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Predicting Mortality in Gastrointestinal Bleeding: Serum Copeptin Levels or Age, Systolic Blood Pressure and Shock Index-A Cross-Sectional Study

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Abstract

Aim: Vital signs, blood parameters, and some blood biomarkers in patients with gastrointestinal (GI) bleeding vary depending on the severity of the bleeding. The aim of this study is to investigate the association of vital signs and copeptin levels with transfusion requirements, and patient prognosis, including hospitalization duration and 30-day mortality.

Materials and Methods: Prospective, cross-sectional, observational study, conducted in the emergency department (ED) of a tertiary care university hospital, between June 2021 and May 2022. Admission serum copeptin levels and vital parameters of patients with a diagnosis of GI bleeding were noted and evaluated in terms of outcome measures.

Results: The study included 118 patients, 75 (63.6%) of whom were male. The median age was 72 years (interquartile range: 58-83). A total of 18 (15%) patients died within 30 days. Serum copeptin levels did not differ between deceased patients and survivors. Logistic regression analysis showed that a shock index above 0.70 and patients aged 75 years and older together [p=0.017, odds ratio (OR)=6.824; 95% confidence interval (CI): (1.419-32.811)] lead to an increase in 30-day mortality. Lower systolic blood pressure at the admission to the ED was associated with increased 30-day mortality [p=0.003, OR=0.952; 95% CI: (0.922-0.983)].

Conclusion: Although serum copeptin levels failed to predict 30-day mortality in patients admitted to the ED due to GI bleeding, our models demonstrated that age over 75 years, lower systolic blood pressure, and the shock index, were superior predictors of mortality.

Keywords: Copeptin, elderly, gastrointestinal bleeding, mortality, prognosis, shock index

Introduction

Gastrointestinal (GI) system bleeding can range from microscopic levels detectable only through laboratory tests to visible amounts detected macroscopically in feces or vomit (1,2). It frequently leads to emergency department (ED) admissions for medical interventions such as blood transfusions and endoscopic procedures. Given the significant morbidity and mortality associated with GI bleeding (1-4), understanding the factors influencing prognosis and accurately predicting outcomes in GI bleeding cases can facilitate early treatment planning and management strategies.

The blood losses due to GI bleeding cause various changes in the vital signs, blood parameters and hormonal status of patients (5). Copeptin, which is a glycosylated peptide consisting of a leucine-rich core composed of 39 amino acids, is released in equimolar amounts with the antidiuretic hormone (6,7). Studies have shown

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that the release of copeptin is stimulated by processes such as hypovolemia or stress, correlates with plasma osmolarity, can be influenced by sex, remains constant with age, and does not exhibit circadian variations (7-10). The in vitro stability of copeptin and its long half-life in circulation contribute to its stable serum levels. This makes copeptin an ideal biomarker (8,9).

The relationship between copeptin and cardiovascular, pulmonary, neurological, and infectious conditions is investigated in many studies such as heart failure (11), systemic inflammatory response syndrome, sepsis, septic shock (12), and acute stroke (13). In 2013, Salt et al. (5) investigated copeptin levels in patients with acute GI bleeding and a control group and found a significant difference between the groups. However, the study did not evaluate the relationship between copeptin and prognosis.

Our study aims to assess serum copeptin levels in patients with GI bleeding and to investigate the correlation between copeptin levels, transfusion requirements, and patient prognosis, including hospitalization duration and 30-day mortality.

Materials and Methods

Ethical Statement

The ethical suitability of this research was approved at the meeting of Pamukkale University the Non-Interventional Clinical Research Ethics Committee (decision number: 10, date: 25.05.2021). Written informed consent was obtained from all participants in accordance with the ethical principles for research involving human subjects as stated in the Declaration of Helsinki.

Study Group

This prospective, cross-sectional, observational study was conducted in the ED of Pamukkale University Hospital, a tertiary care facility that receives approximately 200,000 patient visits annually. Over the course of 12 months (June 2021-May 2022), 206 patients aged 18 years and older with a preliminary diagnosis of GI bleeding were admitted to the ED and voluntarily enrolled in the study. Patients were initially evaluated according to the predefined inclusion and exclusion criteria (Figure 1). A total of 10 patients were excluded at this stage because they met the exclusion criteria. Additionally, 78 patients who were initially suspected of having GI bleeding but were subsequently ruled out by GI endoscopy were excluded (Table 1). After these exclusions, 118 patients with a final diagnosis of GI bleeding were included in the final analysis.

The inclusion criteria for the study were the age of 18 years or older and the presence of one of the following complaints: hematemesis (bloody vomiting), bloody stools, or melena. Patients or their legal guardians signed an informed consent form to participate in the study. Exclusion criteria included patients with end-stage renal failure (glomerular filtration rate <15 mL/min), patients with known diseases affecting the hypothalamic-pituitary axis (e.g., diabetes insipidus), pregnant women, patients who had received vasoactive drugs or blood or

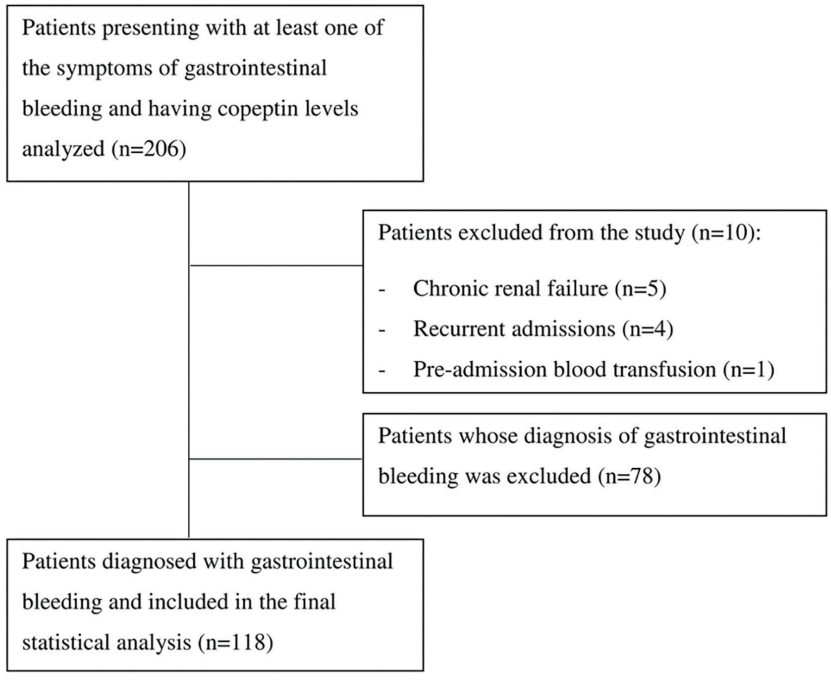

Figure 1. Flowchart of the study

blood product transfusions before admission, and patients with recurrent admissions.

Patient demographics, comorbidities, medications, symptoms at admission to the ED, symptom duration, vital signs, shock index (heart rate/systolic blood pressure), mean arterial pressure, serum copeptin levels, biochemistry results, blood gas values, GI endoscopy findings, transfusion treatments, and admission outcomes (discharge, hospitalization, mortality) were recorded on the study form. The study endpoints included duration of hospitalization and 30-day mortality.

Copeptin Measurement and Laboratory Analysis

To measure copeptin levels, 5 mL of venous blood was collected from 206 patients who presented with symptoms of GI bleeding at their first admission to the ED. Following a 10-15-min rest at room temperature, the blood samples were centrifuged at 3000 rpm for 20 min. The separated serum samples were then stored at -80 °C freezer for subsequent analysis. A double-antibody sandwich ELISA was used to measure copeptin levels in the serum. The analyses were conducted in the laboratories of the Physiology Department. Copeptin levels were measured using a human copeptin ELISA kit (Bioassay Technology Laboratory, Human Copeptin ELISA Kit, Cat. No. E1129Hu) in accordance with the manufacturer's recommendations.

Statistical Analysis

The SPSS v.25 software package (IBM SPSS Statistics 25, Armonk, NY: IBM Corp.) was used to analyze the data. Descriptive statistics included number and percentage for categorical variables, and arithmetic mean, standard deviation, median, and interquartile range (IQR) (1^{st}-3^{rd} quartile) for continuous variables. Categorical variables were compared using the chi-square test. The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to assess the normality of the dataset. Since the assumptions for parametric tests were not met, the Mann-Whitney U test and Kruskal-Wallis test were used to compare independent group differences. The Spearman correlation test was used to assess the correlation between numerical variables. Backward logistic regression analysis was conducted to explore the independent effects of factors on 30-day mortality. Statistical significance was set at $p<0.05$.

Results

Of the 128 patients who received the final diagnosis of GI bleeding, 10 were excluded for reasons including undergoing dialysis for chronic renal failure (n=5), recurrent admissions (n=4), and pre-admission blood transfusion (n=1) (Figure 1). Serum copeptin was 2.972 (2.386-3.61) ng/mL among patients with GI bleeding and 2.663 (2.00-3.18) ng/mL among those without GI bleeding (p=0.026) (Table 1).

Of the 118 patients, 75(63.6%) were male; the median age was 72 years (IQR: 58-83). A total of 94 patients (79.7%) had chronic diseases, with hypertension (43%) and diabetes mellitus (31.4%) being the most common (Table 2).

Three patients were discharged after receiving treatment in the ED and refused admission to the ward or intensive care unit, and the median duration of symptoms was 24 (5-24) hours. The median length of hospital stay was found to be 4 (3-5) days. Among, among patients with upper GI bleeding, no correlation was found between serum copeptin levels and the duration of symptoms, length of hospital stay, or number of erythrocyte suspension transfusions in the ED (Table 3).

Within 30 days of diagnosis, 18 (15%) patients died. Serum copeptin levels of the deceased patients did not differ from the survivors (3.28±1.79 ng/mL vs. 3.63±2.76 ng/mL, respectively). At admission, these patients had lower systolic blood pressure and mean arterial pressure and higher shock index values than those who survived. Patients older than 75 years had a higher 30-day mortality rate (p=0.007) (Table 4).

Table 1. Copeptin levels and age and gender characteristics of patients diagnosed with gastrointestinal bleeding

		Gastrointestinal bleeding diagnosis				
		No (n=78)*		Yes (n=118)*		p
		Median (IQR)		Median (IQR)		
Copeptin level (ng/mL)		2.663 (2.00-3.18)		2.972 (2.38-3.61)		**0.026**
Age		69 (55-82)		72 (58-83)		0.335
Gender		N	%	n	%	0.175
	Male	42	53.80	75	63.60	
	Female	36	46.20	43	36.40	

*Of the 196 patients initially presenting with a preliminary diagnosis of gastrointestinal bleeding, the diagnosis was confirmed in 118 patients, whereas it was ruled out in 78 patients. IQR: Interquartile range

Table 2. Distribution of patients' chronic diseases		
	n	%
Presence of chronic disease	94	79.7
Chronic diseases[a]		
Hypertension	51	43.0
Diabetes mellitus	37	31.4
Coronary artery disease	34	28.8
Malignancy	21	17.8
Hepatic disease	12	10.2
Congestive heart failure	11	9.3
Chronic obstructive pulmonary disease	10	8.5
Others (asthma, chronic renal failure, rheumatological disease)	12	9.7
Medication		
Antihypertensives	49	41.50
Antiaggregants	48	40.70
Anticoagulants	38	32.20
Antidiabetics	33	28.00
Proton pump inhibitors	16	13.60
Nonsteroidal anti-inflammatory drugs	10	8.50
[a]There may be more than one chronic disease		

We performed logistic regression analysis to determine the factors affecting mortality and observed that, in patients aged 75 years and older, a shock index above 0.70 [p=0.017, odds ratio (OR)=6.824; 95% confidence interval (CI): (1.419-32.811)] was associated with increased 30-day mortality. Low systolic blood pressure at admission to the ED was associated with increased 30-day mortality [p=0.003, OR=0.952; 95% CI: (0.922-0.983)] (Table 5).

Discussion

In our study, which aimed to demonstrate the effectiveness of copeptin levels in predicting hospitalization duration and 30-day mortality, we observed no association between these predictors. Among markers reported in the literature for assessing prognosis of GI bleeding, we found that the shock index, also considered a vital sign, and age of 75 years or older were better predictors of 30-day mortality than copeptin. Additionally, we found a weak correlation between serum copeptin levels and the amount of FFP transfused.

Table 3. Correlation analysis of serum copeptin levels and symptom duration, length of hospital stay, amount of erythrocyte suspension, and fresh frozen plasma transfusions administered in the ED of patients with upper gastrointestinal bleeding						
		Age	Symptom duration (hours)	Length of stay in hospital (days)	Amount of ES transfusion in the ED	Amount of FFP transfusion in the ED
Copeptin level (ng/mL)	R	-0.069	-0.099	-0.012	-0.012	0.201
	p	0.456	0.287	0.898	0.894	0.261
ED: Emergency department; ES: Erythrocyte suspension; FFP: Fresh frozen plasma						

Table 4. Comparison of age, copeptin levels, vital signs, and laboratory parameters in surviving and deceased patients					
	30 days mortality (mean ± SD)				P
	Survivors (n=100)		Deceased (n=18)		
Copeptin level (ng/mL)	3.631±2.759		3.277±1.786		0.513
Systolic blood pressure (mmHg)	119±23		98±17		**<0.001**
Diastolic blood pressure (mmHg)	66±14		56±9		**0.001**
Mean arterial pressure	83.67±15.65		69.7±10.52		<0.001
Pulse rate (beats/min)	94±20		97±15		0.319
Shock index	0.82±0.25		1.03±0.33		**0.002**
Lactate (mmol/L)	3.0±2.3		3.6±3.8		0.847
BE	4.7±4.5		7.8±6.7		0.108
pH	7.4±0.08		7.38±0.12		0.270
Age	N	%	N	%	
<65	37	37	2	11.1	**0.007**
65≤ - <75	25	25	2	11.1	
75≤	38	38	14	77.8	
BE: Base excess, SD: Standard deviation					

Table 5. Logistic regression analysis of factors associated with 30-day mortality					
Predictors	**P**	**OR**	**95% CI**		**Nagelkerke R^2**
			Lower	**Upper**	
MODEL 1					0.140
Age					
<65	Ref	Ref	Ref	Ref	
65≤ - <75	0.704	1.48	0.195	11.208	
75≤	**0.015**	6.81	1.448	32.087	
MODEL 2					0.230
Age					
<65	Ref	Ref	Ref	Ref	
65≤ - <75	0.642	1.625	0.209	12.62	
75≤	**0.017**	6.824	1.419	32.811	
Shock index					
<0.7	Ref	Ref	Ref	Ref	
≥0.7	**0.045**	8.409	1.045	36.634	
MODEL 3					0.300
Age					
<65	Ref	Ref	Ref	Ref	
65≤ - <75	0.767	1.373	0.169	11.128	
75≤	**0.03**	5.889	1.187	29.215	
Systolic blood pressure	**0.003**	0.952	0.922	0.983	

Backward logistic regression method was used. Since systolic blood pressure and shock index were highly correlated, they were not included in the same model
Model 1: Age is included in the model.
Model 2: Age and shock index are included in the model.
Model 3: Age and systolic blood pressure are included in the model.
OR: Odds ratio, CI: Confidence interval

In studies conducted with healthy volunteers, there is evidence indicating that copeptin levels are influenced by gender, with levels being significantly higher in men (8,14). For instance, Salt et al. (5) found no association between gender and copeptin levels in their study of patients with GI bleeding. Our study revealed no significant correlation between copeptin levels and age, consistent with findings from previous research (7,8). However, we observed an increase in 30-day mortality among individuals aged 75 and older, aligning with reports from earlier studies indicating a higher mortality rate in older individuals (15). Notably, our findings corroborate the literature, which has consistently highlighted age as a significant factor influencing mortality outcomes in patients with GI bleeding. For instance, a study conducted between 1999-2003 on patients with GI bleeding demonstrated varying 90-day mortality rates across different age groups, with mortality rates rising with increasing age (16).

Although copeptin has been studied as a prognostic and severity marker for many medical and traumatic acute conditions (11-13,17,18), our study found no relationship between serum copeptin levels and 30-day mortality in patients admitted to the ED due to GI bleeding. That most of the vital signs of the patients included in our study at admission were within normal ranges suggests that they did not yet have a significant fluid deficit and that the effects of acute stress were not clearly evident. This may be explained by the absence of an association between copeptin and prognosis in patients with GI bleeding, under the aforementioned circumstances. Therefore, future studies may consider collecting serial measurements of serum copeptin and calculating the delta copeptin value in cases of vital sign changes and severe bleeding.

The presumed prognostic value of copeptin may be justified by the positive correlation between individual stress levels and the magnitude of the stressor, or in other words, the severity of the disease (7,19). Copeptin levels were elevated in trauma patients with hemorrhagic shock, predicting the need for massive transfusions (18). In patients with severe bleeding who require massive transfusion, erythrocyte suspensions are supplemented with FFP and platelet transfusions to ensure adequate management of blood loss and coagulopathy (18,20,21). The number of critically ill patients requiring emergency transfusion

in our cohort was limited, and the average vital signs of the patients were within normal ranges. However, a considerable proportion of patients were using anticoagulants. Taken together, these findings suggest that further studies with larger patient populations incorporating bleeding severity classifications and subgroup analyses of patients on anticoagulant therapy are needed to better elucidate the relationship between copeptin levels FFP and ES administration, thereby contributing to the literature and improving patient care processes.

In our investigation, we extended the application of the shock index primarily studied in trauma patients and other hemorrhagic conditions to patients with GI bleeding. In addition to prior studies, which have linked the shock index with thirty-day mortality (22,23), by establishing a cut-off value of 0.7, we found that this threshold correlates with an elevated 30-day mortality risk in patients with GI bleeding. Notably, a previous study reported inferior outcomes for the shock index compared to other prognostic scores regarding 30-day mortality, casting doubt on its clinical utility (24). Consequently, the literature presents conflicting evidence regarding the prognostic value of the shock index. In our study, although patients with fatal outcomes from GI bleeding exhibited high shock index values, the prognostic significance of the shock index was accentuated when considered alongside age. We hypothesize that the limited sample size may have contributed to this observation.

Study Limitations

A primary limitation of our study is the relatively small number of patients. This can be attributed to our city having multiple hospitals equipped to manage GI bleeding cases. Thus, such patients are often transported to other state hospitals via the pre-hospital health care system. Therefore, our dataset may have been insufficient to establish a definitive relationship between serum copeptin levels and prognosis. Additionally, we acknowledge that incorporating a standardized classification of GI bleeding severity could have provided clearer insight into the relationship between copeptin levels and vital signs across different degrees of bleeding. Nevertheless, our study revealed a significant association between the shock index and prognosis. Further research is needed to validate the hypothesis regarding the impact of the shock index on prognosis in the context of GI bleeding.

Conclusion

While serum copeptin levels failed to predict 30-day mortality in patients admitted to the ED for GI bleeding, our model demonstrated that age over 75 years, lower systolic blood pressure, and the shock index, easily calculated from vital signs, were superior predictors of mortality in this patient group.

Ethics

Ethics Committee Approval: The ethical suitability of this research was approved at the meeting of Pamukkale University the Non-Interventional Clinical Research Ethics Committee (decision number: 10, date: 25.05.2021).

Informed Consent: Written informed consent was obtained from the patients to be involved in the study.

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Footnotes

Authorship Contributions

Concept: E.A., A.O., M.A., M.Ö., O.T.E., M.B., K.İ.T., Design: E.A., A.O., Ö.K.E., M.A., M.Ö., O.T.E., M.B., K.İ.T., Data Collection or Processing: E.A., A.O., Ö.K.E., M.A., M.Ö., A.Y., M.S., O.T.E., M.B., K.İ.T., Analysis or Interpretation: E.A., A.O., Ö.K.E., M.A., M.Ö., A.Y., M.S., M.B., K.İ.T., Literature Search: E.A., A.O., M.A., O.T.E., Writing: E.A., A.O., M.A., A.Y., M.S., O.T.E.

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