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C-reactive protein for simple prediction of mortality in patients with acute non-variceal upper gastrointestinal bleeding
A retrospective analysis

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Abstract

In upper gastrointestinal bleeding (UGIB), scoring systems using multiple variables were developed to predict patient outcomes. We evaluated serum C-reactive protein (CRP) for simple prediction of patient mortality after acute non-variceal UGIB.

The associated factors for 30-day mortality was investigated by regression analysis in patients with acute non-variceal UGIB (N = 1232). The area under the receiver operating characteristics (AUROC) curve was analyzed with serum CRP in these patients and a prospective cohort (N = 435). The discriminant validity of serum CRP was compared to other prognostic scoring systems by means of AUROC curve analysis.

Serum CRP was significantly higher in the expired than survived patients (median, 4.53 vs 0.49; $P < .001$). The odds ratio of serum CRP was 4.18 (2.10–9.27) in multivariate analysis. The odds ratio of high serum CRP was higher than Rockall score (4.15 vs 1.29), AIMS65 (3.55 vs 1.71) and Glasgow-Blatchford score (4.32 vs 1.08) in multivariate analyses. The AUROC of serum CRP at bleeding was 0.78 for 30-day mortality ($P < .001$). In the validation set, serum CRP was also significantly higher in the expired than survived patients, of which AUROC was 0.73 ($P < .001$). In predicting 30-day mortality, the AUROC with serum CRP was not inferior to that of other scoring systems.

Serum CRP at bleeding can be simply used to identify the patients with high mortality after acute non-variceal UGIB.

Abbreviations: AUROC = area under the receiver operating characteristics, CI = confidence interval, CRP = C-reactive protein, GBS = Glasgow-Blatchford bleeding score, UGIB = upper gastrointestinal bleeding.

Keywords: gastrointestinal bleeding, gastrointestinal endoscopy, prognostic indicator, validation

1. Introduction

Upper gastrointestinal bleeding (UGIB) is a common cause of admission, whose incidence ranges from 20 to 60 per 100,000 population.[1,2] In spite of declining incidence, advances of medication, and therapeutic techniques in UGIB,[3–6] non-variceal UGIB still remains a significant medical problem and its mortality rate remains fairly constant of approximately 10%.[7–10] To provide appropriate intervention and to minimize morbidity and mortality, patients with non-variceal UGIB should be stratified into low- and high-risk groups by using prognostic scales, on the basis of clinical, laboratory, and endoscopic criteria.[11]

There have been well-known risk predictors for rebleeding or mortality after acute UGIB such as old age, unstable hemodynamics, poor overall health status, comorbid illnesses, transfusion requirement, hematochezia, hematemesis, sepsis, low hemoglobin levels, and high blood urea, creatinine or aminotransferase levels.[3] Based on these factors, several prognostic scoring systems have been developed to identify high-risk patients or to predict the mortality, rebleeding, and the need for endoscopic interventions after UGIB.[12–17] However, these systems are not always readily applicable in clinical settings, due to their use of many variables, the need for calculation, or the requirement of endoscopic scoring in some systems.

C-reactive protein (CRP) is a nonspecific marker of inflammation, and its elevation has been studied for association with increased severity in several diseases such as ischemic heart disease, heart failure, chronic renal disease, and chronic liver disease.[18–22] In our previous study, high serum CRP at bleeding was independently associated with rebleeding risk in patients with non-variceal UGIB even after adjustment for confounding factors including age, blood pressure, and hemoglobin level.[23] In the present study, we have postulated that serum CRP might have a possibility of significant association with mortality after acute non-variceal UGIB. In the present study, we derived the serum CRP at bleeding as an independent risk factor and simple predictor for mortality in the patients with non-variceal UGIB, which was validated by comparison with the previously known scoring systems and by measuring the reproducibility in the prospective cohorts.

2. Methods

2.1. Study cohort

A consecutive database that included all patients admitted to Seoul St. Mary's Hospital for UGIB from January 2009 to December 2015 was used in the derivation study. Data were prospectively collected and retrospectively analyzed in this study. A total of 1,832 patients with UGIB were included in the derivation study. Patients who were younger than 18 years old (n=7), who did not have endoscopic evaluation within 24 hour from initial symptoms (n=6), whose endoscopic examination revealed variceal bleeding after endoscopic examination (n= 393), whose bleeding was of small bowel (n=20) or obscure (n= 75) origin, who were not examined with the serum CRP level at the initial visit (n=29), and who did not re-visit our clinic (n=70) were excluded. The remaining 1232 patients were analyzed.

A reproducibility study was carried out prospectively in consecutive non-variceal UGIB patients from January 2016 to October 2017. A total of 652 patients who were suspicious of UGIB visited our hospital. Among them, the following patients were excluded: age less than 18 years old (n=1), esophagogastroduodenoscopy examination after 24 hour (n=36), variceal bleeding (n=106), small bowel (n=17) or obscure (n=7) bleeding. In the end, 435 patients were analyzed in the reproducibility study.

Patient characteristics were recorded for the following variables: age, sex, initial blood pressure, and pulse rate, initial symptoms suggestive of UGIB (melena, hematemesis, and hematochezia), prior history of UGIB, and medication history. We defined major comorbidities when the patients had malignancy, heart failure, ischemic heart disease, liver failure or renal failure. Medications that pose a risk for UGIB such as aspirin, non-steroidal anti-inflammatory drug, anti-platelet agent, anti-thrombotics (heparin, or warfarin) were recorded. We defined major comorbidities when the patients had malignancy, heart failure (reduced left ventricular function; ejection fraction $\leq 40\%$), ischemic heart disease (patients with acute coronary syndrome or stable angina), liver failure (patients with liver cirrhosis diagnosed by imaging study or liver biopsy) or renal failure (decreased kidney function for 3 or more months; estimated glomerular filtration rate $< 60\,mL/min/1.73\,m^2$).

This study was approved by Seoul St. Mary's Hospital Institutional Review Board (IRB No. KC16RISI0606).

2.2. Laboratory tests and endoscopic examinations

Laboratory tests included initial hemoglobin, serum CRP, serum blood urea nitrogen, and white blood cell count. Serum CRP levels were measured using a high-sensitivity turbidimetric immunoassay (Wako Pure Chemical Industries, Ltd., Osaka, Japan) with the Hitachi 7600 analyzer (Hitachi, Tokyo, Japan).

All endoscopic examinations were performed within 24 hour from the index UGIB event of each patient. During this study period, standard endoscopes (GIF-XQ260, Olympus, Japan) were used. Endoscopic data included the presence of blood in the stomach, cause of bleeding, and presence or absence of endoscopic treatment. The collected data were used to calculate the Rockall score, AIMS65, and Glasgow-Blatchford bleeding score (GBS) as previously described.[24]

2.3. Clinical outcomes

Primary end-point was 30-day overall mortality, which was defined as any death occurring within 30 days of the index bleeding episode. Patients were grouped into those who were dead or alive within 30 days after the index bleeding episode (expired and survived groups, respectively). Rebleeding was defined by the presence of fresh hematemesis and/or melena associated with the development of shock or a reduction in hemoglobin concentration greater than 2g/dL over 24hour.[25] In this study, we evaluated rebleeding within 7 days after the index bleeding episode.

2.4. Statistical analysis

Descriptive statistics were used to characterize the demographic features of the study population. For the univariate analysis, continuous variables were expressed as means (± standard deviation) or medians (interquartile range) and were compared using the Student t-test or the Mann–Whitney U test. Categorical variables were expressed as numbers (percentage) and compared between groups using Chi-square or Fisher exact test as appropriate. A logistic regression model was used to assess predictive factors of 30-day mortality. Variables showing P values $< .05$ after univariate analysis and those that were considered clinically relevant were included in a multivariate logistic regression model to identify independent factors. In the multivariate analysis, we performed backward step-wise elimination regression. For significant variables, coefficients and odds ratios with 95% confidence intervals were reported. After multivariate analysis, the most significant variable was selected for the prognostic predictability of the outcome of interest, which was subsequently used to compute individual probabilities for mortality and to produce the receiver operating characteristic

(ROC) curve. The area under the ROC (AUROC) was calculated for the predictability for 30-day mortality, which was compared to other scoring systems using DeLong test.[26] Statistical analysis was performed using Statistical Analysis System software (version 8.02, SAS Institute, Cary, NC). P values < .05 were considered to be significant.

3. Results

3.1. Derivation study
3.1.1. Patients. The baseline demographic characteristics are shown in Table 1. Male patients comprised 68.8% (n = 848). The mean age was 63.8 ± 16.4 (range, 18–99), and the proportion of patients of 60 years or above was 64.1%. Patients with major comorbidity were found in 41.4%. Among initial bleeding symptoms, melena was the most commonly observed (58.5%), followed by hematemesis (36.5%) and hematochezia (11.1%). Systolic blood pressure (SBP) was 114.0 ± 23.4 mmHg at the initial visit and SBP less than 100 mmHg were observed in 23.8% of the patients. Mean pulse rate was 92.8 ± 18.7/min. In the initial laboratory findings, the mean hemoglobin level was 9.1 ± 3.5 g/dL, and the median CRP level was 0.57 mg/dL (range, 0.02–34.1).

Within 30 days from the initial UGIB event, 81 patients (6.6%) expired in a total of 1,232 patients with non-variceal UGIB. Among them, 35 (43.2%) expired due to non-variceal UGIB. Rebleeding within 7 days from the initial event was observed in 15% of all patients. The frequency of rebleeding was significantly higher in the expired than in the survived group (49.3% vs 12.6%, P < .001).

The expired group comprised of a higher proportion of patients who are male and patients above 60 years of age compared to the survived group (Table 1). Among the main symptoms, melena was observed more frequently in the survived group, but hematochezia was more frequently observed in the expired group (both P < .001). Patients in the expired group had more major comorbidities (65.4% vs 39.7%, P < .01). The proportion of malignancy and liver failure was significantly higher in the expired group (P < .001). In the past drug history, the use of antiplatelet agents was more frequently observed in the survived group (P < .01). Initial hemodynamic status was significantly more unstable in the expired than in the survived group. In the laboratory findings, mean hemoglobin level was 9.2 g/dL and 8.0 g/dL in the survived and expired group, respectively (P = .003). Other comparisons are shown in Table 1 between the survived and expired group.

3.1.2. Causes of bleeding. At the initial endoscopic examination, blood in the gastric lumen was observed in 61.6% of patients. The most common cause of non-variceal UGIB was peptic ulcer disease (61.0%), followed by GI malignancies (11.1%) and Mallory-Weiss tear (8.4%). Other causes of bleeding are shown in Table 2. Endoscopic treatment was performed in 48.6% of the patients.

Endoscopically, fresh blood or old blood clots in the gastric lumen was observed more frequently in the expired group than in the survived group (82.7% vs 60.1%, P < .001). Peptic ulcer was a more frequent cause of bleeding in the survived than in the expired group (62.2% vs 44.4%, P = .002). Malignancy was a more common cause in the expired than in the survived group

Table 1

Baseline characteristics of study population.

	Total (n = 1,232)	Survived group (n = 1,151)	Expired group (n = 81)	P
Age (Mean ± SD, years old)	63.8 ± 16.4	63.5 ± 16.6	67.1 ± 13.5	.027
Male (n, %)	848 (68.8%)	790 (68.6%)	58 (71.6%)	.621
Past history of upper GI bleeding	203 (16.4%)	192 (16.6%)	11 (13.5%)	.467
Symptoms				
Melena	720 (58.5%)	697 (60.6%)	23 (28.4%)	<.001
Hematemesis	450 (36.5%)	414 (36.0%)	36 (44.4%)	.130
Hematochezia	137 (11.1%)	118 (10.3%)	19 (23.5%)	<.001
Comorbidity				
Malignancy	349 (28.3%)	301 (26.1%)	48 (59.3%)	<.001
Heart failure	59 (4.7%)	54 (4.6%)	5 (6.2%)	.550
Ischemic heart disease	173 (14.0%)	165 (14.3%)	8 (9.8%)	.264
Liver failure	137 (11.1%)	119 (10.3%)	18 (22.2%)	.003
Renal failure	107 (8.6%)	102 (8.9%)	5 (6.2%)	.405
Drugs				
Anti-platelets	334 (27.1%)	322 (28.0%)	12 (14.8%)	.010
NSAIDs	77 (6.2%)	75 (6.5%)	2 (2.5%)	.102
Anti-thrombotics	64 (5.2%)	63 (5.5%)	1 (1.3%)	.097
Vital signs				
Systolic pressure (mmHg)	114.0 ± 23.4	115.6 ± 22.9	105.9 ± 28.2	<.001
Diastolic pressure (mmHg)	67.8 ± 15.5	68.4 ± 15.5	61.0 ± 16.2	<.001
Pulse rate (>100 beats/min)	377 (30.6%)	337 (29.3%)	40 (49.3%)	<.001
Laboratory findings				
Blood urea nitrogen (mg/dL)	40.3 ± 29.5	40.1 ± 29.6	44.6 ± 28.9	.180
Hemoglobin (g/dL)	9.1 ± 3.5	9.2 ± 3.6	8.0 ± 2.2	.003
White blood cell (10^3/mm^3)	10.5 ± 16.2	10.4 ± 16.6	12.0 ± 6.6	.402
Serum CRP (mg/dL)				
Median (range)	0.57 (0–34)	0.49 (0–34)	4.53 (0–26)	<.001
≥ 0.5 mg/dL	643 (52.1%)	571 (49.6%)	72 (88.9%)	<.001

GI = gastrointestinal, NSAID = non-steroidal anti-inflammatory drug.

Table 2

Causes of bleeding by esophagogastroduodenoscopy.

	Total (n=1,232)	Survived (n=1,151)	Expired (n=81)	P
Peptic ulcer	752 (61.0%)	716 (62.2%)	36 (44.4%)	.002
Mallory-Weiss tear	104 (8.4%)	101 (8.8%)	3 (3.7%)	.079
UGI malignancy	137 (11.1%)	121 (10.5%)	16 (19.8%)	.019
No lesion	76 (6.1%)	68 (5.9%)	8 (9.9%)	.182
Esophageal ulcer	38 (3.1%)	36 (3.1%)	3 (3.7%)	.780
Angiodysplasia	36 (2.9%)	36 (3.1%)	0 (0.0%)	.026
L-tube injury	31 (2.5%)	16 (1.4%)	4 (4.9%)	.045
Dieulafoy lesion	23 (1.8%)	20 (1.7%)	3 (3.7%)	.260
Hemorrhagic gastritis	19 (1.5%)	15 (1.3%)	4 (4.9%)	.031
Other causes[*]	17 (1.4%)	16 (1.4%)	1 (1.2%)	1.000

CRP = C-reactive protein, UGI = upper gastrointestinal.

[*] post-operative anastomosis site bleeding (n=14), fistula bleeding (n=2), hemobilia (n=1).

(19.8% vs 10.5%, P=.019). Frequency of endoscopic treatment was not significantly different between the expired and survived group (51.9% vs 48.4%). Table 2 shows other comparisons of endoscopic findings between the survived and expired group.

3.1.3. Predictive factors for 30-day mortality. In univariate analysis (Table 3), the significant poor prognostic factors were old age (≥ 60 years), initial symptom of hematochezia, presence of major comorbidity, hypotension (SBP < 90 mm Hg), tachycardia (≥ 100/min), low level of initial hemoglobin (< 10 g/dL), high level of initial serum CRP (≥ 0.5 mg/dL), presence of upper GI malignancy, and rebleeding within 7 days after initial event. Initial symptom of melena and the use of antiplatelet agents were favorable prognostic factors in univariate analysis.

We performed multivariate regression analyses to find independent prognostic factors before endoscopic evaluation (Table 3). Bleeding from upper GI malignancy was not significantly associated with 30-day mortality in multivariate regression model. The presence of major comorbidity, tachycardia, and high serum CRP level were independently associated with poor prognostic factors, while melena and the use of antiplatelet agents were independent favorable prognostic factors

(Table 3). Among them, serum CRP level had the odds ratio of 4.18 [95% confidence interval, 2.104–9.270] in the multivariate analysis.

3.1.4. Relationship between serum CRP concentration and 30-day mortality. Initial level of serum CRP was significantly higher in the expired group than in the survived group (4.53 vs 0.49, P < .001; Fig. 1A), which was also observed in the disease-specific expired group than in the survived group (3.25 vs 0.55, P < .001; Supplementary Figure 1A, http://links.lww.com/MD/F397). The 30-day overall mortality and disease-specific mortality increased in correspondence with the elevation of serum CRP level in patients with acute non-variceal UGIB. When the initial level of serum CRP was divided into 4 groups, the overall and disease-specific mortality rate increased as the initial level of serum CRP was elevated (Fig. 1B and Supplementary Figure 1B, http://links.lww.com/MD/F397, respectively; both P for trend < .01).

3.1.5. Predictability of serum CRP for 30-day mortality in non-variceal UGIB. As shown in Figure 2, the AUROC of CRP for 30-day mortality was 0.78, and that of the Rockall score,

Table 3

Univariate and multivariate analysis for 30-day mortality after acute non-variceal upper GI bleeding.

	Univariate analysis		Multivariate analysis	
Factors	**Odds ratio (95% CI)**	**P**	**Odds ratio (95% CI)**	**P**
Age ≥ 60 yr (vs < 60)	1.65 (1.004–2.807)	.048	1.53 (0.854–2.742)	.153
Melena	0.26 (0.154–0.418)	<.001	0.28 (0.166–0.483)	<.001
Hematochezia	2.68 (1.515–4.562)	.001	1.43 (0.759–2.696)	.268
Presence of comorbidity[*]	4.95 (2.796–9.459)	<.001	2.01 (1.196–3.370)	.008
Use of anti-platelet agents	0.45 (0.228–0.806)	.006	0.56 (0.287–1.096)	.091
Systolic pressure < 90 mmHg (vs. ≥ 90 mmHg)	3.71 (2.151–6.226)	<.001	1.27 (0.733–2.184)	.398
Tachycardia (vs. <100/min)	2.36 (1.494–3.714)	<.001	1.91 (1.154–3.145)	.012
Hemoglobin < 10 g/dL (vs. ≥10 g/dL)	2.49 (1.425–4.668)	.001	1.49 (0.762–2.899)	.245
Serum CRP ≥ 0.5 mg/dL (vs. < 0.5 mg/dL)	8.13 (4.244–17.588)	<.001	4.65 (2.236–9.649)	<.001
Rebleeding[†]	6.69 (4.180–10.707)	< .001	5.37 (3.227–8.940)	<.001
Cause of bleeding				
Peptic ulcer	0.49 (0.309–0.765)	.002	0.65 (0.345–1.226)	.183
UGI malignancy	2.10 (1.175–3.737)	.011	0.87 (0.384–1.946)	.725
L-tube injury	3.69 (1.203–11.291)	.015	1.89 (0.471–7.552)	.370
Hemorrhagic gastritis	3.93 (1.275–12.140)	.010	1.96 (0.539–7.154)	.306

CRP = C-reactive protein, GI = gastrointestinal, Hgb = hemoglobin.

[*] Presence of malignancy, heart failure, ischemic heart disease, liver failure, or renal failure.
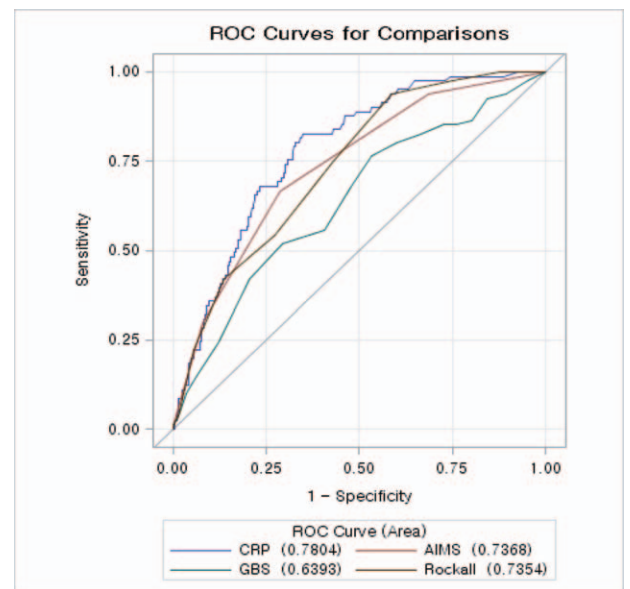
[†] within 7 days after admission.
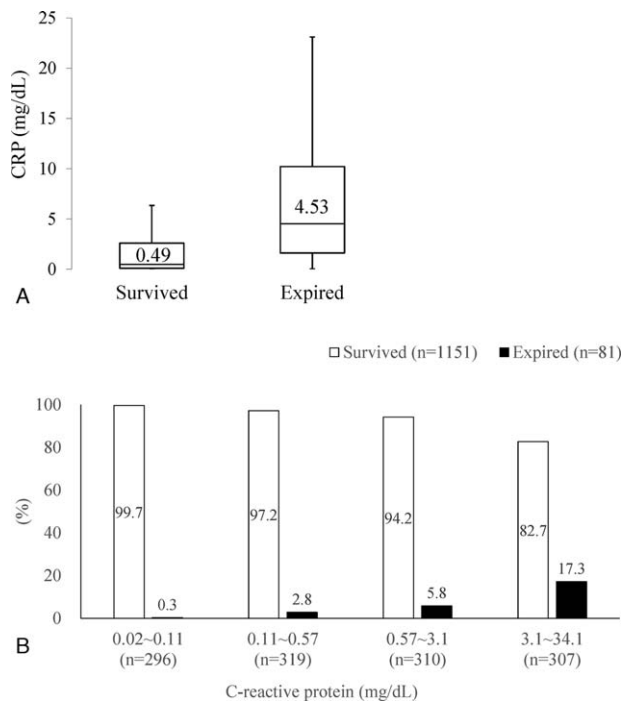
Figure 1. Serum C-reactive protein (CRP) level and patient mortality in acute non-variceal upper gastrointestinal bleeding. (A) Serum CRP at bleeding was significantly higher in the expired patients and disease-specific patients than the survived within 30- days after admission. (B) As increase of serum CRP level, the 30-day mortality rate was significantly increased in the patients with non-variceal upper GI bleeding.

Figure 2. AUROC analysis of CRP, Rockall score, AIMS65 score and Glasgow-Blatchford score for 30-day overall mortality.

AIMS65, and GBS was 0.74 ($P=.186$ vs CRP), 0.74 ($P=.200$ vs CRP), and 0.64 ($P<.01$ vs CRP), respectively. The AUROC of CRP for 30-day disease-specific mortality was 0.73, and that of the Rockall score, AIMS65, and GBS was 0.79, 0.74 and 0.70, respectively ($P=.176$, .741, and .674 vs AUROC of CRP; Supplementary Figure 2, http://links.lww.com/MD/F398). With a cut-off of 0.5 mg/dL of CRP, the sensitivity and specificity for predicting overall mortality was 0.89 and 0.61, respectively.

3.2. Validation study

3.2.1. Patients. A total of 434 patients were enrolled in the validation study. Male patients comprised 71.4% (n=310). The mean age was 66.4±14.5 and 70% of them were over 60 years old. The endoscopic findings and other factors were similar with the derivation study, including the initial vital signs, past histories and the proportion of bleeding causes. There were no differences between survived and expired group in gender, past history of upper GI bleeding, symptoms, comorbidity (except malignancy), medication history (except anti-platelets), diastolic pressure, lab findings (except serum CRP), and cause of bleeding (except UGI malignancy). Patient characteristics and endoscopic findings were shown in Supplementary Table 1, http://links.lww.com/MD/F395.

Within 30 days from the initial UGIB event, 35 patients (7.8%) expired in a total of 434 patients with non-variceal UGIB. Among them, 6 (17.1%) expired due to non-variceal UGIB. Rebleeding within 7 days from the initial event was observed in 9.0% (n= 39). The frequency of rebleeding was higher in the expired than in the survived group in the validation set (17.1% vs 8.3%, $P=.147$).

3.2.2. Relationship between serum CRP concentration and 30-day mortality. The initial level of serum CRP was significantly higher in the expired group than and in the survived group (6.3 vs 0.5, $P<.001$; Supplementary Figure 3A, http://links.lww.com/MD/F399), which was also observed in the disease-specific expired group compared to the survived group (3.2 vs 0.6, $P<.001$; Supplementary Figure 3B, http://links.lww.com/MD/F399).

The 30-day overall mortality and disease-specific mortality increased in correspondence with the elevation of serum CRP level in patients with non-variceal UGIB. When the initial level of serum CRP was divided into 4 groups, the overall and disease-specific mortality rate increased as the initial level of serum CRP was elevated (Supplementary Figure 4A and 4B, http://links.lww.com/MD/F400, respectively; both P for trend $<.01$).

When we put serum CRP and each of well-known prognostic scores (ie, Glasgow-Blatchford, AIMS 65, Rockall score) together in the regression model, high serum CRP was independently associated with 30-day mortality rate in patients with acute non-variceal upper GI bleeding (Supplementary Table 2, http://links.lww.com/MD/F396).

3.2.3. Predictability of serum CRP for 30-day mortality in non-variceal UGIB. In the validation study, the AUROC of serum CRP at bleeding was 0.79 for 30-day mortality, which was not significantly different from that of the Rockall score (0.77, $P=.549$; supplementary Figure 5, http://links.lww.com/MD/F401). However, the AUROC of AIMS65 and GBS was significantly lower than that of serum CRP (0.65, and 0.61, respectively; both $P<.01$; supplementary Figure 5, http://links.lww.com/MD/F401).

4. Discussion

In this study, we assessed the predictability of patient mortality with serum CRP at bleeding. Serum CRP was an independent risk factor for high mortality after acute non-variceal UGIB. The

mortality predictability of serum CRP was validated in 2 ways: discriminant validity from the comparisons with well-validated scoring systems and reproducibility from the prospective cohorts. High serum CRP level was significantly higher in the expired than in the survived group. This single factor could predict the patient mortality after acute non-variceal UGIB with accuracy not inferior to that of other prognostic scoring systems. Furthermore, the mortality predictability of serum CRP was prospectively validated in the following cohort study.

In the derivation study, patients with acute non-variceal UGIB presented 6.6% overall mortality and 1.9% disease-specific mortality within 30 days after index bleeding. Mortality was increased in patients with old age, hematochezia, presence of major comorbidity, hypotension, tachycardia, anemia, presence of upper GI malignancies in the initial assessment, and episode of rebleeding after admission. On the other hand, melena and antiplatelet use was associated with a favorable outcome. These factors were consistent with previous reports.[13,27–29] However, we have newly found that high serum CRP level was significantly associated with overall and bleeding related mortality in the multivariate analysis.

While the incidence UGIB has been declining, mortality rate after UGIB has been maintained at approximately around 10%.[11,30,31] Several studies reported scoring systems as a way to predict the mortality of UGIB, which were large scale, multicenter studies and have undergone thorough validation processes. However, some scoring systems require endoscopic findings or more than 4 variables, or involve complex calculation.[13–16] As such, they are not always readily applicable with ease in clinical practice, especially in emergent circumstances. Therefore, a single simple factor can be very useful, but it should have a high predictability. A recent study reported that an increase in blood urea nitrogen at 24 hour compared to the initial level can be a solitary and significant predictor of increased mortality in patients with acute non-variceal UGIB.[32]

In our previous study, we have shown that initial serum CRP concentration has a significant association with rebleeding in patients with non-variceal UGIB.[23] Because rebleeding is 1 of the major prognostic factors in non-variceal UGIB patients,[33] we evaluated the association between initial serum CRP level and mortality, the most important outcome of the patient, in the present study. Furthermore, initial serum CRP level could predict the 30-day mortality with an AUROC of greater than 0.7 after non-variceal UGIB. These results showed that the simple measurement of serum CRP level can be used as a marker to predict patient mortality after non-variceal UGIB.

CRP is a widely used nonspecific marker of inflammation. Inflammation causes the release of cytokines such as interleukin-6, interleukin-1, tumor necrosis factor-alpha, which stimulate the synthesis and release of acute phase reactants like CRP in the liver.[18,19,21,22] CRP comprises the physiologic and biochemical response to most forms of tissue damage, infection, inflammation, and malignant neoplasia. Because these processes are nonspecific, many clinicians have not adopted the use of CRP as a diagnostic test in clinical medicine [18,19]. Acute phase proteins including CRP can be elevated in response to many mucosal or submucosal inflammatory cells by gastric mucosal injury.[34] In an animal study, increased levels of many cytokines were observed in the serum as well as in the damaged mucosal site after post-hemorrhage mucosal injuries,[35] which could generate acute phase reactants such as CRP, ferritin, fibrinogen. In GI diseases, serum CRP was reported to predict complications after

percutaneous endoscopic gastrostomy or mortality in cirrhotic patients.[36,37] There were previous studies that reported the association between CRP and UGIB. One small sample sized study reported that the combination of elevated CRP could predict the mortality of UGIB patients in univariate analysis, but it was not evaluated in multivariate analysis.[38] Another study reported the predictive degree of mortality by CRP/albumin ratio in 300 admitted patients, which turned out to be predictive only in the elderly.[39] Another small sample sized study reported that a decrease in hemoglobin level or an increase in CRP concentration within 3 months strongly predicted mortality in acute UGIB patients.[40] In the present study, these major comorbidities were found in 39.7% of the overall population and 65.4% of expired group, with an odds ratio of 3 in multivariate analysis. This could explain why CRP has a significant association with mortality in this study.

There are some limitations in the present study. First, the data of the derivation study were collected prospectively, but the analysis and data review were performed retrospectively. However, we performed a prospective validation study. Second, the present study did not have full information for the infection of *Helicobacter pylori*, although this organism is known as 1 of major risk factors of peptic ulcer bleeding.[4] Furthermore, the test method for *Helicobacter pylori* was not uniformly performed. Third, this study was performed in a single center. Therefore, generalizability should be confirmed in future studies. Fourth, this study did not investigate other acute phase reactants such as ferritin, haptoglobin, or fibrinogen, which would not fully address the precise action mechanism of serum CRP. There are many factors that elevate CRP. In order to strongly suggest a prognostic factor more detailed study is needed. Finally, even though CRP predicted patient mortality after UBIB in the setting of critically-ill patient, we could not collect data about infectious events because of the retrospective nature of the present study.

In conclusion, high level of serum CRP at bleeding was an independent poor prognostic risk factor and associated with an increased mortality in patients with non-variceal UGIB. This simple evaluation can be used as a marker for prediction of patient mortality after non-variceal UGIB, and also as a triage tool for the assignment of disease severity to decide the order of treatment in non-variceal UGIB patients.

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