

Change ratio of hemoglobin has predictive value for upper gastrointestinal bleeding

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Abstract. The present study aimed to identify novel predictors of upper gastrointestinal (GI) bleeding by assessing change ratios of blood test variables. Records of 1,023 patients (431 men and 592 women) who underwent endoscopy between October 2014 and September 2015 at the National Hospital Organization Shimoshizu Hospital (Yotsukaido, Japan) were retrospectively analyzed. Patients whose blood test variables for the time-point of endoscopy and three months previously were available were enrolled and subsequently categorized into a group with and another one without upper GI bleeding (n=32 and 84, respectively), and the respective change ratios were calculated for each group. One-way analysis of variance revealed that in patients with upper GI bleeding, change ratios of white blood cell count and alkaline phosphatase were significantly higher than those in patients without, while change ratios of hemoglobin (Hb), total protein and albumin were significantly reduced. Logistic regression analysis demonstrated that the change ratio of Hb was significantly correlated with upper GI bleeding. Receiver-operator characteristic analysis revealed that an 18.7% reduction of Hb was the threshold value for the prediction of upper GI bleeding. In conclusion, the present study revealed that a $\geq 18.7\%$ reduction in Hb over three months has predictive value for upper GI bleeding.

Introduction

Upper gastrointestinal (GI) bleeding occurs proximal to the Treitz ligament and may be caused by gastric or duodenal ulcers or gastric cancer (1). The mortality rate of patients with

upper GI bleeding ranges from 3.5 to 7.4% (2,3). Upper GI bleeding is diagnosed by endoscopy (4). Upper GI bleeding is treated with endoscopy, such as clipping and bipolar electrocoagulation (4). However, for patients for whom endoscopic treatment fails, interventional radiology is applied (5,6). The mortality rate rises to 40% when patients become hemodynamically unstable (7); therefore, it is important to predict upper GI bleeding prior to this.

The Glasgow-Blatchford Scores, Modified Early Warning Score and Pre-endoscopic Rockall scores are useful for stratification of patients with regard to unstable state, requirement of transfusion and hospitalization (8,9). These scoring systems are useful for triage and management of upper GI bleeding (10). Analyses of data from emergency departments or intensive care units identified malignancy, hypotension on admission, low Glasgow coma scale and kidney dysfunction as predictors of poor outcome (11). It would be beneficial to diagnose upper GI bleeding in patients prior to presentation at the emergency department. Moreover, certain patients with upper GI bleeding do not exhibit any symptoms (12). Therefore, it is desirable to diagnose upper GI bleeding prior to the advancement of affected patients to the unstable state.

As blood test variables are easy to obtain and reliable, the present study investigated the predictive value of their changes with regard to upper GI bleeding. The change ratios of blood test variables at the time-point of endoscopy and 3 months previously were evaluated.

Materials and methods

Ethics statement. The Ethics Committee of the National Hospital Organization Shimoshizu Hospital approved the present study, which was not assigned as a clinical trial because it was based on daily clinical practice. Patient records were anonymized and retrospectively analyzed. Written informed consent was obtained from all patients who were subjected to endoscopy.

Patients. Between October 2014 and September 2015, a total of 1,023 patients were subjected to endoscopy at the National Hospital Organization Shimoshizu Hospital (Yotsukaido, Japan). Endoscopy was indicated due to anemia, tarry stool or abdominal pain, or was performed for screening

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Table I. Indications for assessment of upper GI bleeding by endoscopy.

Symptom	All patients (n)	Patients with bleeding/ no bleeding, n (%)
Anemia	9	5/4 (15.6/4.8)
Hematemesis	5	4/1 (12.5/1.2)
Tarry stool	8	7/1 (21.9/1.2)
Others ^a	94	16/78 (50/92.8)
Total	116	32/84 (100/100)

Bleeding was diagnosed by endoscopy and in positive patients, colonoscopy was performed within one month after endoscopy. ^aIncluded patients undergoing screening (n=47, 49.5%).

Table II. Causes of upper gastrointestinal bleeding.

Cause	No. of patients
Gastric ulcer	17
Gastric cancer	4
Hemorrhagic gastritis	4
Reflux esophagitis	3
Duodenal ulcer	2
Acute gastric mucosal lesion	1
Esophageal varices	1
Total	32

purposes (Table I). From these subjects, patients whose blood test variables at the time-point of endoscopy and three months previously were available were enrolled in the present study. For these patients, change ratios of blood test variables between these two time-points were evaluated. The group with upper GI bleeding (n=32) comprised 15 males and 17 females (mean age, 69.3±12.9), while the group without upper GI bleeding (n=84) comprised 37 males and 47 females (mean age, 69.0±13.9). At three months prior to endoscopy, the presence of upper GI bleeding was not known for any of the patients. Colonoscopy was not performed for patients who were negative for bleeding on endoscopy.

Endoscopy. The devices GIF-N260H, GIF-XP260NS, GIF-PfG260, GIF-XQ260 and GIF-Q260 (Olympus, Tokyo, Japan) were used for endoscopy. Bleeding from a gastric or duodenal ulcer was restricted to a spurting vessel, an oozing vessel, a visible vessel or a clot, according to the Forrest classification system (13). In Table II the diagnoses of the patients are listed.

Blood test variables. The following blood test variables were analyzed: White blood cell count (WBC), hemoglobin (Hb), platelet count, C-reactive protein, total protein (TP), albumin (Alb), alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase (ALT), gamma-glutamyl transpeptidase, lactate dehydrogenase, uric acid, blood urea nitrogen (BUN),

Table III. Comparison of change ratios of blood test variables between patients with and without upper gastrointestinal bleeding.

Characteristic/parameter	Upper gastrointestinal bleeding		P-value
	(-)	(+)	
Gender (male/female), n	37/47	15/17	
Mean age, years	69.0±13.9	69.3±12.9	0.983
WBC	1.02±0.29	1.23±0.64	0.050
Hb	0.97±0.15	0.75±0.23	<0.001
Plt	2.69±12.8	1.32±0.52	0.663
CRP	2.62±3.69	15.5±5.95	0.074
TP	0.99±0.10	0.84±0.16	<0.001
Alb	0.97±0.12	0.81±0.21	0.010
ALP	1.02±0.20	0.74±0.19	0.006
AST	1.13±0.68	1.74±1.92	0.056
ALT	1.14±0.51	1.94±2.72	0.037
γ-GTP	1.20±0.73	2.55±4.25	0.134
LDH	1.02±0.43	1.01±0.35	0.946
UA	0.98±0.13	1.04±0.37	0.420
BUN	0.96±0.33	1.02±0.73	0.739
TG	0.94±0.50	1.61±1.00	0.051
HDL	1.08±0.46	0.90±0.12	0.443
LDL	1.02±0.32	0.93±0.22	0.519
BG	0.92±0.17	1.40±1.12	0.056
HbA1c	0.94±0.11	1.03±0.11	0.345

WBC, white blood cell count; Hb, hemoglobin; Plt, platelets; CRP, C-reactive protein; TP, total protein; Alb, albumin; ALP, alkaline phosphatase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP, γ-glutamyl transpeptidase; LDH, lactate dehydrogenase; UA, uric acid; BUN, blood urea nitrogen; TG, triglyceride; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; BG, blood glucose; HbA1c, hemoglobin A1c.

Table IV. Results of the logistic regression analysis.

Parameter	Odds ratio	P-value
WBC	1.056xe8	0.999
Hb	8.13xe23	0.017
TP	7.74xe-14	0.999
Alb	4.36xe9	0.999
ALP	9.77xe-11	0.999

e, Napier's constant of natural logarithm (2.71828); WBC, white blood cell count; Hb, hemoglobin; TP, total protein; Alb, albumin; ALP, alkaline phosphatase.

triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, blood glucose and hemoglobin A1c. Change ratios were calculated using the following equation:

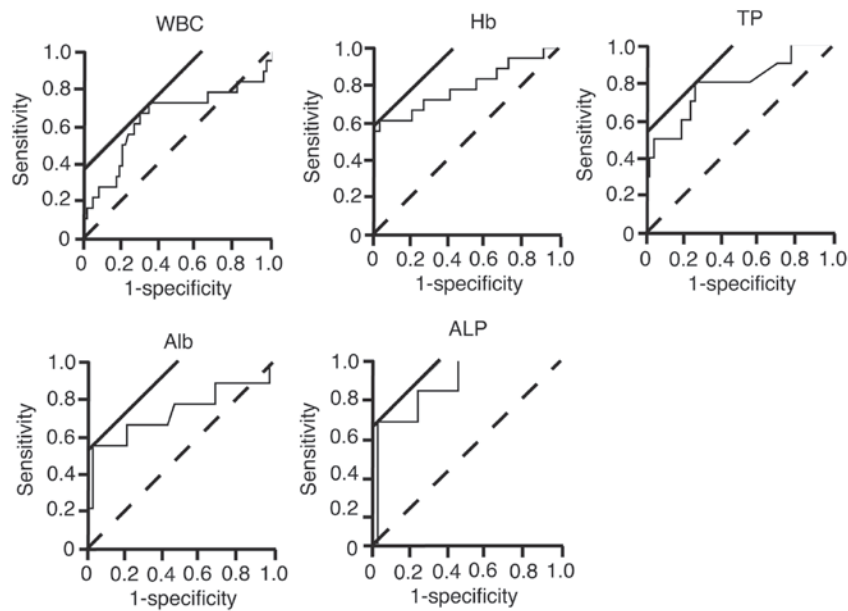


Figure 1. Receiver-operator characteristic analysis was performed to determine a threshold value for the prediction of upper gastrointestinal bleeding using the change ratio of WBC, Hb, TP, Alb and ALP. Threshold values were determined as values that was in contact with the line with an increment of 45° (solid straight line) and had the greatest distance from the reference line (broken line). WBC, white blood cell count; Hb, hemoglobin; TP, total protein; Alb, albumin; ALP, alkaline phosphatase.

(result at 3 months prior to endoscopy - result on the date of endoscopy)/result at 3 months prior to endoscopy.

Statistical analysis. One-way analysis of variance was applied to compare change ratios between patients with and without upper GI bleeding. Logistic regression analysis was applied to identify blood test variables whose change ratios were significantly associated with upper GI bleeding. Receiver-operator characteristic (ROC) analysis was used to determine threshold values for the prediction of upper GI bleeding. $P < 0.05$ was considered to indicate a statistically significant difference. JMP 10.0.2 (SAS Institute, Inc., Cary, NC, USA) was used to perform statistical analyses.

Results

To identify blood test parameters whose changes were significantly associated with upper GI bleeding, change ratios were compared between patients without or with upper GI bleeding using one-way analysis of variance (Table III). The change ratios of WBC ($P = 0.05$) and ALT ($P = 0.037$) in patients with upper GI bleeding were higher than in patients without bleeding. Furthermore, the change ratios of Hb ($P < 0.001$), TP ($P < 0.001$) and Alb ($P = 0.01$) in patients with upper GI bleeding were lower than in those without bleeding. These results suggested that the change ratios of WBC, Hb, TP, Alb and ALT were significantly associated with upper GI bleeding.

Logistic regression analysis was performed to identify blood test variables with change ratios that were strongly associated with upper GI bleeding (Table IV). The change ratio of Hb was determined to be significantly associated with upper GI bleeding ($P = 0.017$); whereas no significant correlation was identified for the change ratios of the remaining blood test variables with P -values close to 1. These results suggested that the change ratio of Hb was significantly correlated with upper GI bleeding.

Table V. Variables with receiver-operator characteristics.

Parameter	Area under curve	Threshold value	Sensitivity (%)	Specificity (%)
WBC	0.634	1.047	72.2	64.6
Hb	0.780	0.813	61.1	95.4
TP	0.780	0.952	80.0	73.2
Alb	0.732	0.771	55.6	96.6
ALP	0.854	0.759	66.7	95.8

Values are stated as change ratios. WBC, white blood cell count; Hb, hemoglobin; TP, total protein; Alb, albumin; ALP, alkaline phosphatase.

ROC analysis was performed to determine the threshold values of change ratios for the prediction of upper GI bleeding (Fig. 1). A threshold value was determined as a value that was in contact with the line with an increment of 45° (Fig. 1, solid straight line) and had the greatest distance from the reference line (Fig. 1, broken line). Variables obtained via ROC analysis are presented in Table V. The threshold value of the change ratio of Hb was 0.813, which was converted into the threshold of the change rate using the following formula: $(1.000 - 0.813) \times 100\% = 18.7\%$. Therefore, a 18.7% reduction of Hb over three months was the threshold value for the prediction of upper GI bleeding.

Discussion

To date, only a limited number of studies have assessed the association of change ratios of blood test variables with upper GI bleeding. It has been previously demonstrated that

the change ratio of the Model for End-Stage Liver Disease score is useful for the prediction of bleeding from esophageal varices (14); however, this model is applicable to patients with liver cirrhosis only and was therefore not used in the present study.

Decreased Hb has been previously reported to be associated with upper GI bleeding (15). However, a limitation with regard to evaluation of Hb is that results differ between first-time and repeated sampling (16). Hb below the normal range indicates upper GI bleeding. The present study further assessed the predictive value of the change ratio of blood parameters with regard to upper GI bleeding. In a previous study by our group, a 21.3% reduction of Hb within 3 months was determined to be the threshold value for the prediction of upper GI bleeding (17). In line with this, an 18.7% reduction was determined to be the threshold value for the prediction of upper GI bleeding in the present study. Although the patient cohorts were totally different between the two studies, the threshold was ~20% in each, suggesting that a change ratio of Hb of ~20% or above is of predictive value regarding upper GI bleeding.

A limitation of the present study was the difficulty in differentiating between upper and lower GI bleeding, which may have affected the assessment of the association of the change ratio of Hb with upper GI bleeding (18). To differentiate between upper and lower GI bleeding, an elevated BUN value may be useful (19), as higher BUN indicates severe upper GI bleeding (20). In the present study, BUN was not significantly different between patients with or without upper GI bleeding. This result may suggest that upper GI bleeding was not very severe in the patients.

In conclusion, an 18.7% reduction of Hb over three months was shown to be associated with upper GI bleeding in the present study. These findings suggested that patients with this change ratio of Hb are at risk of upper GI bleeding. It is recommended that patients are subjected to endoscopic examination if presenting with symptoms of upper GI bleeding and Hb levels lowered by $\geq 20\%$.

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