

## Retrospective Study

# Patient characteristics with high or low blood urea nitrogen in upper gastrointestinal bleeding

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## Abstract

**AIM:** To examine characteristics of patients with blood urea nitrogen (BUN) levels higher and lower than the normal limit.

**METHODS:** Patient records between April 2011 and March 2014 were analyzed retrospectively. During this time, 3296 patients underwent upper endoscopy. In total, 50 male ( $69.2 \pm 13.2$  years) and 26 female ( $72.3 \pm 10.2$  years) patients were assessed. Patients were divided into two groups based on BUN levels: higher than the normal limit (21.0 mg/dL) (H) and lower than

the normal limit (L). One-way analysis of variance was performed to reveal differences in the variables between the H and L groups. Fisher's exact test was used to compare the percentage of patients with gastric ulcer or gastric cancer in the H and L groups.

**RESULTS:** White blood cell count was higher in the H group than in the L group ( $P = 0.0047$ ). Hemoglobin level was lower in the H group than in the L group ( $P = 0.0307$ ). Glycated hemoglobin was higher in the H group than in the L group ( $P = 0.0264$ ). The percentage of patients with gastric ulcer was higher in the H group ( $P = 0.0002$ ). The H group contained no patients with gastric cancer.

**CONCLUSION:** Patients with BUN  $\geq 21$  mg/dL might have more severe upper gastrointestinal bleeding.

**Key words:** Blood urea nitrogen; Forrest classification; Hemoglobin; White blood cell count

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**Core tip:** Blood urea nitrogen (BUN) is a useful predictor of upper gastrointestinal (GI) bleeding. However, BUN is within the normal range in some patients with upper GI bleeding. Patient records were analyzed retrospectively. Patients were divided into two groups: higher than the normal limit (21.0 mg/dL) (H) and lower than the normal limit (L). White blood cell count was higher and hemoglobin was lower in the H group. Higher BUN was associated with severe upper GI bleeding. The H group suggested more severe upper GI bleeding.

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## INTRODUCTION

Upper gastrointestinal (GI) bleeding is defined as bleeding that occurs proximal to the ligament of Treitz. Causes of upper GI bleeding include gastric ulcers, duodenal ulcers, and gastric cancer<sup>[1]</sup>. The mortality rate of upper GI bleeding ranges from 3.5% to 7.4%<sup>[2,3]</sup>. Upper GI bleeding is diagnosed with endoscopy, and treated using methods such as clipping and bipolar electrocoagulation<sup>[4]</sup>. When patients do not respond to these therapies, arteriography with embolization is performed<sup>[5,6]</sup>. Although treatment methods have improved, the mortality rate is 40% for patients with GI bleeding who are hemodynamically unstable<sup>[7]</sup>. Accurate diagnosis of upper or lower

GI bleeding is important because early endoscopy significantly reduces mortality rates<sup>[8]</sup>. Blood testing is recommended before upper GI endoscopy or colonoscopy is performed because of the low cost and minimal risks of complications<sup>[9]</sup>.

Blood urea nitrogen (BUN) is a measure of the amount of urea nitrogen in the blood<sup>[10]</sup>. BUN represents the terminal products of protein metabolism *via* ammonia<sup>[11]</sup>. When upper GI bleeding occurs, the blood is digested to protein<sup>[12]</sup>. This protein is transported to the liver *via* the portal vein, and metabolized to BUN in the urea cycle<sup>[13]</sup>. Higher BUN values are therefore associated with the digestion of blood<sup>[14]</sup>. Mean BUN is  $37.7 \pm 26.4$  g/mL in patients with upper GI bleeding who need blood transfusion and admission to intensive care<sup>[15]</sup>. BUN is not as useful as reduced hemoglobin (Hb) level for predicting upper GI bleeding<sup>[16]</sup>.

In this study, we compared the characteristics of patients with upper GI bleeding and BUN higher or lower than the upper normal limit to determine the reason for the difference between the two groups.

## MATERIALS AND METHODS

### Patients

Patient records between April 2011 and March 2014 were analyzed retrospectively. Patients were divided into two groups: those with BUN higher than the normal limit (21.0 mg/dL) (H), and those with BUN lower than the normal limit (L). Gastric or duodenal ulcer bleeding was defined as coming from either a spurting vessel (1a), an oozing vessel (1b), a visible vessel (2a), or a clot (2b) according to the Forrest classification system<sup>[17]</sup>. Our study was reviewed by our institutional Ethics Committee and was not designated as a clinical trial because it was performed as part of routine clinical practice. Patient anonymity was maintained.

### Upper GI endoscopy and colonoscopy

Patients received an upper GI endoscopic examination for screening, examination of abdominal symptoms, or anemia. The endoscopic devices used were the GIF-N260H, GIF-XP260NS, GIF-PG260, GIF-XQ260, and GIF-Q260 (Olympus Corp., Tokyo, Japan).

### Blood test variables

The blood test variables analyzed were white blood cell (WBC) count, Hb, C-reactive protein, platelet, total protein, albumin, total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transpeptidase, lactate dehydrogenase, uric acid, BUN, creatinine (Cre), total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, blood glucose, glycated Hb (HbA1c), body mass index, carcinoembryonic antigen, and carbohydrate antigen 19-9.

**Table 1** Causes of upper gastrointestinal bleeding in this study

Cause	Total (n)	BUN analyzed (n)
Gastric ulcer	31	29
Gastric cancer	28	18
Duodenal ulcer	7	3
Acute gastric mucosal lesion	4	1
Esophageal ulcer	2	1
Esophageal varix	2	2
Esophagitis	1	1
Gastric invasion of pancreatic cancer	1	1
Total	76	56

BUN: Blood urea nitrogen.

**Table 2** Comparison of variables between patients with blood urea nitrogen higher and lower than 21.0 mg/dL

Variable	No. of patients	H group (n = 20)	L group (n = 36)	P value
Age (yr)	56	69.7 ± 17.3	71.1 ± 9.4	0.7040
WBC (10 <sup>3</sup> /μL)	56	9575 ± 5088	6700 ± 2187	0.0047
Hb (g/dL)	56	8.64 ± 3.47	10.6 ± 3.09	0.0307
CRP (mg/dL)	39	1.66 ± 2.03	0.99 ± 0.85	0.1557
Plt (10 <sup>4</sup> /μL)	54	23.1 ± 8.4	29.4 ± 12.8	0.0629
TP (g/dL)	35	5.70 ± 0.98	6.20 ± 0.68	0.0874
Alb (g/dL)	36	3.32 ± 0.69	3.53 ± 0.62	0.3546
T-Bil (mg/dL)	44	0.62 ± 0.40	0.71 ± 0.63	0.6461
ALP (IU/L)	32	178 ± 53	260 ± 159	0.1449
AST (IU/L)	51	23.7 ± 12.0	27.1 ± 25.3	0.6062
ALT (IU/L)	53	25.9 ± 26.0	18.0 ± 14.9	0.1654
γ-GTP (IU/L)	29	22.6 ± 14.3	82.8 ± 107	0.2031
LDH (IU/L)	15	42.7 ± 6.6	46.0 ± 10.8	0.6261
UA (mg/dL)	24	5.84 ± 2.47	5.00 ± 1.93	0.3638
BUN (mg/dL)	56	36.3 ± 17.3	12.3 ± 3.8	< 0.0001
Cre (mg/dL)	56	1.09 ± 0.37	0.83 ± 0.32	0.0086
BUN/Cre	56	35.0 ± 13.2	16.1 ± 6.3	< 0.0001
T-Chol (mg/dL)	21	143 ± 37	145 ± 47	0.9102
TG (mg/dL)	16	98 ± 68	101 ± 48	0.9408
HDL (mg/dL)	15	42.7 ± 6.6	46.0 ± 10.8	0.6261
LDL (mg/dL)	14	72.7 ± 38.4	95.5 ± 30.5	0.2954
BG (mg/dL)	32	164 ± 92	121 ± 34	0.0622
HbA1c (%)	21	6.31 ± 1.04	5.54 ± 0.46	0.0264

H group: Patients with BUN > 21.0 mg/dL; L group: Patients with BUN < 21.0 mg/dL; WBC: White blood cell count; Hb: Hemoglobin; CRP: C-reactive protein; Plt: Platelet; TP: Total protein; Alb: Albumin; T-Bil: Total bilirubin; ALP: Alkaline phosphatase; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; γ-GTP: Gamma-glutamyl transpeptidase; LDH: Lactate dehydrogenase; UA: Uric acid; BUN: Blood urea nitrogen; Cre: Creatinine; T-Chol: Total cholesterol; TG: Triglyceride; HDL: High-density lipoprotein cholesterol; LDL: Low-density lipoprotein cholesterol; BG: Blood glucose; HbA1c: Glycated hemoglobin.

### Statistical analysis

One-way analysis of variance was performed to reveal differences in the variables between the H and L groups, and between patients for whom BUN was examined and those for whom it was not. Logistic regression analysis was performed to reveal variables that were significantly associated with the difference between the H and L groups. Fisher's exact test was used to compare the percentage of patients with

**Table 3** Comparison of variables between patients examined for blood urea nitrogen or not

Variable	No. of patients	BUN examined group (n = 56)	BUN not examined group (n = 20)	P value
Age (yr)	76	70.6 ± 1.7	69.9 ± 2.8	0.8353
WBC (10 <sup>3</sup> /μL)	68	7726 ± 3731	6266 ± 1624	0.1905
Hb (g/dL)	68	9.92 ± 3.34	10.8 ± 2.39	0.3817
CRP (mg/dL)	46	1.22 ± 1.40	2.21 ± 1.66	0.1024
Plt (10 <sup>4</sup> /μL)	65	27.2 ± 11.8	27.9 ± 8.1	0.8639
TP (g/dL)	43	5.96 ± 0.86	6.44 ± 0.69	0.1513
Alb (g/dL)	38	3.48 ± 0.64	2.95 ± 0.64	0.2851
T-Bil (mg/dL)	46	0.68 ± 0.58	0.87 ± 0.11	0.6543
ALP (IU/L)	34	236 ± 142	232 ± 89	0.9649
AST (IU/L)	58	26.1 ± 21.9	19.6 ± 3.8	0.4409
ALT (IU/L)	62	20.7 ± 19.5	17.6 ± 6.46	0.6379
γ-GTP (IU/L)	33	59.0 ± 93.8	37.0 ± 16.8	0.6477
LDH (IU/L)	45	187 ± 55	195 ± 36	0.7244
UA (mg/dL)	29	5.32 ± 2.13	5.00 ± 0.77	0.7459
Cre (mg/dL)	64	0.92 ± 0.36	0.94 ± 0.28	0.9148
T-Chol (mg/dL)	28	144 ± 41	202 ± 31	0.0018
BG (mg/dL)	36	134 ± 61	117 ± 8	0.5669

WBC: White blood cell count; Hb: Hemoglobin; CRP: C-reactive protein; Plt: Platelet; TP: Total protein; Alb: Albumin; T-Bil: Total bilirubin; ALP: Alkaline phosphatase; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; γ-GTP: Gamma-glutamyl transpeptidase; LDH: Lactate dehydrogenase; UA: Uric acid; Cre: Creatinine; T-Chol: Total cholesterol; BG: Blood glucose.

gastric ulcer or gastric cancer in the H and L groups. Pearson's  $\chi^2$  test was applied to assess the correlation in percentage of different Forrest classifications in the H and L groups. A  $P < 0.05$  indicated statistical significance. JMP 10.0.2 software (SAS Institute, Cary, NC, United States) was used for all statistical analyses.

## RESULTS

During this time, 3296 patients underwent upper GI endoscopy. In total, 50 male (69.2 ± 13.2 years) and 26 female (72.3 ± 10.2 years) patients were identified with upper GI bleeding. The etiologies of upper GI bleeding in these patients are listed in Table 1. Patient characteristics were compared to determine the variables affecting the differences between the H and L groups (Table 2). WBC was higher in the H group than in the L group ( $P < 0.05$ ). Hb level was lower in the H group than in the L group ( $P < 0.05$ ). BUN and BUN/Cre ratio were both higher in the H group than in the L group ( $P < 0.05$ ). These results were expected because the two groups were divided based on BUN. Cre was higher in the H group than in the L group ( $P < 0.05$ ). HbA1c was higher in the H group than in the L group ( $P < 0.05$ ). The lower Hb level in the H group suggested that the H group contained patients with more severe bleeding. One major difference between the H group and the L group was the cause of the upper GI bleeding. The H group had no patients with gastric cancer.

There might be biases regarding the physicians' decisions to examine BUN. To analyze the potential

**Table 4 Results of logistic regression analysis**

Variable	$\chi^2$	Odds	P value
WBC	0.10	0.999918	0.7471
Hb	6.36	0.545371	0.0116
Cre	3.31	489.6214	0.0688
HbA1c	4.73	13.58043	0.0296

WBC: White blood cell count; Hb: Hemoglobin; Cre: Creatinine; HbA1c: Glycated hemoglobin.

**Table 5 Association of blood urea nitrogen and gastric ulcer or cancer**

Group	Gastric ulcer	Gastric cancer	Total
BUN <sup>1</sup> (mg/dL) $\geq$ 21.0	15	0	15
BUN <sup>1</sup> (mg/dL) < 21.0	14	18	32
Total	29	18	47

<sup>1</sup>P = 0.0002 between groups *via* Fisher's exact probability test. BUN: Blood urea nitrogen.

biases, patient characteristics were compared between patients with upper GI bleeding ( $n = 76$ ) for whom BUN was or was not examined (Table 3). All the variables showed no significant difference except total cholesterol ( $P < 0.05$ ).

To clarify the strength of the association between the H and L groups in the blood test parameters, logistic regression analysis was performed (Table 4). Hb had the largest  $\chi^2$  value and the smallest  $P$  value ( $P < 0.05$ ).

Most of the enrolled patients had gastric cancer or gastric ulcers. The percentage of patients with gastric cancer or gastric ulcer was compared between the H and L groups (Table 5). There were no patients with gastric cancer in the H group.

The association between different Forrest classifications and the two groups was intriguing. A  $\chi^2$  test was performed to reveal the association (Table 6), and no statistically significant relationship was found.

## DISCUSSION

Higher BUN is associated with upper GI bleeding<sup>[18]</sup>. Lower Hb level is associated with the severity of upper GI bleeding<sup>[16]</sup>. It is speculated that higher BUN has a strong association with lower Hb, however, there is no direct evidence for this. In the present study, the Hb level was lower in the H group than in the L group. Logistic regression analysis clearly showed that the strongest association was between higher BUN and lower Hb. These results indicate that bleeding was more severe in the H group than the L group. It was speculated that larger amounts of Hb in the digestive tract are the source of higher BUN in blood. This hypothesis was supported by the fact that ammonia is liberated from Hb in the digestive tract<sup>[19]</sup>.

Elevated WBC is associated with the severity and

**Table 6 Association of blood urea nitrogen and Forrest classification**

Group	1b	2a	2b	Total
BUN <sup>1</sup> (mg/dL) $\geq$ 21.0	5	7	3	15
BUN <sup>1</sup> (mg/dL) < 21.0	4	5	5	14
Total	9	12	8	29

<sup>1</sup>P = 0.6322 between groups *via*  $\chi^2$  test. BUN: Blood urea nitrogen.

mortality rate of upper GI bleeding<sup>[20]</sup>. Patients with a WBC > 12000/ $\mu$ L need urgent upper GI endoscopy<sup>[21]</sup>. In the present study, WBC was higher in the H group than in the L group. One reason for elevated WBC is inflammation<sup>[22]</sup>. Gastric ulceration is a form of inflammation similar to inflammatory bowel disease<sup>[23]</sup>. Elevation of WBC was, therefore, associated with the severity of upper GI bleeding. Our results and the previous reports support the hypothesis that higher BUN is associated with the severity of upper GI bleeding.

A BUN/Cre ratio > 30 is a useful metric by which to diagnose upper GI bleeding<sup>[24]</sup>. The association between elevated BUN/Cre and upper GI bleeding has previously been made clear with Tc-99m-labeled red blood cells<sup>[25]</sup>. On the other hand, Chalasani *et al.*<sup>[26]</sup> reported that BUN/Cre is not always reliable for diagnosing upper GI bleeding. They speculated that BUN/Cre does not increase without hematemesis. Akimoto *et al.*<sup>[27]</sup> added that BUN/Cre is elevated due to reduced hydration. In some cases, elevated BUN is indeed a consequence of upper GI bleeding and hypovolemia<sup>[14]</sup>. In the present study, BUN and BUN/Cre were strongly correlated. Together, these data suggest that BUN might be within the normal range in some patients with upper GI bleeding.

One limitation of the present study is that it included a limited number of patients with more severe bleeding, such as the spurting type. Although without statistical significance, 1b and 2a were more frequent in the H group than in the L group. With more patients, there is the possibility Forrest classification might correlate with BUN.

Another limitation is that the study was retrospective. Determination of choice of blood variables depended upon the physicians. This was the reason that some data of blood variables were missing. There might be a selection bias in patient characteristics between those with BUN and those without BUN, although Table 3 did not show significant statistical significance.

In conclusion, patients with BUN  $\geq$  21 mg/dL might have more severe upper GI bleeding. It is recommended that severe upper GI bleeding be considered when BUN is higher than 21.0 mg/dL.

## COMMENTS

### Background

Upper gastrointestinal (GI) bleeding is defined as bleeding that occurs



proximal to the ligament of Treitz. Causes of upper GI bleeding include gastric ulcers, duodenal ulcers, and gastric cancer. Although treatment methods have improved, the mortality rate is 40% for patients with GI bleeding who are hemodynamically unstable. Accurate diagnosis of upper GI bleeding is important because early endoscopy significantly reduces mortality rates. Blood testing is recommended before upper GI endoscopy or colonoscopy is performed because of the low cost and minimal risks of complications.

### Research frontiers

Blood urea nitrogen (BUN) represents the terminal products of protein metabolism *via* ammonia. When upper GI bleeding occurs, the blood is digested to protein metabolized to BUN in the urea cycle within the liver. Higher BUN values are therefore associated with the digestion of blood. Mean BUN is  $37.7 \pm 26.4$  g/mL in patients with upper GI bleeding who need blood transfusion and admission to intensive care. Lower hemoglobin (Hb) is associated with GI bleeding. Direct association between Hb and BUN has not been clear in upper GI bleeding.

### Innovations and breakthroughs

Patients were divided into two groups: the H group with BUN > 21.0 mg/dL, and the L group with BUN < 21.0 mg/dL. Patient characteristics were compared between the H group and the L group. White blood cell count was higher in the H group. Hb was lower in the H group. Logistic regression analysis was performed to investigate what variables are associated with BUN. Hb had the strongest association with BUN. Low Hb was associated with the severity of the upper GI bleeding. These results suggest that patients with BUN > 21.0 mg/dL have more severe upper GI bleeding.

### Applications

Patients with BUN  $\geq 21$  mg/dL might have more severe upper GI bleeding. It is recommended that severe upper GI bleeding be considered when BUN is higher than 21.0 mg/dL.

### Peer-review

This study examines variables associated with higher than normal BUN levels and GI bleeding. The results show that patients with high BUN have higher WBC counts and lower Hb, suggestive of more severe GI bleeding.

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