

The Role of the K/iCa Ratio in Predicting in Hospital Mortality in Patients with Upper Gastrointestinal Bleeding

Handan Özen Olcay¹, Emine Emektar¹, Şeref Kerem Çorbacioğlu¹, Metin Uzman², Sedat Akkan¹, Yunsur Çevik¹

¹Ankara Atatürk Sanatorium Training and Research Hospital, Clinic of Emergency Medicine, Ankara, Türkiye

²Ankara Atatürk Sanatorium Training and Research Hospital, Clinic of Gastroenterology, Ankara, Türkiye

Abstract

Aim: Upper gastrointestinal bleeding (UGIB) is a common cause of emergency department presentation. Risk stratification of patients presenting to the emergency department with UGIB is important to predict active bleeding, need for blood transfusion, and mortality. In this study, we aimed to investigate the effect of potassium (K) and ionized calcium (iCa) on disease severity and mortality in UGIB patients.

Materials and Methods: This is a retrospective, single-center study. Patients aged 18 years and older who presented to the emergency department with UGIB, underwent blood gas analysis within the first half hour of presentation to the emergency department, were admitted to the hospital by the gastroenterology department, underwent endoscopy, and had complete data records were included in the study.

Results: The study included 699 patients. The in-hospital mortality rate was 7.7%. In the ROC analysis performed to determine the cut-off value of the K/iCa ratio for predicting mortality and active bleeding, the area under the curve values were 0.892 [95% confidence interval (CI): 0.845-0.939, $p < 0.001$] and 0.832 (95% CI: 0.792-0.871, $p < 0.001$), respectively. Patients were divided into 2 groups: those with a K/iCa ratio lower than 5.02 and those with a ratio higher than 5.02. This ratio has a high specificity value in terms of mortality prediction. Hemodynamic instability, active bleeding, need for erythrocyte suspension, length of hospital stay, and mortality were higher in the high K/iCa ratio group ($p < 0.001$ for all values).

Conclusion: In patients presenting to the emergency department with suspected UGIB, assessment of the K/iCa ratio using blood gas analysis may help to predict the risk of active bleeding and in-hospital mortality as a rapid, inexpensive, and practical assessment method. Patients with a high K/iCa ratio may be candidates for early endoscopy and closer hemodynamic monitoring.

Keywords: Emergency department, upper gastrointestinal bleeding, in hospital mortality, K/iCa ratio

Introduction

Upper gastrointestinal bleeding (UGIB) is a common cause of emergency department (ED) visits. More than 70% of these bleedings are due to non-variceal etiologies, and gastroduodenal ulcer disease is one of the most common causes (1). Although pharmacologic and endoscopic treatments have been developed in recent years for the management of UGIB, it is still associated with significant morbidity and mortality. It can present with clinical symptoms ranging from massive bleeding leading to shock and death to occult bleeding leading to iron deficiency anemia from chronic blood loss (1,2). Risk stratification of patients presenting to the ED with UGIB is important to predict active

bleeding, transfusion requirements, and mortality. Although various clinical scoring systems, biomarkers, and other risk factor assessments have been used for risk stratification, none of them have sufficient clinical reliability in routine clinical practice. Therefore, the search for simple, cheap and reliable prognostic markers continues.

We think that an important candidate for this research may be the ratio of potassium to ionized calcium (K/iCa ratio), the prognostic value of which has been the subject of recent studies, especially in critically ill and hemorrhagic patients. Calcium acts as a cofactor for many important functions, including the coagulation cascade, cardiac and smooth muscle contraction,



Corresponding Author: Handan Özen Olcay MD, Ankara Atatürk Sanatorium Training and Research Hospital, Clinic of Emergency Medicine, Ankara, Türkiye
E-mail: hozen84@hotmail.com **ORCID ID:** orcid.org/0000-0002-1634-2684

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vasoconstriction, inotropy, and chronotropy; thus, calcium is essential for hemodynamic stability. Hypocalcemia can lead to coagulopathy in patients at high risk for bleeding. As in trauma patients, hypocalcemia is common in UGIB patients and may indicate the need for more blood transfusions and risk of death (3-5). iCa, the active form of serum calcium, can be measured directly and rapidly by blood gas analysis, which is available in many EDs and intensive care units.

Another electrolyte disturbance that may occur in hemorrhagic patients, including UGIB, is hyperkalemia. Hyperkalemia may be caused by mechanisms such as K release from red blood cells during degradation, tissue damage, decreased renal perfusion as a result of massive blood loss, and decreased urinary K excretion. The association of hyperkalemia with mortality in UGIB patients has been demonstrated in some studies (6). A recent study in traumatic hemorrhagic patients has shown that the K/iCa ratio has better prognostic value than the use of K or iCa alone (7).

We hypothesize that early K elevations, in addition to low iCa levels, may have a high predictive value for in-hospital mortality and active bleeding in UGIB patients. Therefore, in this study, we aimed to evaluate the prognostic value of K/iCa ratio on disease severity and mortality in UGIB patients.

Materials and Methods

Study Design

This study is a diagnostic-prognostic value study based on a retrospective cross-sectional analytical design and was conducted in the emergency department of Ankara Atatürk Sanatorium Training and Research Hospital, a 780-bed tertiary care center located in a large provincial center. The study was approved by the Local Ethics Committee Atatürk Sanatorium Training and Research Hospital (decision number: 20-KAEK15/2854, date: 27.12.2023). Our study was designed and reported in accordance with the Standards for Reporting of Diagnostic Accuracy Studies statement (8,9).

Data Collection

Data were collected from electronic medical records and patient charts. The chart review (clinical and demographic characteristics of the patients, including endoscopy results) was performed retrospectively by two different emergency physicians with at least 5 years of experience (9).

Study Population

We analyzed the consecutive database of all patients who presented to the ED with UGIB and underwent endoscopy performed by the gastroenterology department between January 2019 and January 2024. Patients aged 18 years and older, who

presented to the ED with UGIB, underwent blood gas analysis within the first half hour of presentation to the ED, underwent endoscopy after admission to the gastroenterology department, and had complete data records were included in the study. Pregnant women were excluded from the study as well as patients who did not undergo endoscopy, those with lower gastrointestinal (GI) bleeding, chronic renal failure, known parathyroid disease, known gastric cancer, indications for hospitalization other than UGIB, referred from another center, and missing data. In addition, the blood gas K level was compared with the biochemical K level. Patients with a biochemical hemolysis index greater than 1 were excluded.

Patients were classified in the hospital data system according to international statistical classification of diseases, tenth revision codes (K25, K25.4, K26, K26.4, K27, K27.4, K28, K28.4, K92.1). Demographic information, comorbidities (chronic hypertension, diabetes mellitus, coronary artery disease, liver disease), medications, admission vital signs, laboratory results, endoscopy results, blood and blood product indications, hospitalization, and mortality were recorded. Blood gas samples were analyzed using the Siemens RAPIDLab 1265 device within 5 minutes of collection. A systolic blood pressure of less than 90 mmHg, a heart rate of 100 beats/min or more, and/or a history of syncope with onset of symptoms were considered to be hemodynamically unstable. Gastritis, gastric/duodenal ulcer, esophageal varices, gastric cancer, Dieulafoy's lesion, Mallory-Weiss tear, angiodysplasia, and active bleeding were analyzed in the endoscopy results. Treatments applied during endoscopy, such as sclerotherapy, hemoclip, heater probe, and band ligation, were recorded. The K/iCa ratio of the patients was obtained from the results of blood gas analysis. Demographic and clinical data of patients were compared in relation to the K/iCa ratio and mortality status (in-hospital mortality).

Index and Reference Tests

The index test was determined as K/iCa ratio, and the primary reference test was determined as in-hospital mortality status of patients. In addition, active bleeding after endoscopy was determined as a secondary reference test. Active bleeding was defined as forest classification 1a, 1b, and active esophageal varices bleeding.

Statistical Analysis

All data collected throughout the study and recorded on the study form were analyzed using IBM SPSS 20.0 (Chicago, IL, USA). The Kolmogorov-Smirnov test was used to determine whether the distribution of discrete and continuous numerical variables was normal. Descriptive statistics were presented as median [interquartile range (IQR): 25-75] for discrete and

continuous numerical variables, and as the number of cases (%) for categorical variables. Categorical variables were evaluated by the chi-squared test and continuous variables by the Mann-Whitney U test. The ROC curve and area under curve (AUC) were calculated to determine the predictive and threshold values of K/iCa ratio for in-hospital mortality and active bleeding (10). The critical alpha value was considered 5% for all statistical analyses.

Results

During the study period, 1388 patients diagnosed with UGIB were evaluated. The study included 699 patients with complete data (Figure 1). 68% of patients were male and the median age was 63 years (IQR: 25-75, 47-74).

Endoscopic findings and endoscopic interventions are shown in Table 1. The most common endoscopic finding was gastritis (71.1%); gastric/duodenal ulcer was observed in 69.5% of patients. The percentage of active bleeding was found to be 18.7% and the in-hospital mortality rate was 7.7%. Among patients with gastric/duodenal ulcers (n=486), 2.1% were classified as Forrest 1a, 18.9% as Forrest 1b, 9.9% as Forrest 2a, 29.2% as Forrest 2b, and 23% as Forrest 2c.

The median K/iCa ratio was 3.85 (IQR: 25%-75%: 3.43-4.24) in the survivor group and 4.85 (IQR: 25%-75%: 4.44-5.26) in the non-

survivor group, and the difference was statistically significant ($p<0.001$). Other clinical and demographic characteristics of the survivor and non-survivor patients are presented in Table 2. In addition, the median K/iCa ratio was 3.80 (IQR: 25%-75%: 3.38-4.15) in patients without active bleeding, and 4.6 was (IQR: 25%-75%: 4.16-5) in patients with active bleeding, and the difference was statistically significant ($p<0.001$) between the two groups.

In the ROC analysis performed to determine the cut-off value of the K/iCa ratio for predicting mortality and active bleeding, the AUC values were 0.892 [95% confidence interval (CI): 0.845-0.939, $p<0.001$] and 0.832 (95% CI: 0.792-0.871, $p<0.001$), respectively (Figure 2). The best cut-off values for the K/iCa ratio were determined to be 4.3 for mortality and 4.1 for active bleeding according to Youden's index. Sensitivity, specificity, and likelihood ratio values for the optimal cut-off value and various K/iCa ratio levels are presented in Table 3.

Patients were divided into 2 groups as those with K/iCa ratio lower and higher than 5.02 according to the K/iCa ratio of 5.02, which has a high specificity value in terms of mortality prediction. Hemodynamic instability was significantly more frequent in the high K/iCa ratio group (88.9% vs. 19.2%, $p<0.001$). Similarly, active bleeding occurred in 86.1% of patients in the high K/iCa ratio group, compared to 15.1% in the low K/iCa ratio group ($p<0.001$). RBC suspension was required in 97.2% of the high K/iCa ratio

Table 1. The endoscopic findings, forest classification and endoscopic interventions	
Endoscopic diagnoses	n (%), all patients
Gastric erosion/gastritis	497 (71.1)
Gastric/duodenal ulcer	486 (69.5)
Esophageal varices	46 (6.6)
Cancer stomach	44 (6.3)
Dieulafoy's lesion	38 (5.4)
Mallory-Weiss tear	15 (2.1)
Angiodysplasia	1 (0.1)
Active bleeding	131 (18.7)
Forrest classification for gastric/duodenal ulcer, n=486	n (%)
1a	10 (2.1)
1b	92 (18.9)
2a	48 (9.9)
2b	142 (29.2)
2c	112 (23)
3	82 (16.9)
Endoscopic intervention	n (%)
Sclerotherapy	262 (37.5)
Hemoclip	96 (13.7)
Endoscopic band ligation	42 (6)
Heater probe	7 (1)
Somatostatin	33 (4.7)
Subtotal gastrectomy	7 (1)
Some patients presented with more than 1 endoscopic finding	

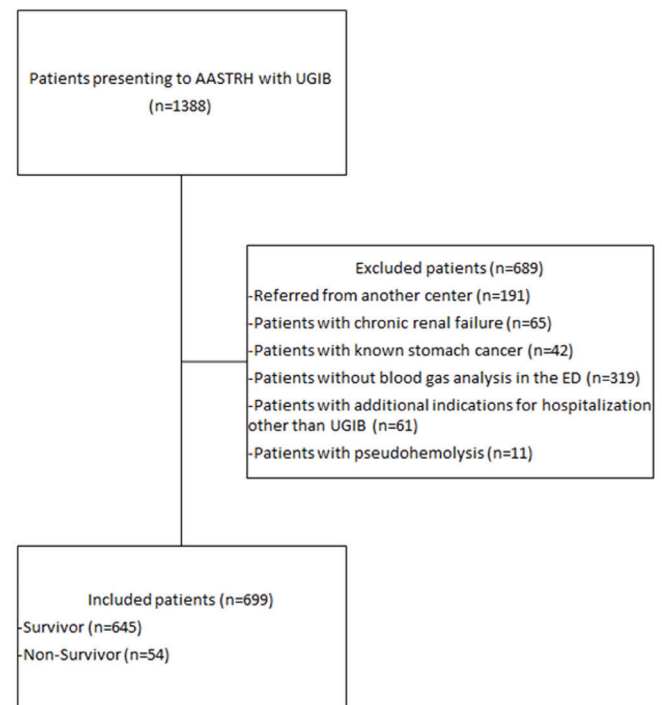


Figure 1. Flowchart showing number of patients of the study
UGIB: Upper gastrointestinal bleeding, AASTRH: American Association for the Surgery of Trauma-Regional Hospital

group, whereas 59.6% of the low K/iCa ratio group required transfusions ($p<0.001$). Additionally, patients with a high K/iCa ratio had a significantly longer hospital stay (median: 6.5 days vs. 4 days, $p=0.007$). Mortality was significantly higher in the high K/iCa ratio group, occurring in 63.9% of these patients compared to 4.7% in the low K/iCa ratio group ($p<0.001$). Table 4 presents the comparison of K/iCa ratio with other clinical characteristics.

Discussion

In our study investigating the prognostic value of K value in patients with UGIB, the K/iCa ratio may be a helpful prognostic

test for in-hospital mortality and active bleeding in patients with UGIB. Although the likelihood ratios of the best cut-off value of the K/iCa ratio do not have sufficient prognostic value, considering that K and iCa values are inexpensive parameters routinely studied in patients with UGIB, we think that cut-off values with higher specificity or sensitivity, can be helpful instead of the optimal cut-off value of the K/iCa ratio for predicting in-hospital mortality and active bleeding.

In patients presenting to the ED with UGIB, it is difficult to obtain data on bleeding-related factors such as the location, cause, or extent of bleeding. The extent of bleeding should be determined

Table 2. A comparison of patient characteristics with respect to in-hospital mortality (survivor/non-survivor)

	Survivor (n=645)	Non-survivor (n=54)	p value
Age, median, (IQR ¹ 25-75)	63 (45-73)	72 (67-81)	<0.001
Gender, n (%)			
Male	443 (68.7)	32 (59.3)	0.154
Female	202 (31.3)	22 (40.7)	
Comorbidities, n (%)			
Hypertension	330 (51.2)	42 (77.8)	<0.001
Diabetes mellitus	123 (19.1)	20 (37)	0.002
CAD ² /heart failure	224 (34.7)	31 (57.4)	0.001
Liver disease	26 (4)	15 (27.8)	<0.001
Drugs, n (%)			
Oral anticoagulants	84 (13)	10 (18.5)	0.256
Antiplatelets	46 (7.1)	2 (3.7)	0.572
Acetyl salicylic acid	156 (24.2)	13 (24.1)	0.985
Hemodynamic instability, n (%)	107 (16.6)	52 (96.3)	<0.001
Median, (IQR 25-75)			
K ³ (mmol/L)	4.10 (3.78-4.34)	4.69 (4.18-5.20)	<0.001
iCa ⁴ (mmol/L)	1.07 (1.01-1.12)	0.96 (0.92-1.00)	<0.001
K/iCa ratio	3.85 (3.43-4.24)	4.85 (4.40-5.28)	<0.001
Lactate (mmol/L)	1.75 (1.21-2.39)	3.94 (2.82-4.95)	<0.001
Hemoglobin (g/dL)	9.7 (8.00-12.4)	7.25 (5.97-8.22)	<0.001
Albumin (g/L)	36 (33-39)	27 (24-29)	<0.001
INR ⁵	1.1 (1.04-1.21)	1.35 (1.20-1.67)	<0.001
Endoscopic diagnoses, n (%)			
Gastric/duodenal ulcer	443 (68.7)	43 (79.6)	0.093
Esophageal varices	29 (4.5)	17 (31.5)	<0.001
Cancer stomach	34 (5.3)	10 (18.5)	0.001
Dieulafoy's lesion	33 (5.1)	5 (9.3)	0.205
Active bleeding	89 (13.8)	42 (77.8)	<0.001
Need to repeat endoscopy	83 (12.9)	14 (25.9)	0.008
Blood transfusion, n (%)			
RBC ⁶ suspension	376 (58.3)	54 (100)	<0.001
Fresh frozen plasma	58 (9)	39 (72.2)	<0.001
PCC ⁷	19 (2.9)	4 (7.4)	0.094
Rockall score stratification			
Low-risk	537 (83.3)	2 (3.7)	<0.001
Moderate-risk	87 (13.5)	37 (68.5)	
High-risk	21 (3.3)	15 (27.8)	

IQR: Interquartile range, CAD²: Coronary artery disease, K³: Potassium, iCa⁴: Ionized calcium, INR⁵: International normalized ratio, RBC⁶: Red blood cell, PCC⁷: Prothrombin complex concentrate

based on the patient's chief complaint, vital signs, and laboratory test results while awaiting the patient's referral for endoscopy. In EDs, especially in developing countries, blood gas analysis is advantageous because it provides results in a much shorter time than other laboratory tests and is inexpensive. K and iCa are parameters that can be obtained by blood gas analysis.

Approximately 45% of calcium, a divalent cation found both inside and outside the cell, is biologically active and ionized, while 55% is bound to proteins such as albumin and citrate. Changes in serum levels of these proteins can lead to imbalances in total body stores and serum calcium levels (4,5,11). Although hypocalcemia in bleeding trauma patients is thought to be related to citrate infusion with blood products, recent studies have shown that most trauma patients have calcium loss prior to blood transfusion due to blood loss, and this is exacerbated by citrate from transfusion (11,12). Furthermore, hypocalcemia on admission has been reported to be a predictor of the need

for massive and repeated transfusion (12-14). The same is true for patients with GI bleeding experiencing acute blood loss (1,3). In our study, low iCa was associated with mortality, similar to findings reported in the literature.

Serum K levels in patients with UGIB can vary for several reasons. Serum K levels may decrease due to hemorrhage or increase as a result of the development of prerenal azotemia due to volume depletion in large hemorrhage, direct tissue damage, and K absorption due to digestion of blood from the GI tract (6,7,15). In a retrospective study of trauma patients requiring massive transfusion, the relationship between the K/iCa ratio and mortality was evaluated. The best cut-off value for the K/iCa ratio to distinguish between living and deceased patients was found to be 5.07, and the sensitivity and specificity of this value were reported to be 63.2% and 77.6%, respectively. Patients with a K/iCa ratio above the cut-off had a 4-fold increased risk of death [hazard ratio (HR): 3.97, 95% CI: 1.89-8.32, $p < 0.001$] (7). Another prospective study of trauma patients requiring massive transfusion examined the relationship between the K/iCa ratio measured within 1 hour of hospital admission and mortality. When survivors were compared with deceased patients, a significantly higher mean K/iCa ratio was found ($p < 0.01$). Multivariate logistic regression analysis showed that the total number of blood products was associated with higher K/iCa (odds ratio: 1.02; 95% CI: 1.01-1.04, $p = 0.01$). Cox regression analysis showed a significant association between K/iCa and mortality (HR: 4.12, 95% CI: 1.89-8.96, $p < 0.001$) (16). Based on these studies, we compared the K/iCa ratio with variables such as mortality, transfusion requirement, and hospitalization status in our study of patients with UGIB. In the ROC analysis, we used the cut-off value of the K/iCa ratio between the deceased and living patient groups as 5.02, and the sensitivity and specificity of this

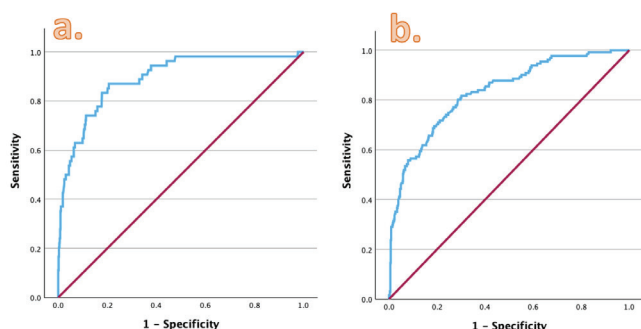


Figure 2. a) ROC analysis to determine K/iCa ratio threshold between non-survivor and survivor groups b) ROC analysis to determine the K/iCa ratio threshold between those with and without active bleeding

K: Potassium, iCa: Ionized calcium

Table 3. The prognostic values for different K/iCa ratio levels to prediction of mortality and active bleeding in patients with UGIB

	AUC ¹ (95% CI)	Cut-off value	Sensitivity (95% CI)	Specificity (95% CI)	PLR ² (95% CI)	NLR ³ (95% CI)	Accuracy (95% CI)
		5.02	42.5 (29.2 to 56.7)	97.9 (96.5 to 98.9)	21.1 (11.3 to 39.1)	0.59 (0.47 to 0.74)	93.7 (91.6 to 95.3)
For mortality	0.892 (0.845-0.939)	4.3*	87 (75.1 to 94.6)	79.3 (76 to 82.4)	4.22 (3.51 to 5.07)	0.16 (0.08 to 0.32)	79.9 (76.8 to 82.8)
		3.88	98.1 (90.1 to 99.9)	52.5 (48.3 to 56.1)	2.06 (1.89 to 2.25)	0.04 (0.01 to 0.28)	55.7 (52 to 59)
		4.73	61.1 (46.8 to 74)	93.3 (91.1 to 95)	9.17 (6.41 to 13.1)	0.42 (0.3 to 0.59)	90 (88.4 to 92.8)
For active bleeding	0.832 (0.792-0.871)	4.1*	80.1 (72.2 to 86.6)	71.3 (67.3 to 74.9)	2.79 (2.39 to 3.26)	0.28 (0.2 to 0.4)	72 (69.5 to 76.2)
		3.64	98 (90 to 99)	36.9 (33 to 40.7)	1.56 (1.46 to 1.67)	0.05 (0.01 to 0.35)	41.6 (37.9 to 45.3)

¹The best cut-off value was calculated according to the Youden index. AUC¹: Area under curve, PLR²: Positive likelihood ratio, NLR³: Negative likelihood ratio, UGIB: Upper gastrointestinal bleeding, CI: Confidence interval

Table 4. Comparison of patient characteristics with respect to the K/iCa ratio			
	K/iCa ¹ ratio<5.02 (n=663)	K/iCa ratio>5.02 (n=36)	p value
Hemodynamic instability, n (%)	127 (19.2)	32 (88.9)	<0.001
Active bleeding, n (%)	100 (15.1)	31 (86.1)	<0.001
Need to repeat endoscopy, n (%)	88 (13.3)	9 (25)	0.077
Blood transfusion, n (%) RBC ² suspension	395 (59.6)	35 (97.2)	<0.001
Somatostatin, n (%)	24 (3.6)	9 (25)	<0.001
Rockall score stratification, n (%) Low-risk Moderate-risk High-risk	532 (80.2) 105 (15.8) 26 (3.9)	7 (19.4) 19 (52.8) 10 (27.8)	<0.001
Median, (IQR ³ 25-75) Number of RBC suspensions Length of hospital stay Length of ICU ⁴ stay	2 (0-3) 4 (2-6) 3 (3-6)	6 (4-8) 6.5 (2-16.25) 5 (2-17.5)	<0.001 0.007 0.140
Mortality, n (%) Non-survivor	31 (4.7)	23 (63.9)	<0.001
K/iCa ¹ ratio: Potassium/ionized calcium ratio, RBC ² : Red blood cell, IQR ³ : Inter quartile range, ICU ⁴ : Intensive care unit			

value were 42% and 98%, respectively. In addition, hemodynamic instability, active bleeding, and number of blood products administered and hospital days were found to be higher in the higher K/iCa ratio group ($p<0.05$). These studies have shown that K levels increase and iCa levels decrease during acute blood loss. In trauma patients, K levels increase proportionally to tissue damage. In UGIB patients, there is a linear relationship between the amount of bleeding and K levels. This is because bleeding causes tissue damage, blood is hemolyzed in the GI tract, and K is reabsorbed. Particularly in elderly patients, acute deterioration of renal function may occur when significant volume depletion is added to an already low glomerular filtration rate. This may also contribute to elevated K levels. In the setting of acute blood loss, we found a decrease in iCa levels in our study and in previous studies. It is known that K levels increase and calcium levels decrease, due to citrate binding to calcium, especially when blood products are transfused to hemodynamically unstable patients with active bleeding. For these reasons, we suggest that a high K/iCa ratio may be a helpful marker for the determination of mortality risk in UGIB patients.

Study Limitations

This study was conducted retrospectively at a single health center. Some symptoms or medical histories may not have been accurately recorded due to missing information. The sample size of our study is limited, and we may not have sufficient statistical power for some subgroup analyses. The cut-off value for the K/iCa ratio used in our study may be different in other studies.

Patients with chronic renal failure who were already expected to have high K levels and patients with other indications for hospitalization were not included in the study. If these patients had been included, the mortality rate in patients with a high K/iCa ratio may have changed. In addition, only in-hospital mortality was analyzed. The study did not examine factors that influence long-term mortality.

Conclusion

In patients presenting to the ED with suspected UGIB, assessment of the K/iCa ratio using blood gas analysis may help to predict the risk of active bleeding and in-hospital mortality as a rapid, inexpensive and practical assessment method. Particularly, a cut-off value of 5.02 demonstrated high specificity in predicting mortality and should be considered in clinical practice. Furthermore, a high K/iCa ratio has been observed to be associated with adverse clinical outcomes such as hemodynamic instability, active bleeding, need for erythrocyte suspension, and prolonged hospital stay. Therefore, patients with a high K/iCa ratio may be candidates for early endoscopy and closer hemodynamic monitoring. However, these findings need to be confirmed by larger prospective studies before clinical application.

Ethics

Ethics Committee Approval: The study was approved by the local ethics committee Atatürk Sanatorium Training and Research Hospital (decision number: 20-KAEK15/2854, date: 27.12.2023).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.U., H.Ö.O., E.E., Concept: H.Ö.O., Y.Ç., E.E., Design: S.K.Ç., Y.Ç., E.E., Data Collection or Processing: H.Ö.O., S.A., Analysis or Interpretation: E.E., H.Ö.O., S.K.Ç., Literature Search: S.A., H.Ö.O., Writing: H.Ö.O., E.E.

Conflict of Interest: The authors declare that they have no conflict of interest.

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