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Incidence, Predictive Factors, Clinical Characteristics and Outcome of Non-variceal Upper Gastrointestinal Bleeding – A Prospective Population-based Study from Hungary

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ABSTRACT

Background & Aims: Acute non-variceal upper gastrointestinal bleeding (UGIB) is associated with significant morbidity and mortality. Our aim was to evaluate the incidence, management, risk factors and outcomes of acute non-variceal UGIB in a population-based study from Hungary.
Methods: The present prospective one–year study involved six major community hospitals in Western Hungary covering a population of 1,263,365 persons between January 1 and December 31, 2016. Data collection included demographics, comorbidities endoscopic management, Glasgow-Blatchford score (GBS), Rockall score (RS) transfusion requirements, length of hospital stay and mortality.
Results: 688 cases of acute non-variceal UGIB were included with an incidence rate of 54.4 (95%CI: 50.5-58.6) per 100,000 per year. Endoscopy was performed within 12 hours in 71.8%. 5.3% of the patients required surgical treatment and the overall mortality was 13.5%. Weekend presentation was associated with increased transfusion requirements (p=0.047), surgery (p=0.016) and mortality (p=0.021). Presentation with hemodynamic instability or presence of comorbidities was associated with transfusion (p<0.001 both), second look endoscopy (p<0.001 both), re-bleeding (p<0.001 both), longer in-hospital stay (p<0.001 both) and mortality (p=0.017 and p<0.001). GBS was associated with transfusion requirement (AUC:0.82; cut-off: GBS >7points), while mortality was best predicted by the post-endoscopic RS (AUC:0.75; cut-off: RS >5points).
Conclusions: Incidence rates of acute non-variceal UGIB in Western Hungary are in line with international trends. Longer pre-hospital time, comorbidities, hemodynamic instability, weekend presentation, treatment with anticoagulants or non-steroidal anti-inflammatory drugs was associated with worse outcomes.

Key words: gastrointestinal bleeding – non-variceal – incidence – risk factors – endoscopy – mortality.

Abbreviations: ASA: American Society of Anesthesiologists; AUC: Area Under the ROC Curve; GBS: Glasgow-Blatchford score; GI: gastrointestinal; *H. pylori*: *Helicobacter pylori;* NSAID: non-steroidal anti-inflammatory drug; PPI: proton-pump inhibitor; ROC: receiver-operating characteristic; RS: Rockall score; SD: standard deviation; UGIB: upper gastrointestinal bleeding.

INTRODUCTION

Acute non-variceal upper gastrointestinal bleeding (UGIB) is one of the most common gastrointestinal (GI) emergencies and associated with significant morbidity, mortality, and health economic burden. The reported incidence ranges from 36 to 172/100,000 inhabitants per year [1, 2].

The latest data show a change in the epidemiology of GI bleeding, with a decreasing incidence of UGIB and increasing incidence of lower GI bleeding [3-5]. The declining incidence trend of acute non-variceal UGIB may be attributed to widespread *Helicobacter pylori* (*H. pylori*) eradication, the increased use of proton pump inhibitors (PPIs) and improved endoscopic therapy. The reported mortality varies widely in different regions, but despite the improvement of medical treatment, therapeutic endoscopic technique, invasive radiology, surgical techniques and intensive care, the reported mortality of acute non-variceal UGIB in most surveys has remained high (between 5 and 14%) in the last decades [6-9]. The aging population with multiple comorbidities is postulated in the background of this discrepancy [10].

Crucial questions in the management of acute non-variceal UGIB are early risk stratification, resuscitation of critically

ill patients, transfusion threshold, timing of endoscopy, appropriate use of therapeutic endoscopic procedures, role of surgery and interventional radiology [11, 12].

There are very few published data of the epidemiology and clinical characteristics of acute non-variceal UGIB, moreover, of the use of known risk stratification scores and other predictive factors in the management of acute non-variceal UGIB from everyday clinical practice from Eastern Europe [3, 14]. The aim of the study was to evaluate incidence, characteristics, risk factors and outcomes in the management of acute non-variceal UGIB in a large multi-center study from Hungary.

METHODS

This present prospective one–year study involved six major community hospitals in Western Hungary covering a population of 1,263,365 persons in 2016. Seven hundred and ninety-six patients were treated and included in this registry with the principal diagnosis of acute UGIB between January 1 and December 31, 2016. Among these patients, n=688 (86.4%) consecutive and unselected cases who presented with a UGIB of non-variceal origin were included in our analysis. Case ascertainment was carried out in two steps. First, potential acute non-variceal UGIB cases were selected soon after presentation from hospital admission units, or in-patient cases from the treating departments. Case definition included visible blood loss originating from the GI tract (hematemesis, melena), or suspected GI bleeding based on clinical signs and laboratory results. Second, when the patient had been discharged or had died, relevant patient data confirming the initial diagnosis of acute non-variceal UGIB and details of the management process were collected from the hospital records. Demographic data were obtained from the official statistical yearbook of Hungary.

Data collection included demographic characteristics, symptom assessment of acute non-variceal UGIB and hemodynamic instability, comorbidities and parallel medications, elapsing time to hospital admission and endoscopy, laboratory results, endoscopic interventions, endoscopic findings, transfusion requirements, length of hospital stay and mortality. Risk assessment tools of Glasgow-Blatchford score (GBS), pre- and post- endoscopic Rockall score (RS) were obtained. The American Society of Anesthesiologists (ASA) physical status score of all patients were also registered. In peptic ulcer cases, the modified Forrest classification [15] of the lesion was obtained.

Descriptive statistics were applied for the characterization of demographic data, and features and processes of acute non-variceal UGIB management. Medians, interquartile ranges, means and standard deviation (SD) were calculated for continuous variables. Chi-Square test or Fisher's exact test was used in univariate analyses to assess prognostic factors in the management of acute non-variceal UGIB. Receiver-operating characteristic (ROC) analysis was used to assess the predictive potential of GBS and RS tools for clinical outcomes. Statistical analysis was performed using SPSS software v. 20.0 (Chicago, IL); $p<0.05$ was considered statistically significant.

Ethical approval was acquired from the National Medical Research Council [ETT TUKEB 52133- /2015/EKU (0423/15)].

RESULTS

Incidence of non-variceal UGIB and demographic data

A total of 688 cases of acute non-variceal UGIB were registered in the study period. In 117/688 cases (17%) the bleeding episode presented during in-hospital stay. Mean age at presentation was 68.6 years (Fig. 1), 61.3% (n=422) of the patients were male.

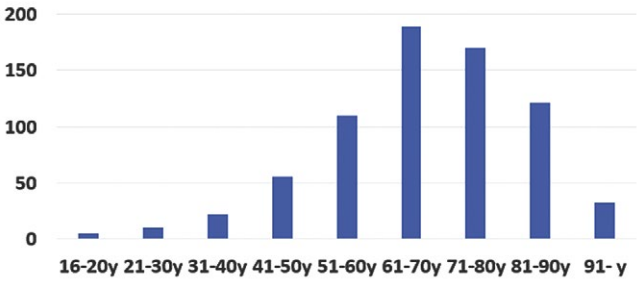

Fig. 1. Age distribution (n=688).

Based on these registered cases of acute non-variceal UGIB and the total population coverage (1,263,365 persons) of the six community hospitals, we estimated an incidence rate of 54.42 per 100,000 persons per year (95%CI: 50.5-58.6) in Western Hungary.

Time to presentation/admission and endoscopy

Time from symptom onset to presentation at the emergency department or to the dedicated admission units was <6 hours in 35.9% and <12 hours in 52.7% of the cases (n=571). Endoscopy was performed within 6 hours from hospital admission in 55.7%, <12 hours in 71.8% and <24 hours in 87.4% of the patients (n=678) (Fig. 2).

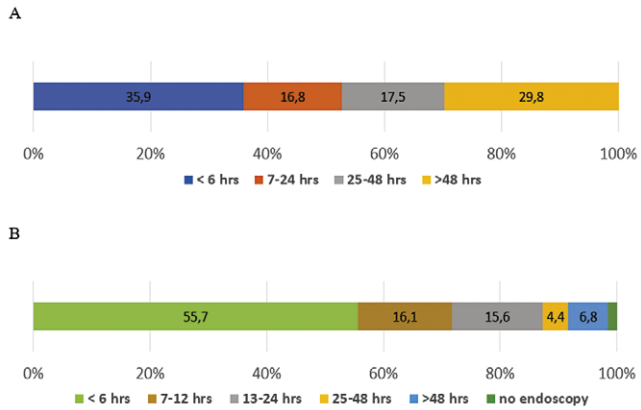

Fig. 2. A) Time from symptom onset to presentation at the emergency room (pre-hospital time); B) Time from hospital admission to endoscopy.

Diagnoses and severity of lesions in non-variceal UGIB patients

Most frequent diagnostic findings were duodenal ulcer (21.9 %), gastric ulcer (23.8%), gastroesophageal reflux disease (12.8%), erosive gastritis/duodenitis (11.3%) and Mallory-Weiss syndrome (9.4%), while malignancy and arteriovenous malformation were present in 4.7% and 4.4% in the upper GI

tract. For detailed distribution of all endoscopic findings in acute non-variceal UGIB cases see Table I. Among patients with gastric or duodenal ulcer, Forrest stage was Ia-b, IIa-b-c and III in 7.1%, 17.6%, 15.7%, 13.0%, 13.6% and 33% of the cases (n=323). Tissue sampling for *H. pylori* testing was performed in 232/688 cases (33.7%), *H. pylori* positivity was observed in 30.6% of the tested cases.

Table I. Distribution of primary diagnostic findings in acute non-variceal UGIB patients

Lesions	%
Gastric ulcer	23.8
Duodenal ulcer	21.9
Esophagitis	12.8
Erosive gastritis	11.3
Mallory-Weiss syndrome	9.4
Malignancy	4.7
Arteriovenous malformation	4.4
Congestive gastropathy	1.7
Jejunal ulcer	0.6
Other	4.2
No definitive lesion	3.6
Lack of endoscopy	1.5

Endoscopic interventions and medical therapy

Therapeutic intervention on initial endoscopy was performed in 37.1%, while 35.9% of patients required second look endoscopy. Nasogastric tube was placed in 18.9% of the cases. 5.3% of the patients required surgical treatment due to ineffective endoscopic therapy. Endoscopic therapy was performed in 49.5% of patients with gastric/duodenal ulcers. For treating high risk lesions (Forrest Ia-b, IIa) the use of hemoclip was the most preferred primary intervention. Endoscopic injection therapy with epinephrine as primary intervention was still applied in a significant proportion of patients; however its use was most frequent in conjunction with other hemostatic methods serving as complementary therapy (Fig. 3). Interventional radiologic procedure was applied in two patients in our cohort. Recurrent bleeding was registered in 19.7% (n=135) of the patients (confirmed on endoscopy in 23.8% of these cases).

Intravenous PPI therapy was applied in 78.8% of patients (16.4% received 72 hours i.v. PPI perfused therapy), while 20.3% of the patients received oral PPI therapy. Blood transfusion was given to 65.7% of the patients. Hospitalization stay exceeded 7 days in 50.3% of the patients. Mortality was 11.6% among patients with bleeding episode presenting outside the hospital (n=571), while the overall mortality rate (including in-hospital bleedings) was 13.5%.

Risk factors for outcomes: transfusion requirements, re-bleeding, second look endoscopy, length of hospital stay and mortality

Presentation with symptoms of hemodynamic instability at admission (i.e. tachycardia, hypotension or syncope) was associated with increased transfusion needs ($p<0.001$), second-look endoscopy ($p<0.001$), re-bleeding rates ($p<0.001$), longer in-hospital stay ($p<0.001$) and mortality ($p=0.017$). Longer time elapsing from symptom onset to presentation at the emergency department predicted transfusion requirements ($p=0.038$).

Time from hospital admission to endoscopy did not show significant association with transfusion rates, second look endoscopy, re-bleeding rates, hospitalization length or mortality. Similarly, in a sub analysis of patients presenting with hemodynamic instability, no significant association was found between time to endoscopy and the above mentioned endpoints.

Bleeding presentation at weekends was associated with increased transfusion requirements ($p=0.047$), surgery rates ($p=0.016$) and mortality ($p=0.021$). There was also a tendency for higher re-bleeding rates ($p=0.08$).

Initial patient admission to internal medicine/gastroenterology general ward was associated with lower transfusion rates (OR=0.54; 95%CI: 0.38-0.75; $p<0.001$), and fewer endoscopic hemostatic intervention (OR=0.37; 95%CI: 0.25-0.53; $p<0.001$) compared to dedicated emergency department, intensive care unit, or sub-intensive unit admissions. There were no significant differences in mortality or re-bleeding rates. Of note, 46.1% of patients were first

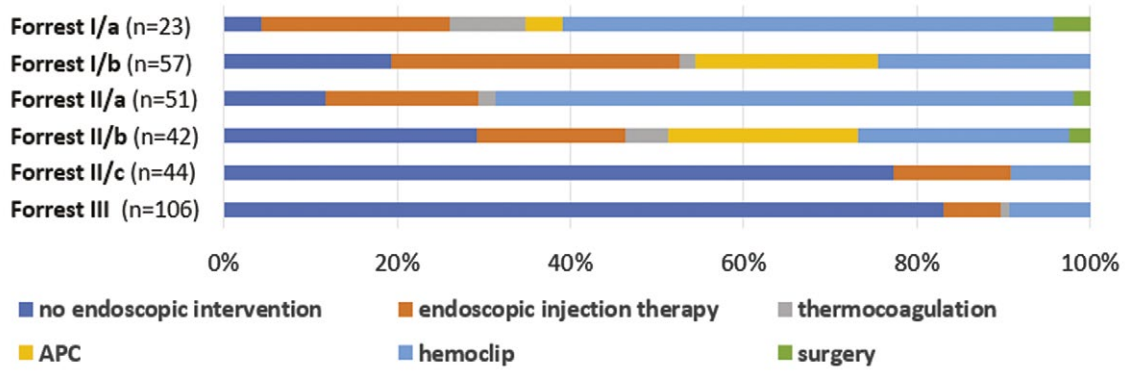

Fig. 3. Distribution of primary endoscopic interventions in patients with gastric/duodenal ulcer based on Forrest classification of the lesion (n=323). Overall rate of secondary endoscopic injection therapy applied as a complementary haemostatic method to mechanical or thermal modalities: Forrest I/a: 43.5%; Forrest I/b: 43.9%; Forrest II/a: 58.8%; Forrest II/b: 42.9%; Forrest II/c: 9.1%; Forrest III: 7.5%

admitted to the emergency care unit, 31.5% to internal medicine ward, 13.7% to sub-intensive care and 6.1% to intensive care units and 2.3% to surgical ward at presentation.

Patients on anticoagulant, antithrombotic or non-steroidal anti-inflammatory drug (NSAID) medications had higher transfusion needs (p<0.001), second look endoscopy (p=0.006), re-bleeding rates (p=0.04) and longer in-hospital stay (p=0.004), but no increased mortality (p=0.571).

The ASA Physical Status Score of 1-2 points versus 3-4 points correlated with transfusion requirements (p<0.001), second look endoscopy (p=0.06), re-bleeding rates (p<0.001) endoscopic intervention (p=0.033), mortality (p<0.001) and hospitalization length (p<0.001) (Table II).

In a ROC analysis, the GBS was best predictive of transfusion requirements (AUC: 0.82; cut-off: GBS >7points; sensitivity: 71.9% specificity: 78%), while mortality was strongly associated with the post-endoscopic RS (AUC: 0.75; cut-off: RS >5points; sensitivity: 68.8% specificity: 68.9%) (Fig. 4).

DISCUSSION

Our study represents a comprehensive, prospective one–year report on the management of acute non-variceal UGIB cases involving six major community hospitals in Western Hungary covering a population of 1,263,365 people. The calculated incidence rate of acute non-variceal UGIB in Hungary (54.4 per 100,000 persons per year, 95%CI: 50.5-58.6) is in the mid-range compared to reported international trends. Longer pre-hospital time, comorbidities, hemodynamic instability or weekend presentation, treatment with anticoagulants or NSAIDs was associated with worse outcomes.

Incidence rates of acute non-variceal UGIB represent a large geographic variation, ranging from 36 to 172 cases per 100,000 population per year in the last two decades in Europe [1, 2, 15-20]. Possible explanations for the reported variations are differences in case-definition, population characteristics, prevalence of gastroerosive medications, (i.e. aspirin and NSAIDs), prevalence of comorbidities and *H. pylori* infection. The annual incidence of peptic ulcer bleeding was 47.6 per 100,000 persons in 2002-2004 in an Italian population-based study [21]. Most time-trend studies report a significant decline in incidence of all-cause of UGIB, which is driven by the decrease of non-variceal UGIB cases [5, 21]. Consistent reports from earlier years show higher incidence rates of UGIB among males and the elderly [1, 2, 16, 17]. Results from more recent large multicenter observational data of non-variceal UGIB from Italy and the UK also reported a mean age of patients over 60 years and a higher incidence among men [12, 22].

Despite advances in diagnosis and treatment of acute non-variceal UGIB, the condition carries considerably high mortality. A systematic review of 18 studies (10 using administrative databases and 8 using patient registries) showed mortality rates in non-variceal UGIB ranging from 1.1% (Japan) to 11% (Denmark), while the majority of studies included showed a mortality rate around 5% [23]. Based on data from a Canadian bleeding registry of 6 community and 12 tertiary care institutions, overall mortality was 5.5% in the period 1999–2001 for patients presenting with non-variceal UGIB [24]. On the other hand, higher mortality rates have been published by a retrospective study using administrative claims database in the UK, which estimated the 28-day mortality of non-variceal UGIB to be as high as 13.1% in 2007, and a total of 14.3% between 1999 and 2007 [25]. Another nationwide audit of the management of UGIB in the UK, including 6,750 patients, estimated a crude in-hospital mortality of 10% in all UGIB cases [12]. Based on endoscopic diagnoses, peptic ulcer disease patients showed a mortality rate 8.9%. In parallel with our results, there were substantial differences in mortality comparing new admissions and inpatients (in-hospital presentation of bleedings). In-hospital bleeders reached a high 22% mortality rate in peptic ulcer disease [25]. Comparing

Table II. Potential prognostic factors in the management of acute non-variceal gastrointestinal bleeding

	Transfusion	Endoscopic intervention	Second-look endoscopy	Re-bleeding	Mortality	Hospitalization length
Time from symptom onset to presentation at the ER (<6 hrs; 7-24 hrs; 25-48 hrs; >48 hrs)	p=0.038	p=0.32	p=0.93	p=0.32	p=0.07	p=0.45
Time from hospital admission to endoscopy (<6 hrs; 7-12 hrs; 13-24 hrs; 25-48 hrs; >48 hrs)	p=0.22	p=0.325	p=0.53	p=0.09	p=0.54	p=0.48
Bleeding presentation at weekends versus weekdays	OR 1,43; [1,0-2,0]; p=0.047	OR 0.97; [0.69-1.36]; p=0.85	OR 1.01; [0.72-1.42]; p=0.95	OR 1.92; [1.38-2.66]; p=0.09	OR 1,72; [1,1-2,7]; p=0.021	p=0.22
Symptoms of hemodynamic instability (i.e. tachycardia, hypotension, syncope)	OR 3,57; [2,6-5,0]; p<0.001	OR 1.74; [0.78-3.36]; p=0.12	OR 1.92; [1.38-2.66]; p<0.001	OR 2.15; [1.42-3.7]; p<0.001	OR 1,80; [1,1-2,9]; p=0.017	p<0.001
Anticoagulant, antithrombotic or NSAID medications	OR 1,77; [1,3-2,4]; p<0.001	OR 1.24; [0.90-1.69]; p=0.19	OR 1,57; [1,13-2,17]; p=0.006	OR 1,49; [1,01-2,21]; p=0.04	OR 1.17; [0.75-1.83]; p=0.49	p=0.004
ASA Physical Status Score (1-2 points vs. 3-4 points)	OR 2,95; [2,1-4,1]; p<0.001	OR 1,40; [1,1-1,9]; p=0.033	OR 1.34; [0.98-1.84]; p=0.06	OR 1.89; [1.28-2.79]; p<0.001	OR 8,97; [4,7-17,2]; p<0.001	p<0.001

OR: odds ratio; ER: emergency room; ASA: American Society of Anesthesiologists; NSAID: non-steroidal anti-inflammatory drug; ORs are shown for all 2x2 tables.

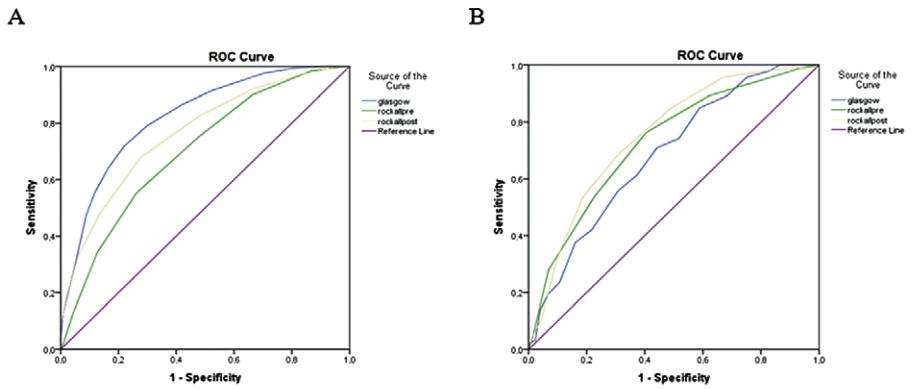

Fig. 4. Predictive potential of Glasgow-Blatchford Score, pre- and post- endoscopic Rockall Score for transfusion requirements (Fig. 4A) and mortality (Fig. 4B). Fig. 4A: pre-endoscopic RS: AUC 0.700; post-endoscopic RS: AUC 0.763; GBS: AUC 0.822; Fig 4B: GBS: AUC 0.684; pre-endoscopic RS: AUC 0.728; post-endoscopic RS: AUC 0.75.

outpatients presenting with non-variceal UGIB to those who started hemorrhaging while hospitalized, a threefold greater mortality was observed in the latter group based on the above mentioned Canadian bleeding registry [26].

The cohort characteristics, and major indicators of therapy, such as patient demographics, endoscopic findings, prevalence of stigmata, PPI therapy, transfusion requirements, re-bleeding rates were comparable to previously published data on non-variceal UGIB [2, 4, 6, 12, 21, 24]. The overall rate of endoscopic therapy was very much comparable to data from a Canadian bleeding registry of ~1,800 patients with non-variceal UGIB (in both studies: 37% for all cause stigmata), as was the modest use of combination injection plus thermal therapy, and the relatively high rate of injection alone therapy [24]. Based on prospective data from Italy, injection therapy alone was performed in 43.4%, isolated thermal coagulation in 29.2%, hemoclip in 19.1%, and combined endotherapy with injection and thermal coagulation in 8.3% of patients with non-variceal bleeding [22]. Embolization techniques were used in two patients in our cohort, one related to duodenal ulcer and one to pancreatic malignancy. Interventional radiology may have a somewhat diminished role in the management of UGIB in our study compared to other multicenter data [12, 24]. However our cohort comprises mainly county hospitals, where these procedures have more limited availability. Our study reported higher re-bleeding rates. High re-bleeding rates were also reported in UK (~13%), but considerably lower rates by Italian prospective data; however, definitions of recurrent bleeding vary [12, 24].

We examined several potential predictors for outcome parameters (transfusion requirements, re-bleeding, length of hospital stays and mortality), and identified 'weekend effect', symptoms of hemodynamic instability, risk medications and the ASA physical status score as prominent predictors of clinical outcomes. Similarly to our results, Barkun et al. [24] found age, hemodynamic instability (OR=1.18, 95%CI: 1.08 – 1.30), more than one existing comorbidities (OR=1.19, 95%CI: 1.04 – 1.35), in-patient status at bleeding onset (OR=2.77, 95%CI: 1.64 – 4.66) and general health status (class 1 or 2 versus others as determined by the ASA score; OR: 9.52, 95%CI: 3.37 – 26.31) as significant baseline predictors of increased mortality in a large Canadian registry of non-variceal UGIB. In a prospective analysis of consecutive patients with non-variceal UGIB at 23 community and tertiary care institutions from Italy in 2003 and 2004, authors found that age (< 80 years), presence of severe comorbidity, low hemoglobin levels at presentation, and worsening health status (defined by ASA score 3 or 4) were independent predictors of 30-day mortality [22].

Endoscopy was performed within 24 hours in the majority of our patients (87.6%) and less than 12 hours of admission in 71.8%. Although the majority of available literature data supports no additional benefit in clinical outcomes when differentiating within the 24 hours time frame of 'urgent endoscopy', the role of more urgent endoscopy (<6hours, <12hours) remains controversial, as the performance of identifying high-risk lesions may increase [27, 28]. A recent prospective study investigated the role of endoscopy within 6 hours (urgent-endoscopy group) or between 6 and 24 hours (early-endoscopy group) in a large, randomized cohort of acute UGIB patients (Glasgow–Blatchford score of 12 or higher). No difference was observed in 30-days all-cause mortality or 30-days re-bleeding rates. Endoscopic treatment administered during initial endoscopy was higher in the urgent-endoscopy group; however, this did not translate into a lower incidence of further bleeding or fewer deaths [29]. We found no association between the timing of endoscopy and any of our endpoints. Timing of endoscopy was not found to be a significant predictor of outcome in other similar studies either [22, 24]. No differences were observed either in outcome parameters based on the time elapsed between symptom onset and presentation to the emergency department in our study, except for transfusion needs. Bleeding presentation at weekends versus weekdays however, impacted mortality and transfusion needs, and there were trends towards higher re-bleeding rates as well. In an administrative database analysis from Scotland, weekend admissions showed a consistently higher mortality and greater lengths of stay compared with weekdays in the management of acute UGIB [30]. Similar findings on the 'weekend effect' were reported by Shaheen et al. [31] from Canada with higher rates of mortality and surgical intervention, prolonged hospital stays, and increased hospital

charges. Even after adjusting for the timing of endoscopy, weekend admission remained an independent predictor of mortality (OR=1.12; 95%CI: 1.05-1.20).

Risk stratification in patients with acute non-variceal UGIB is essential for optimal management. In our study, the Rockall scores and Glasgow-Blatchford score were recorded during data collection, both being prospectively and externally validated as effective tools to predict clinical/endoscopic intervention need, complications or death [32, 33]. A considerable advantage of the GBS is that it can be calculated using only clinical data available on presentation, whereas the RS include endoscopic findings. The clinical RS is a derivate of the RS by only using the pre-endoscopy clinical parameters. We determined the predictive performance of these three score systems in terms of transfusion requirements and mortality. Blood transfusion was best predicted by a GBS of more than 7 points, while in-hospital mortality was best predicted by a post-endoscopic RS of more than 5 points in our cohort. Several studies have compared the RS with the GBS and other existing risk stratification tools. Tang et al. [34] compared the performance of risk assessment scores in an emergency department setting with 395 subjects, showing that GBS was superior to the pre-endoscopic RS in predicting 30-day mortality. In a recent large, multicenter study of more than 3,000 subjects, comparing several pre-endoscopic (AIMS65, GBS, pre-endoscopic RS) and post-endoscopic (full RS, Progetto Nazionale Emorragia Digestiva [PNED]) risk assessment tools, the GBS was superior to all other scores at predicting blood transfusion, interventional endoscopy, surgery, or inpatient death [35]. The best score cut-offs for predicting 30-day mortality were ≥4 points for pre-endoscopic RS, and ≥5 points for full RS and GBS. A threshold of GBS of 8 points was best predicting blood transfusion [34].

The strengths of the study include the prospective, population-based nature of the study and extensive data capture, including endoscopic management, possible risk factors and several important outcome parameters. The limitations of the study include the lack of harmonized patient management in the different hospitals, endoscopy units, differences in the availability of endoscopic techniques and differences in the admission wards (availability of specified gastrointestinal ward vs. internal medicine ward). Despite these limitations we believe that our data provide a valid portray of the incidence, risk factors and management of non-variceal UGIB in a well-defined geographic area from Eastern Europe.

CONCLUSIONS

Incidence rates of acute non-variceal UGIB in Western Hungary are in line with international trends. Longer pre-hospital time, comorbidities, hemodynamic instability or weekend presentation, treatment with anticoagulants or NSAIDS were identified as important predictors of outcomes, while ASA physical status score, GBS and RS predicted clinical outcomes and transfusion requirements. We observed higher mortality rates; mainly among elderly patients because higher comorbidity rates can be observed in this population. These factors should be taken into account in the optimization of the management of non-variceal UGIB

Conflicts of interest: None to declare.

Authors' contribution: L.L. developed the protocol, collected data, drafted and revised the manuscript. L.G. analysed data and drafted the manuscript. L.L., F.I., A.P., I.R., B.G., L.V.S. and A.I. equally contributed to the data collection and scientific interpretation of the results, manuscript revision. P.L. was responsible for research planning and result interpretation, statistical analysis, supervised the manuscript preparation and is acting as guarantor of submission. All authors read and approved the final manuscript including the authorship list.

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