patient had a hs-CRP/albumin ratio of > 6.44 , the risk of in-hospital death was 16.4%. If a patient had a hs-CRP/albumin ratio of < 6.44 , the risk of survival hospital discharge was 97.7%.

The increasing elderly population is a big social and health problem.¹ Elderly patients visit the ED more frequently than young adults. Moreover, accurate diagnosis and treatment is more complex because they have multiple comorbidities, increasing the difficulty of predicting mortality. The association between risk factors and in-hospital mortality in older adults admitted to the ED has rarely been investigated. Therefore, a strategy based on the targeting of high-risk patients has been proposed.⁶ The results of this study may also assist in the identification of older patients at high risk of mortality. One interesting finding of our results is that the history of hypertension and CAD decreased the odds for in-hospital mortality in univariate logistic regression analysis. Further testing should be done to determine the association between a history of hypertension and CAD and in-hospital mortality among older patients.

Albumin levels are a sensitive index for nutritional status. Many factors influence serum levels of albumin such as kidney disease and the patient's state of hydration. Hypoalbuminemia is associated with higher mortality during hospital stays in older patients.^{15,16} However, it remains to be proven whether adequate correction of hypoalbuminemia can reduce mortality.

CRP is an acute-phase reactant and a nonspecific marker in the diagnosis of various conditions such as infectious diseases and autoimmune and rheumatologic disorders. The clinical usefulness of CRP has widened with the availability of high-sensitivity assays that can measure CRP levels as low as 0.1 mg/L. Elevated levels of hs-CRP are associated with the prognosis of various diseases such as CAD, ischemic stroke, sepsis, and cancer.⁹⁻¹⁴

Both hs-CRP and albumin could be prognostic markers for outcomes in various clinical settings, but the combination of these markers may have more value than either one alone because this would include both inflammatory and nutritional information.¹⁸ The CRP/albumin ratio was associated with 90-day and 180-day mortality in patients with sepsis,^{17,20} and the CRP/albumin ratio had a higher predictive value than CRP alone. In our study, the hs-CRP/albumin ratio at ED admission was positively correlated with mortality among patients older than 65 years. Our study suggests that the hs-CRP/albumin ratio may serve as an early surrogate marker for mortality of the entire spectrum of acute disease in elderly patients and is not confined to any specific disease.

The prediction of in-hospital mortality or risk stratification among older patients admitted to the ED has rarely been investigated. Some authors have suggested scoring systems, but they have not been externally validated.²¹ Vital signs and level of consciousness, which have been used in other scoring systems, were not included in our study. However, we included a SOFA score that includes mean arterial pressure and the Glasgow Coma Scale.²² Therefore, this is not a limitation of our study.

There are some limitations in this study. The first limitation is that this study used a retrospective observational design at a single center, which raises the concern of potential unknown confounding factors and limits the generalizability of its results. Second, the primary outcome of this study was all-cause in-hospital mortality, and we could not identify the association between the hs-CRP/albumin ratio and cause-specific mortality because only 73 patients (9.0%) died during their hospital stay. Third, the physicians were not blinded to the hs-CRP and albumin results because they are routinely reported in our hospital. This could be a potential source of bias and could affect the prognostic value of the hs-CRP/albumin ratio. However, the hs-CRP/albumin ratio was not used for any clinical decisions such as hospital admission, critical procedure, or discharge from our hospital.

In conclusion, the hs-CRP/albumin ratio at admission to the ED was associated with all-cause in-hospital mortality among patients older than 65 years. The hs-CRP/albumin ratio may serve as a surrogate marker of disease severity. A high hs-CRP/albumin ratio at initial presentation to the ED among older patients may provide evidence to aid in the decision-making process regarding admission to the hospital regardless of etiology.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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