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Urea-to-hemoglobin ratio for patients with upper gastrointestinal bleeding

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ABSTRACT

Aims: Upper gastrointestinal bleeding develops due to various pathologies in a wide region, including esophagus, stomach, and duodenum. The clinical presentation is highly variable between patients and can rapidly deteriorate and even be fatal without follow-up. Medical agents, endoscopic interventions, and surgery may be required in the treatment of the patient, and a high blood transfusion may be required. The accurate identification of patients who are at a higher risk and require immediate attention is crucial for the appropriate management of patient care. The ratio of urea to hemoglobin (UHR) has been identified as a potentially valuable tool for determining the necessity of endoscopy due to its simplicity, quick applicability, and reliability.

Methods: This was a single-center retrospective study in which 361 patients treated for upper gastrointestinal bleeding were investigated. Age and gender data, endoscopy records, and blood tests of the patients were analyzed within the scope of the study. Median UHR values were significantly higher in intensive care indication, endoscopic indications, and blood transfusion indications ($p<0.05$).

Results: The majority of patients were male, with 72.3%. The median age was 56 years (15-96). Peptic ulcer (70.9%) was the most common etiologic cause, and angioectasia (6.65%) was the second most common etiologic cause. Intensive care follow-up was required in 29.1%, erythrocyte replacement in 36.01%, and endoscopic treatment in 46.81% of patients. 13 patients died (3.6%). The median value was 58 for urea, 10.50 for hemoglobin and 5.75 for UHR.

Conclusion: Upper gastrointestinal bleeding is a variable and rapidly deteriorating clinical entity. Patients may not always be encountered under ideal conditions and may need to be managed with limited resources. Therefore, there is a need for easy-to-access, rapid, and reliable auxiliary techniques to differentiate patients who may need urgent treatment and interventions from others. Urea and Urea/hemoglobin ratio fulfill these requirements, and their significance in terms of upper gastrointestinal bleeding should be investigated.

Keywords: Gastrointestinal hemorrhage, peptic ulcer, emergency intervention, endoscopy, urea

INTRODUCTION

Upper gastrointestinal bleeding (UGIB) defines hemorrhages that develop due to pathologies in the gastrointestinal tract up to the ligament of Treitz.[1] Many pathologies that may cause bleeding in this region, including esophagus, stomach, and duodenum, have been described. Although these pathologies differ in terms of the way they occur and the severity of the clinic they cause, the basic goals in the management of these clinics are the same. When bleeding is detected, hemodynamic stabilization of the patient should be targeted, preparation should be made for the need for resuscitation and transfusion, proton pump inhibitor and somatostatin treatment should be started in selected patients, and intervention should be planned to identify and stop the bleeding focus.[2]

While around 80% of instances of upper gastrointestinal bleeding (UGIB) exhibit spontaneous recovery, it is important to note that 13% of these cases may result in mortality.[2,3] Given the diverse range of clinical presentations and the potential for acute manifestations, it is imperative to ascertain the relative risk and prioritize patients accordingly, taking into account both individual patient well-being and the overall clinic population. This is particularly important due to the frequency of bleeding incidents and the limited capacity for simultaneous endoscopic procedures. Hence, there exists a must for methodologies capable of forecasting which patients necessitate a blood transfusion due to their severity, as well as identifying those who require an expedited endoscopy. These procedures should possess attributes

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of simplicity, expediency, and sufficient accuracy to be effectively employed in emergency scenarios. The scope of blood tests that may be conducted in emergency scenarios and yield prompt answers is constrained. However, existing literature suggests that certain available assays can provide indirect indications regarding the extent of bleeding and the clinical status.

Urea is a blood test that can be easily and rapidly studied, even in centers with the most limited facilities. Although it is known as an integral part of renal function tests, it has been widely observed to give abnormal results in gastrointestinal bleeding. There are data showing a significant correlation between elevated urea and mortality in patients with UGIB.[4] Considering the effect of uremia on intestinal mucosa and platelet functions, the value of urea in predicting prognosis and the need for treatment in these patients should be investigated.[5]

Tomizawa et al.[6] reported that patients with higher BUN levels may have more severe upper GI bleeding. In a study in 2020 study reported that urea level was an independent predictor of positive endoscopic findings in upper GI bleeding and that early endoscopic intervention should be considered in patients with elevated urea levels.[7] Some studies have used the BUN/Creatinine ratio as an index to differentiate between upper and lower GI bleeding and have shown that a higher BUN/Cr ratio is associated with a higher likelihood of upper GI bleeding.[8,9]

In cases of ongoing bleeding in any area of the body, a decrease in hemoglobin levels is expected. Since both urea and hemoglobin levels are known to change in bleeding states, we thought that a ratio derived from them might be meaningful in upper GI bleeding.

Based on this, we aimed to investigate and reveal the relationship between urea/hemoglobin ratio (UHR) and upper gastrointestinal bleeding and the possible clinical significance of these bleedings.

METHODS

The study was carried out with the permission of the Batman Training and Research Hospital Scientific Researches Ethics Committee (Date: 22.12.2022, Decision No: 324). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This study was conducted retrospectively and single-center in the Gastroenterology Clinic of Batman Dünya Hospital. Patients who were treated in our clinic between January 2010 and December 2022 and were diagnosed with upper gastrointestinal tract bleeding for any reason other than variceal bleeding were included in the study. Patients presenting with variceal bleeding or having nephrological comorbidities (defined as patients with a creatinine value above 1.3 mg/dl at the time of admission) were excluded from the study. Similarly, patients who presented to the outpatient clinic with anemia and who had no evidence of active GI bleeding were not included in the study. The study included 361 patients who met the definition and were treated on those dates. Age and gender data, endoscopy records, and blood tests of the patients were analyzed within the scope of the study.

Patient data collected within the scope of the study were analyzed with IBM Statistical Package for the Social Sciences (SPSS 25.0-IBM, NY, USA) for Windows 25.0 package program. Frequency and percentage for categorical data, and median, minimum, and maximum for continuous data, were given as descriptive values. The conformity of the data to the Gaussian distribution was analyzed by the Kolmogorov-Smirnov test. For intergroup comparisons, the Mann Whitney U-Test was used for two groups, and the Kruskal-Wallis H-Test was used for more than two groups. The relationship between urea/hemoglobin ratio (UHR) and the risk of peptic ulcer bleeding was evaluated by Spearman's correlation analysis. Results were considered statistically significant when the p value was less than 0.05.

RESULTS

The evaluation encompassed a total of 361 patients. **Table 1** displays the distribution of demographic and clinical findings among the patients. Upon analysis of the table, it becomes evident that a significant proportion of the patients were of the male gender, accounting for 72.3% of the total population. The median age of the population under study was 56 years, with a range spanning from 15 to 96 years. The most prevalent etiologic cause of peptic ulcer was found to be 70.9%, whereas angioectasia was identified as the second most common etiologic cause, accounting for 6.65% of cases. A total of 36.39% of the patients exhibited the presence of at least one comorbid disease, with coronary artery disease being the most prevalent among them, affecting 12.46% of the patients. A follow-up in the intensive care unit was necessary for 29.1% of the cases, while erythrocyte replacement was required in 36.01% of the cases, and endoscopic therapy was necessary in 46.81% of the cases. During the subsequent assessment, a total of 13 patients, accounting for 3.6% of the sample, experienced mortality. The median values for urea, hemoglobin, and UHR were 58, 10.50, and 5.75, respectively.

Table 1. Distribution of demographic and clinical findings of the patients

N:361	n (%) or Median (Min-Max)
Gender	
Male	261 (72.3)
Female	100 (27.7)
Age, year	56 (15-96)
Etiology of Bleeding	
Peptic Ulcer	256 (70.9)
Forrest 1a	13
Forrest 1b	42
Forrest 2a	59
Forrest 2b	10
Forrest 2c	38
Forrest 3	94
Erosive gastritis	23 (6.37)
Angioectasia	24 (6.65)
Hemorrhagic gastritis	6 (1.66)
Mallory-Weiss	14 (3.88)
Upper GI cancer	14 (3.88)
GIST	2 (0.55)
Dieulafoy	4 (1.11)
Esophagitis	2 (0.55)
Esophageal ulcer	8 (2.22)
Post-ERCP	2 (0.55)
Post-polypectomy	1 (0.28)
Cameron ulcer	2 (0.55)
Marginal ulcer	2 (0.55)
Swallowed blood (haemoptysis)	1 (0.28)
Place of Hospitalization	
Service	256 (70.9)
Intensive care	105 (29.1)
Medicine	
NSAIDs (ASA and others)	78 (21.61)
Antiaggregant/Anticoagulant	46 (12.74)
Comorbidity	131 (36.39)
Diabetes mellitus	19 (5.26)
Hypertension	27 (7.48)
Coronary artery disease	45 (12.46)
Cerebrovascular disease	7 (1.94)
Chronic obstructive pulmonary disease	2 (0.55)
Arrhythmia	4 (1.11)
Heart valve surgery	8 (2.22)
Gastric surgery	12 (3.32)
Cancer (non-gastric)	8 (2.22)
Erythrocyte Replacement	160 (44.32)
Endoscopic Treatment	169 (46.81)
Last Status	
Alive	348 (96.4)
Deceased	13 (3.6)
Laboratory	
Urea (mg/dl)	58 (11-182)
Creatinine (mg/dl)	0.90 (0.30-1.30)
Albumin (g/dl)	3.70 (1.20-5.29)
INR	1.11 (0.86-12.20)
White blood cell (µl)	9680 (1400-35130)
Neutrophil (µl)	6730 (1700-32870)
Lymphocyte (µl)	1900 (100-10300)
Hemoglobin (g/dl)	10.50 (3.20-18.30)
Platelets (µl)	241.50 (32-888)
UHR	5.75 (0.79-26.01)

Table 2 presents an analysis of probable fluctuations in the urea to hemoglobin ratio among the participants in the study, considering specific variables that are hypothesized to impact this ratio. It was determined that there was no significant difference between genders (p=0.46). Median UHR values were found to be significantly higher in patients who required intensive care follow-up, underwent endoscopic treatment, received erythrocyte administration, and were older than 65 years (p<0.05). In the comparison of peptic ulcer bleeding and other etiologies, UHR was found to be significantly higher in the peptic ulcer group (p<0.001).

Table 2. Distribution of urea/hemoglobin ratio by variables

Variable	UHR Median (Min-Max)	p
Gender		0.46
Male	5.80 (1.21-21.76)	
Female	5.71 (0.79-26.01)	
Age		<0.001
<65	5.05 (0.79-11-7.79)	
≥65	7.68 (1.38-26.01)	
Intensive care follow-up		<0.001
Yes	6.77 (1.62-26.01)	
No	5.22 (0.79-22.98)	
Endoscopic treatment requirement		0.01
Yes	6.10 (0.79-21.76)	
No	5.23 (1.05-26.01)	
Erythrocyte replacement requirement		<0.001
Yes	7.37 (1.38-26.01)	
No	4.17 (0.79-18.02)	
Etiology of bleeding		<0.001
P. Ulcer	6.09 (1.24-26.01)	
Other	4.04 (0.79-22.98)	
Result		0.01
Alive	5.70 (0.79-26.01)	
Deceased	8.60 (2.78-19.13)	

Table 3 shows the relationship between bleeding risk groups and the ratio of urea to hemoglobin. The findings revealed that as the risk level grew, there was a corresponding increase in the ratio of urea to hemoglobin. The correlation analysis revealed a positive, low-level linear association between UHR and the bleeding risk of peptic ulcer (Table 4). The statistical analysis, which employed post-hoc Bonferroni correction, indicated that the observed disparity can be ascribed to the differentiation between the low- and high-risk groups (p=0.013).

Table 3. Urea/hemoglobin ratio according to bleeding risk in peptic ulcer patients

Bleeding risk according to forrest classification	UHR Median (Min-Max)	p
Low	5.48 (1.24-17.65)	
Middle	6.03 (1.25-26.01)	0.04
High	7.00 (1.48-21.76)	

Table 4. Correlation analysis results between peptic ulcer bleeding risk and UHR			
			UHR
Spearman's correlation	Bleeding risk	r p N	.149 0.017 256

Table 5 displays the findings of the analysis that assessed the potential disparity between the groups receiving erythrocyte replacement and those not receiving erythrocyte replacement in relation to UHR, based on baseline hemoglobin values. It is evident that the UHR is significantly greater in the groups that had erythrocyte replacement, regardless of the hemoglobin cut-off levels (p<0.001).

Table 5. Comparison of UHR of those with erythrocyte requirement at follow-up according to baseline hemoglobin levels

	Erythrocyte replacement (n)	UHR Median (Min-Max)	p
Hemoglobin ≥10 (n:213)	Yes (54) No (159)	6.77 (1.38-14.23) 3.58 (0.79-18.02)	<0.001
Hemoglobin ≥7 (n:329)	Yes (130) No (199)	7.02 (1.38-11-19.99) 4.06 (0.79-18.02)	<0.001

DISCUSSION

With a wide spectrum of causes and clinical severity, UGIB is a difficult clinic for clinicians to manage. Treatment of patients is initiated before the nature of the disease is understood and is not known until endoscopy is performed. It is therefore difficult to predict which patients need further treatment more than others and when. Nevertheless, despite all the obstacles, the clinician has to make decisions about intervention with endoscopy, follow-up in the intensive care unit, and early initiation of transfusion, based on the limited findings available to him and needs techniques to support him in this regard.

The age distribution of the cases in our study was quite wide (15-96) and the mean age was 56 years. 72.3% of our patients were male. In a study of UGIB cases conducted in France, the mean age was 63 years, and 2130 cases were male and 1073 cases were female.[5] Although the mean ages were slightly different, they were similarly high, and the difference may be due to demographic differences in life expectancy and age. In terms of gender, the cases were similarly dominated by males. The most common cause of non-variceal UGIB is peptic ulcer.[10] Similar to the literature, peptic ulcer was the most common etiologic cause in our study. In a study conducted by Falcão et al.[11] in 2021, the intensive care unit follow-up rate was reported as 35.6%. Our patients required intensive care unit follow-up at a rate close to this rate (29.1%). Based on this, we performed further analysis in terms of our hypothesis, considering that our study group was in rough agreement with the literature.

In our study, the median value was 58 for urea, 10.50 for hemoglobin and 5.75 for UHR. As far as we know, there is no study directly examining the relationship between UHR and UGIB in the literature, so we tried to compare them indirectly. In a study examining upper and lower gastrointestinal bleeding in Japan, mean hemoglobin was 10.1 g/dl and serum urea nitrogen (BUN) was 21.1 mg/dl in patients with UGIB.12 Based on this data, urea was calculated as 45.153 (BUN was multiplied by 2.14 for conversion to urea), and UHR was calculated as 4.47 and found to be similar to our study.

In the United Kingdom, a study was conducted on early blood transfusion in cases of acute UGIB, and it was observed that 38 of 57 patients with urea values below 6.5 mmol/L at admission did not need blood transfusion in the early period, and this data was statistically significant.[13]

In a retrospective study conducted in Japan to predict the need for emergency endoscopy, the importance of hemoglobin and urea was emphasized.[14] Various factors were examined for the need for hemostatic treatment and blood pressure (p=0.0283), BUN (p<0.001), hemoglobin (p=0.0037), hematemesis (p=0.0030) and pulse (p=0.0137) were found to be directly related. Based on this, hematemesis, pulse rate above 100 beats per minute, hemoglobin below 10 g/dl, blood pressure below 100 mmHg, and BUN values of 22.4 mg/dl and above were determined as indicators associated with the need for endoscopic treatment, and a new scoring system was proposed.

Urea and hemoglobin are used in the Glasgow-Blatchford score, which is one of the severity scores of UGIB. In this score, elevated urea and low hemoglobin cause the patient to have a higher score and are associated with severe UGIB.[15] There are studies showing an association between low hemoglobin and mortality.[16] In our study, UHR was found to be associated with disease severity indicators and mortality. The Forrest classification has been used for risk stratification in nonvariceal ulcer bleeding and is associated with the risk of rebleeding.[17] de Groot et al.[18] reported that there was no relationship between Forrest classification and mortality. The existing literature does not contain any research that have examined the correlation between the urea/hemoglobin ratio and the likelihood of experiencing peptic ulcer bleeding. During the course of our investigation, it was noted that there was a substantial increase in the urea to hemoglobin ratio in instances of peptic ulcer

bleeding. Moreover, a low-level positive correlation was observed between the risk of bleeding as per the Forrest classification and the extent of UHR. Our study is the first to report this relationship.

In patients with upper GI bleeding, erythrocyte replacement is recommended so that hemoglobin is 7-9 g/dl.[19] The European Society of Gastrointestinal Endoscopy (ESGE) recommends a more liberal erythrocyte transfusion strategy in hemodynamically stable patients with acute UGIB and a history of acute or chronic cardiovascular disease, with a hemoglobin threshold of ≤8 g/dl triggering erythrocyte transfusion and a target hemoglobin ≥ 10 g/dl.[20] In our evaluation to need for erythrocyte replacement in the follow-up according to the baseline hemoglobin level, patients with high UHR needed erythrocytes in the follow-up for both cut-off values (7 g/dl and 10 g/dl).

In the study conducted by Kiringa et al.[4] in which UGIB cases were examined, uremia was found in almost half of the cases (44.6%), and it was observed that patients with uremia had a more mortal course (OR 5.4, 95% CI 1.57-18.53, p-value 0.007). Based on this data, it can be claimed that uremia is associated with bleeding and mortality. In our study, median UHR values were found to be significantly higher in patients who required intensive care follow-up, underwent endoscopic treatment, received erythrocyte transfusions, and were older than 65 years; in summary, in patients at high risk of mortality ($p<0.05$).

CONCLUSION

Upper gastrointestinal bleeding (UGIB) remains a complex and challenging condition until the diagnostic procedure of an endoscopy is performed. There are a number of possibilities, including spontaneous cessation of small ulcer bleeding, persistent bleeding from a pulsatile artery, and the presence of a malignant condition. Regardless of the underlying cause, the primary goal of treatment is to maintain hemodynamics and rapidly identify and treat the underlying cause. We assessed UHR in our study to identify patients who are at high risk and require urgent attention for endoscopy. Research findings suggest a significant link between UHR and bleeding. This association is of great importance for understanding and predicting the magnitude and severity of hemorrhagic events. Based on the analysis of the data we collected, it is recommended that the urea/hemoglobin ratio be used as an important prognostic indicator in determining the need for endoscopy, blood transfusion, and subsequent intensive care unit monitoring in cases of upper gastrointestinal bleeding. This recommendation emphasizes the need to incorporate this ratio into routine clinical practice.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of the Batman Training and Research Hospital Scientific Researches Ethics Committee (Date: 22.12.2022, Decision No: 324).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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