Gastroenterología y Hepatología 46 (2023) 178–184

Gastroenterología y Hepatología

www.elsevier.es/gastroenterologia

ORIGINAL ARTICLE

Comparison of urgent and early endoscopy for acute non-variceal upper gastrointestinal bleeding in high-risk patients

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Received 16 January 2022; accepted 10 May 2022

KEYWORDS
Gastrointestinal endoscopy;
Gastrointestinal hemorrhage;
Outcome

Abstract
Objective: Data regarding early (within 24 h) and urgent endoscopy (within 12 h) in non-variceal upper gastrointestinal bleeding (NV-UGIB) revealed conflicting results. This study aimed to investigate the impact of endoscopy timing on the outcomes of high-risk patients with NV-UGIB.
Patients and methods: From February 2020 to February 2021, consecutive high-risk (Glasgow–Blatchford score ≥12) adults admitted to the emergency department with NV-UGIB were analyzed retrospectively. The primary composite outcome was 30-day mortality from any cause, inpatient rebleeding, need for endoscopic re-intervention, need for surgery or angiographic embolization.
Results: 240 patients were enrolled: 152 (63%) patients underwent urgent endoscopy (<12 h) and 88 (37%) patients underwent early endoscopy (12–24 h). One or more components of the composite outcome were observed in 53 (22.1%) patients: 30 (12.5%) had 30-day mortality, rebleeding occurred in 27 (11.3%), 7 (2.9%) underwent endoscopic re-intervention, and 5 (2.1%) required surgery or angiographic embolization. The composite outcome was similar between the groups. Multivariate analysis showed only hemodynamic instability on admission (OR: 3.05, $p = 0.006$), and the previous history of cancer (OR: 2.42, $p = 0.029$) were significant in predicting composite outcome. In terms of secondary outcomes, the endoscopic intervention was higher in the urgent endoscopy group ($p = 0.006$), whereas the number of transfused erythrocyte suspensions and the length of hospital stay was higher in the early endoscopy group ($p = 0.002$ and $p = 0.040$, respectively).

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Conclusions: Urgent endoscopy leads to a significant reduction in the length of hospitalization and the number of transfused erythrocyte suspensions in NV-UGIB, which can contribute to patient satisfaction, reduce healthcare expenditure, and improve hospital bed availability. The composite outcome and its sub-outcomes were the same among both groups.
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PALABRAS CLAVE
Endoscopia gastrointestinal;
Hemorragia gastrointestinal;
Resultado

Comparación entre endoscopia urgente y temprana para hemorragia digestiva alta no varicosa en pacientes de alto riesgo

Resumen
Objetivo: Los datos en relación con la endoscopia temprana (dentro de las 24 h) y urgente (dentro de las 12 horas) en la hemorragia digestiva alta no varicosa (HDA-NV) mostraron resultados contradictorios. El objetivo del estudio fue investigar el impacto del momento de la endoscopia en el desenlace de los pacientes de alto riesgo con HDA-NV.
Pacientes y métodos: Se realizó un análisis retrospectivo de adultos con HDA-NV consecutivos de alto riesgo (puntuación de Glasgow-Blatchford $\geq$ 12) ingresados en el servicio de urgencias entre febrero de 2020 y febrero de 2021. El principal resultado compuesto fue mortalidad a los 30 días por cualquier causa, nueva hemorragia de pacientes hospitalizados, necesidad de una nueva intervención endoscópica o necesidad de cirugía o embolización angiográfica.
Resultados: Se incluyeron 240 pacientes: 152 (63%) se sometieron a endoscopia urgente (< 12 h) y 88 (37%) a endoscopia temprana (12-24 h). Se observaron uno o más de los elementos del resultado compuesto en 53 (22,1%) pacientes: 30 (12,5%) tuvieron mortalidad a los 30 días, se produjo nuevo sangrado en 27 (11,3%), 7 (2,9%) se sometieron a una nueva intervención endoscópica y 5 (2,1%) requirieron cirugía o embolización angiográfica. El resultado compuesto fue similar entre los grupos. El análisis multivariado mostró que solamente la inestabilidad hemodinámica al ingreso (OR: 3,05, p = 0,006) y la historia previa de cáncer (OR: 2,42, p = 0,029) fueron significativos para predecir el resultado compuesto. En relación con los resultados secundarios, la intervención endoscópica fue más frecuente en el grupo de endoscopia urgente (p = 0,006), mientras que el número de transfusiones de suspensiones eritrocíticas y la duración de la estancia hospitalaria fueron mayores en el grupo de endoscopia temprana (p = 0,002 y p = 0,040, respectivamente).
Conclusiones: La endoscopia urgente conduce a una reducción significativa en el tiempo de hospitalización y en el número de transfusiones de suspensiones eritrocíticas en HDA-NV, lo que puede contribuir a la satisfacción del paciente, a la reducción del gasto en los cuidados de la salud y a mejorar la disponibilidad de camas en el hospital. El resultado compuesto y sus resultados secundarios fueron los mismos entre ambos grupos.
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Introduction

Acute upper gastrointestinal bleeding (UGIB) is a gastroenterological emergency with a high mortality rate.[1] Although there are significant advances in endoscopic and pharmacologic treatments, mortality rates of UGIB remain as high as 10%.[2–4] Due to its high mortality rates, detecting high-risk patients is crucial. In this concept, Glasgow–Blatchford score (GBS) has been widely used for classifying high-risk patients.[5,6] Prior studies demonstrated that mortality rates rise to 25% in high-risk patients. Thus, the timing of the endoscopy becomes more critical in this patient group.[7]

First-line treatment for UGIB consists of hemodynamic stabilization, fluid resuscitation, blood transfusion if needed, and proton pump inhibitor (PPI) infusion.[8,9] After the stabilization of the patient, endoscopic procedure is the next step for both diagnosis and treatment.[10,11] According to the current guidelines, it is recommended to perform early endoscopy (within 24 h) after the patient has been stabilized.[12–14] Nevertheless, whether urgent endoscopy (i.e., within 12 h) yields improved outcomes remain unclear, and data regarding the outcome of urgent endoscopy revealed conflicting results.[15–17]

Herein, we aimed to compare the outcomes of urgent (<12 h) and early (12–24 h) endoscopy in high-risk patients with non-variceal UGIB followed at our tertiary referral center.

Material and methods

Patient selection and data collection

The presented study was designed as a retrospective cohort study. From February 1st, 2020, to February 1st,

2021, consecutive high-risk adult patients admitted to the emergency department in Ankara City Hospital (Turkey) with symptoms and signs of UGIB (hematemesis, melena, blood on nasogastric aspirate) and underwent endoscopy were included in this study. Glasgow–Blatchford score (GBS) was used for risk classification, and patients with a score of ≥12 at admission were defined as high-risk patients. The exclusion criteria were defined as follows: GBS < 12, pregnancy, missing data for outcome assessment, altered upper gastrointestinal anatomy, patients who underwent endoscopy after 24 h of hospital admission, patients transferred from other hospitals, patients who developed gastrointestinal bleeding during hospitalization, and patients did not give informed consent to the endoscopic examination. Patients with variceal bleeding were also not included since their high mortality rates. The time of the emergency department (ED) admission and the start of the endoscopic examination were noted for each patient, and the time interval between them was defined as time to endoscopy. Then, patients were separated into two groups as urgent endoscopy (<12 h) and early endoscopy (12–24 h) based on endoscopy timing. The timing of endoscopy was decided by the gastroenterologist's own clinical decision in the ED. Demographic characteristics, medication history, comorbidities, clinical course, laboratory results, and endoscopy records were obtained from the electronic file of the patients. The GBS was calculated by using initial vital and laboratory findings. Before the endoscopic examination, all patients were treated with PPI infusion, fluid resuscitation, and blood transfusion if needed until vital signs were observed to be stabilized. This study was approved by Ankara City Hospital Scientific Research Assessment and Ethics Committee (Approval No: E1/1927/2021). Informed consent was not required because of the retrospective nature of the study.

Clinical outcome

In the presented study, the primary composite outcome was defined as the presence of death from any cause within 30 days, rebleeding within 30 days, need for endoscopic re-intervention, or need for surgery or angiographic embolization. Secondary outcomes were also evaluated, including the need for endoscopic intervention, blood transfusions, intensive care unit (ICU) admission, and length of stay. Rebleeding was defined as recurrence of bleeding demonstrated by new onset of bleeding signs (hematemesis, melena, or hematochezia), instability of vital signs, decrease of more than 2 g/dl in hemoglobin value, or bleeding confirmed on repeat endoscopic examination. Treatment options for rebleeding included endoscopic re-intervention, embolization, and surgical intervention. According to the endoscopist's decision, the remaining patients who did not receive interventional treatments were followed-up with PPI infusion, fluid resuscitation, and transfusion. Endoscopic re-intervention was defined as a repeat endoscopic therapy to control bleeding and achieve hemostasis. All patients were followed up closely during their hospitalization. The data for the outcome evaluation of patients who were discharged earlier than 30 days were obtained from the national health system or control gastroenterology outpatient application.

Statistical analysis

IBM SPSS Statistics for Windows, version 25.0 software (IBM Corp., Armonk, NY, USA) was used for data analysis. The normality of the distribution of numerical variables was determined using the Shapiro–Wilk test. Normally distributed numerical variables were expressed as mean ± standard deviation (SD), and non-normally distributed numerical variables were expressed as median (range). The student's *t*-test was used to compare normally distributed numerical variables between the groups, and the Mann–Whitney *U* test was used for non-normally distributed continuous variables. Categorical variables were described as frequencies (percentages). The Chi-square or Fisher's exact test was used to analyze categorical variables, as appropriate. The variables with a *p*-value ≤0.10 in the univariate regression analysis were taken into a multivariate logistic regression analysis to determine independent factors affecting composite outcomes. The regression analysis results were described using odds ratio (OR), 95% confidence interval (CI), and *p*-value. A *p*-value <0.05 was considered statistically significant.

Results

A total of 240 patients with UIGB were enrolled in the study; 152 (63%) patients underwent urgent endoscopy, and 88 (37%) patients underwent early endoscopy. The baseline characteristics of patients are given in Table 1. The median age of the whole study group was 74 (19–103) years, and 150 (62.5%) of the patients were male. At admission to the emergency department, 34 (14.2%) patients were in shock. Group comparisons of baseline characteristics showed no significant difference, except for endoscopy timing. The median endoscopy timing was 6.2 (3.8–10.4) h for the urgent endoscopy group and 16.4 (12.8–20.4) h for the early endoscopy group ($p < 0.001$).

Endoscopic findings and therapeutic modalities of the patients are given in Table 2. The endoscopic diagnoses expressed as others in Table 2 were: esophagitis, gastritis, duodenitis or erosions, angiodysplasia, and mucosal oozing. No significant difference was found in group comparisons in terms of endoscopic diagnosis. However, active bleeding lesions on endoscopy were significantly higher in the urgent endoscopy group ($p = 0.011$).

Table 3 shows the clinical outcomes and comparisons between the groups. One or more components of the primary composite outcomes were observed in 53 (22.1%) patients: 30 (12.5%) had 30-day mortality, rebleeding occurred in 27 (11.3%), 7 (2.9%) underwent endoscopic re-intervention, and 5 (2.1%) required surgery or angiographic embolization. Composite outcome and its sub-outcomes did not significantly differ between the groups.

Endoscopic intervention was performed on 84 (35%) patients in terms of secondary outcomes. During hospitalization, 222 (92.5%) patients required an erythrocyte suspension transfusion, and the median number of transfused erythrocyte suspensions per patient was 4 (0–8). Forty (16.7%) patients were referred to the intensive care unit. The median length of hospital stay was 6 days (1–48).

Table 1 Baseline characteristics of patients.

	Whole study group (*n*: 240)	Urgent endoscopy (*n*: 152)	Early endoscopy (*n*: 88)	*p* value
Age (years), median (range)	74 (19–103)	73 (19–99)	75.5 (20–103)	0.158
Male, n (%)	150 (62.5%)	99 (65.1%)	51 (58%)	0.268
Vital signs				
SBP (mmHg), mean ± SD	108.75 ± 17.04	108.60 ± 18.14	109.01 ± 15.04	0.852
HR (beats/min), median (range)	88 (44–160)	88 (55–153)	87.5 (44–160)	0.462
Hemodynamic instability (shock), *n* (%)	34 (14.2%)	23 (15.1%)	11 (12.5%)	0.573
Laboratory characteristics				
Hb level on admission, g/dl, mean ± SD	8.12 ± 1.96	8.29 ± 1.92	7.83 ± 2.02	0.087
Platelet, $\times 10^3/mm^3$, median (range)	258 (29–973)	261 (29–973)	254.5 (59–697)	0.803
INR, median (range)	1.2 (0.9–2.97)	1.18 (0.9–2.76)	1.21 (0.9–2.97)	0.563
Medication history				
NSAID use, *n* (%)	45 (18.8%)	30 (19.7%)	15 (17%)	0.607
Any Antiplatelet use, *n* (%)	74 (30.8%)	48 (31.6%)	26 (29.5%)	0.742
Any Anticoagulation use, *n* (%)	40 (16.7%)	21 (13.8%)	19 (21.6%)	0.119
Coexisting diseases				
Ischemic heart disease, *n* (%)	108 (45%)	64 (42.1%)	44 (50%)	0.236
Chronic liver disease, *n* (%)	6 (2.5%)	5 (3.3%)	1 (1.1%)	0.419
Chronic kidney disease, *n* (%)	37 (15.4%)	24 (15.8%)	13 (14.8%)	0.834
Cancer, *n* (%)	37 (15.4%)	27 (17.8%)	10 (11.4%)	0.186
Glasgow–Blatchford score, median (range)	13 (12–19)	13 (12–17)	13 (12–19)	0.384
Time to endoscopy (h), median (range)	8 (3.8–20.4)	6.2 (3.8–10.4)	16.4 (12.8–20.4)	**<0.001**

SD, standard deviation; SBP, systolic blood pressure; HR, heart rate; Hb, hemoglobin; INR, international normalized ratio; NSAID, nonsteroidal anti-inflammatory drug.

Table 2 Endoscopic findings and therapeutic modalities of patients.

	Whole study group (*n*: 240)	Urgent endoscopy (*n*: 152)	Early endoscopy (*n*: 88)	*p* value
Source of bleeding				
Gastric ulcer	48 (20%)	30 (19.7%)	18 (20.5%)	0.893
Duodenal ulcer	73 (30.4%)	50 (32.9%)	23 (26.1%)	0.272
Esophageal ulcer	10 (4.2%)	7 (4.6%)	3 (3.4%)	0.749
Mallory-Weiss injury	13 (5.4%)	10 (6.6%)	3 (3.4%)	0.383
Dieulafoy's lesion	4 (1.7%)	2 (1.3%)	2 (2.3%)	0.625
Malignancy	21 (8.8%)	14 (9.2%)	7 (8%)	0.740
Others	63 (26.3%)	36 (23.7%)	27 (30.7%)	0.235
No abnormality detected	8 (3.3%)	3 (2%)	5 (5.7%)	0.146
Active bleeding lesions on endoscopy	48 (20%)	38 (25%)	10 (11.4%)	**0.011**
Endoscopic intervention	84 (35%)	63 (41.5%)	21 (23.9%)	**0.006**
Diluted epinephrine injection	7 (2.9%)	5 (3.3%)	2 (2.3%)	1
Heater-probe thermocoagulation	6 (2.5%)	4 (2.6%)	2 (2.3%)	1
Hemoclip	12 (5%)	8 (5.3%)	4 (4.5%)	1
Argon plasma coagulation	4 (1.7%)	3 (2%)	1 (1.1%)	1
Combination therapy	55 (22.9%)	43 (28.3%)	12 (13.6%)	**0.009**

The endoscopic intervention was significantly higher in the urgent group ($p = 0.006$), whereas the number of transfused erythrocyte suspensions and the length of hospital stay were significantly higher in the early group ($p = 0.002$ and $p = 0.040$, respectively).

Univariate and multivariate analyses of the predictors of composite outcomes are expressed in Table 4. On univariate analysis, five parameters had a *p*-value of ≤ 0.10 (hemodynamic instability on admission, International Normalized Ratio (INR), systolic blood pressure (SBP), previous history of cancer, and antiplatelet drug use). Multivariate analysis showed that only two parameters were significant in predicting composite outcomes, hemodynamic instability on admission (OR: 3.05, 95% CI: 1.38–6.77, $p = 0.006$) and

Table 3 Clinical outcomes according to endoscopy timing.

	Whole study group (*n*: 240)	Urgent endoscopy (*n*: 152)	Early endoscopy (*n*: 88)	*p* value
Composite outcome	53 (22.1%)	30 (19.7%)	23 (26.1%)	0.249
Primary outcomes				
30-Day mortality, *n* (%)	30 (12.5%)	21 (13.8%)	9 (10.2%)	0.418
Inpatient rebleeding, *n* (%)	27 (11.3%)	13 (8.6%)	14 (15.9%)	0.082
Endoscopic re-intervention, *n* (%)	7 (2.9%)	2 (1.3%)	5 (5.7%)	0.103
Embolization/surgery, *n* (%)	5 (2.1%)	2 (1.3%)	3 (3.4%)	0.359
Secondary outcomes				
Endoscopic intervention, *n* (%)	84 (35%)	63 (41.4%)	21 (23.9%)	**0.006**
Transfusion required, *n* (%)	222 (92.5%)	138 (90.8%)	84 (95.5%)	0.186
Number of units transfused, median (range)	4 (0–8)	3 (0–8)	4 (0–8)	**0.002**
ICU admission, *n* (%)	40 (16.7%)	24 (15.8%)	16 (18.2%)	0.632
Length of stay (days), median (range)	6 (1–48)	5 (1–48)	7.5 (1–34)	**0.033**

ICU, intensive care unit.

Table 4 Univariate and multivariate analyses of predictors of composite outcomes.

	Univariate analysis			Multivariate analysis		
	p value	Odds ratio (95% CI)	95% Confidence interval	*p* value	Odds ratio (95% CI)	95% Confidence interval
Hemodynamic instability (shock)	**0.001**	3.49	1.63–7.49	**0.006**	3.05	1.38–6.77
Any antiplatelet use	**0.036**	0.45	0.21–0.95	0.094	0.52	0.24–1.12
Cancer	**0.014**	2.56	1.21–5.42	**0.029**	2.42	1.07–5.37
SBP (mmHg)	0.056	0.98	0.96–1.00	0.770	1.00	0.98–1.28
INR	0.075	1.74	0.95–3.18	0.064	1.85	0.97–3.54

SBP, systolic blood pressure; INR, international normalized ratio.

the previous history of cancer (OR: 2.42, 95% CI: 1.07–5.37, $p = 0.029$).

Discussion

In this retrospective study, urgent endoscopy was associated with a lower length of hospital stay, a smaller number of transfused erythrocyte suspensions, and a higher endoscopic intervention rate. However, we did not reveal any significant difference between the primary composite outcome and its sub-outcomes, including mortality, rebleeding, need for surgery/angiographic embolization, or endoscopic re-intervention between the urgent and early endoscopy groups. Notably, only two parameters were statistically significant in predicting composite outcomes: hemodynamic instability on admission and the previous history of cancer.

Current guidelines on the management of UIGB recommend performing early endoscopy within 24 h of hospital admission.[12,13] However, the role of endoscopy earlier than 24 h is ambiguous, especially in high-risk patients. In this concept, the impact of endoscopy timing on clinical outcomes was evaluated in several studies with different designs. In a retrospective study with 169 high-risk patients, no significant differences were observed in mortality and rebleeding between the two endoscopy groups (<6 vs. 6–12 h).[18] In another retrospective study of 189 high-risk patients, Tai et al. found that performance of endoscopy within 8 h was not associated with lower mortality compared with endoscopy performed between 8 and 24 h.[19] Another retrospective study by Kumar et al. showed no difference in mortality between the urgent (<12 h) and early (12–24 h) endoscopy groups. Yet, an increased risk of experiencing a composite outcome (mortality, inpatient rebleeding, need for angiographic embolization or surgery, endoscopic re-intervention) was found in the urgent endoscopy group.

Nevertheless, in the high-risk patients sub-group, the timing of endoscopy was not revealed as a significant predictor of the composite outcome.[20] In a prospective study of 961 high-risk patients, Cho et al. found that the urgent endoscopy group (<6 h) showed lower mortality compared to the elective endoscopy group (6–48 h), but no differences were found in terms of rebleeding and ICU admission.[15] However, in a recent randomized trial of 516 high-risk patients, Lau et al. found no difference in mortality and rebleeding between the two endoscopy groups (<6 vs. 6–24 h).[17] Our results are consistent with previous studies, which did not show any significant difference in mortality rates between urgent vs. early endoscopy groups.[17–20] However, the mortality rate of the whole study group was 12.5% in our study.

Our study population's high comorbidity rate and GBS score can explain the high mortality rate since they are associated with poor outcomes.

The relationship between the endoscopy timing and length of hospital stay, endoscopic intervention, or blood transfusion was also evaluated in previous studies. In a retrospective study, Ahn et al. reported that detection of high-risk endoscopic findings and the need for endoscopic intervention was higher in the urgent endoscopy group (<8 h) compared to the early endoscopy group (8–24 h).[21] Similarly, a retrospective study by Schacher et al. showed a significantly increased rate of detection of high-risk lesions and the need for endoscopic intervention in the emergent endoscopy group (3 h) compared to the elective endoscopy group (48 h).[22] In addition, Lin et al. found that endoscopy within 12 h reduces the length of hospital stay and the need for blood transfusion.[23] Also, a population-based study consisting of 2582 patients demonstrated that endoscopy performed within 24 h of presentation significantly reduced the length of hospital stay.[24] Moreover, another prospective multicenter study consisting of 348 patients also reported that endoscopy within 24 h of admission was associated with reduced length of hospital stay.[25] We also observed that urgent endoscopy was associated with a lower length of hospital stay, a lower number of transfused erythrocyte suspensions, and a higher endoscopic intervention rate, consistent with previous studies.[21–25] However, two recent study conflicts with our results which revealed that even higher endoscopic intervention rates were observed, urgent endoscopy group had a higher number of transfused erythrocyte suspensions, and no differences were observed between the groups in terms of length of hospital stay.[15,20] Notably, we demonstrated that active bleeding lesions on endoscopy were significantly higher in the urgent endoscopy group. This might be due to the fact that increment in the time period from ED application to endoscopy results in longer PPI infusion treatment before the endoscopic examination, which can facilitate the resolution of the signs of bleeding in the lesions and downstage risk status of the lesions. Also, the higher endoscopic intervention rate in the urgent endoscopy group can be explained by the higher detection of actively bleeding lesions in the urgent endoscopy group. In addition, the length of hospital stay was lower in the urgent endoscopy group. Endoscopy performed within 12 h could enable early identification of patients with low-risk lesions, which could be managed as an outpatient and may accelerate discharge decisions and shorten the length of hospital stay. However, despite the higher rate of endoscopic intervention and presence of active bleeding lesions in the urgent endoscopy group, whether or not earlier endoscopic intervention may influence the number of transfused erythrocyte suspensions could not be demonstrated since we could not provide the data regarding the success rate of endoscopic therapy. Therefore, in order to reach a conclusion, further prospective studies which investigate the influence of the endoscopists' experience and the success rate of endoscopic intervention on the outcomes are needed.

One of the other important outcomes of this study is that history of cancer and hemodynamic instability were significant in predicting composite outcomes. Previous studies demonstrated that the presence of comorbidity leads to worse outcomes in patients with non-variceal UGIB.[26,27] Therefore, special care should be taken in high-risk patients with a history of cancer and hemodynamic instability in the treatment of UIGB.

The leading limitation of the presented study was its retrospective design. However, despite its retrospective nature, missing data was minimal due to dual data recording by the doctor in ED and the authors as gastroenterology consultants. Secondly, patients with bleeding secondary to malignant lesions were also enrolled in this study which can affect the evaluation of the role of urgent endoscopy on the clinical outcomes since its high mortality rates. However, there was no difference in endoscopic findings between the two groups. Lastly, we defined primary composite outcome, similar to Kumar et al.[20], which can effectively assess the clinical outcomes in non-variceal UGIB.

Conclusions

In conclusion, urgent endoscopy significantly reduced the length of hospital stay and the number of transfused erythrocyte suspensions, which can contribute to patient satisfaction, reduce healthcare expenditure, and improve hospital bed availability. However, no significant differences were observed in both composite outcome and its sub-outcomes between the urgent (<12 h) and early (12–24 h) endoscopy groups in high-risk patients with non-variceal UGIB. Further prospective studies with a larger sample size are needed to evaluate the role of urgent endoscopy on the clinical outcomes of UGIB.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest

The authors declare they have no conflict of interest.

Acknowledgements

None.

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