ORIGINAL ARTICLE

TJG
The Turkish Journal of Gastroenterology

An observational European study on clinical outcomes associated with current management strategies for non-variceal upper gastrointestinal bleeding (ENERGIB-Turkey)

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Background/aims: *This observational, retrospective cohort study assessed outcomes of the current management strategies for non-variceal upper gastrointestinal bleeding in several European countries (Belgium, Greece, Italy, Norway, Portugal, Spain, and Turkey) (NCT00797641; ENERGIB).* ***Materials and Methods:*** *Turkey contributed 23 sites to this study. Adult patients (≥18 years old) consecutively admitted to hospital and who underwent endoscopy for overt non-variceal upper gastrointestinal bleeding (hematemesis, melena or hematochezia, with other clinical/laboratory evidence of acute upper GI blood loss) were included in the study. Data were collected from patient medical records regarding bleeding continuation, re-bleeding, pharmacological treatment, surgery, and mortality during a 30-day follow-up period.* ***Results:*** *A total of 423 patients (67.4% men; mean age: 57.8±18.9 years) were enrolled in the Turkish study centers, of whom 96.2% were admitted to hospital with acute non-variceal upper gastrointestinal bleeding. At admission, the most common symptom was melena (76.1%); 28.6% of patients were taking aspirin, 19.9% were on non-steroidal anti-inflammatory drugs, and 7.3% were on proton pump inhibitors. The most common diagnoses were duodenal (45.2%) and gastric (27.7%) ulcers and gastritis/gastric erosions (26.2%). Patients were most often managed in general medical wards (45.4%). A gastrointestinal team was in charge of treatment in 64.8% of cases. Therapeutic procedures were performed in 32.4% of patients during endoscopy. After the endoscopy, most patients (94.6%) received proton pump inhibitors. Mean (SD) hospital stay was 5.36±4.91 days. The cumulative proportions of continued bleeding/re-bleeding, complications and mortality within 30 days of the non-variceal upper gastrointestinal bleeding episode were 9.0%, 5.7% and 2.8%, respectively. In the Turkish sub-group of patients, the significant risk factors for bleeding continuation or re-bleeding were age >65 years, presentation with hematemesis or shock/syncope, and the diagnosis of duodenal ulcer. The risk of clinical complications after non-variceal upper gastrointestinal bleeding was higher in female patients older than 65 years, in patients with comorbidities, and in patients presenting with shock/syncope, and also according to time to endoscopy. The use of aspirin, non-steroidal anti-inflammatory drugs or warfarin at baseline was negatively associated with the development of bleeding or clinical complications. The risk of death within 30 days after non-variceal upper gastrointestinal bleeding was significantly higher in patients older than 65 years and in those receiving transfusions other than intravenous fluid or red blood cells within 12 hours of presentation.* ***Conclusions:*** *According to the survey results, non-variceal upper gastrointestinal bleeding in Turkey varies from that in other European countries in a number of aspects. These differences could be associated with a younger population and Helicobacter pylori incidence. Despite the diminishing need for surgical intervention and mortality rates for non-variceal upper gastrointestinal bleeding, as is the case in other European countries, non-variceal upper gastrointestinal bleeding remains a serious problem.*

Key words: Non-variceal gastrointestinal bleeding, endoscopy, proton pump inhibitor, bleeding, mortality

Güncel tedaviler ile varis dışı üst gastrointestinal kanamaların klinik sonuçları ile ilişkili gözlemsel Avrupa çalışması (ENERGIB-Türkiye)

Amaç: *Gerçekleştirilen bu gözlemsel ve retrospektif kohort çalışmasında Belçika, Yunanistan, İtalya, Norveç, Portekiz, İspanya ve Türkiye gibi çeşitli Avrupa ülkelerinde varis dışı üst gastrointestinal kanama için mevcut olan güncel yönetim stratejilerine ilişkin sonuçlar değerlendirilmiştir (NCT00797641; ENERGIB).* ***Gereç ve Yöntem:*** *Türkiye çalışmaya 23 merkez ile katılmıştır. Bu çalışmaya sürekli olarak hastaneye başvuran ve overt varis dışı üst gastrointestinal kanama (hematemez, melena veya hematokezya ve bunlarla birlikte akut üst gastrointestinal kanamanın diğer klinik/laboratuvar bulguları) için endoskopi uygulanmış olan erişkinler (18 yaş ve üzeri) dahil edilmiştir. Hastaların tıbbi kayıtlarından 30 günlük bir takip sürecindeki kanama süresi, tekrar ka-*

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Manuscript received: 07.06.2011 **Accepted:** 02.09.2011

Turk J Gastroenterol 2012; 23 (5): 463-477
doi: 10.4318/tjg.2012.0402

nama, farmakolojik tedavi, cerrahi ve mortalite gibi veriler toplanmıştır. ***Bulgular:*** *Türkiye'deki çalışma merkezlerine toplam 423 hasta dahil edilmiştir (% 67.4 erkek, ortalama yaş: 57.8±18.9 yıl) ve bu hastaların %96.2'si varis dışı üst gastrointestinal kanama ile hastaneye başvurmuştur. Hastaneye başvuru anında en sık rastlanan semptom melenadır (%76.1) ve yine başvuru esnasında hastaların %28.6'sı aspirin, %19.9'u non-steroid anti-inflamatuvar ve %7.3'ü de proton pompa inhibitörü kullanmaktadır. En sık konulan teşhis ise duodenal (%45.2) ve gastrik (%27.7) ülser ve gastrit/gastrik erozyondur (%26.2). Hastaların %45.4'ü için yoğun bakım şartlarına ihtiyaç duyulmamıştır. Vakaların %64.8'inin tedavisi bir gastrointestinal tedavi grubu tarafından yürütülmüştür. Hastaların %32.4'ünde endoskopi esnasında terapötik prosedürler de uygulanmıştır. Endoskopi sonrasında hastaların %94.6'sı proton pompa inhibitörü kullanmıştır. Ortalama (SD) hastanede kalış süresi 5.36±4.91 gündür. Varis dışı üst gastrointestinal kanama epizodunu takip eden 30 gün içerisindeki devam eden kanama/tekrarlayan kanama, komplikasyon ve mortaliteye ilişkin kümülatif oran sırasıyla %9.0, %5.7 ve %2.8'dir. Kanamanın devam etmesi ve tekrarlayan kanamaya ilişkin anlamlı risk faktörleri Türk hastalar için 65 yaş ve üzeri olma, hematemez veya şok/senkop ile başvuru ve duodenal ülser tanısı olarak sayılabilir. Varis dışı üst gastrointestinal kanama sonrasında klinik komplikasyon gelişme riski 65 yaş üzerindeki kadın hastalarda, komorbiditeye sahip hastalarda ve şok/senkop ile başvuran hastalarda daha yüksektir. Başlangıçta aspirin, non-steroidal antiinflamatuvar ilaç veya varfarin kullanımı ile kanama gelişimi veya klinik komplikasyonların gelişimi arasında negatif bir ilişki mevcuttur. Varis dışı üst gastrointestinal kanamayı takip eden 30 gün içerisindeki ölüm riski 65 yaş üzerindeki hastalarda ve 12 saat içerisinde IV sıvı veya eritrosit haricinde transfüzyon almış olan hastalarda anlamlı biçimde daha yüksektir.* ***Sonuç:*** *Sağ kalıma ilişkin bulgular göz önünde bulundurulduğunda, Türkiye'de varis dışı üst gastrointestinal kanama Avrupa ülkelerine kıyasla çeşitli açılardan farklılıklar göstermektedir. Söz konusu bu farklılıklar popülasyonun daha genç olması ve Helikobakter pilori insidansı ile ilişkili olabilir. Diğer Avrupa ülkelerinde varis dışı üst gastrointestinal kanamada cerrahi girişimlere olan ihtiyaç ve mortalite oranları giderek azalmaktaysa da bu durum halen ciddi bir sorun teşkil etmektedir.*

Anahtar kelimeler: Varis dışı gastrointestinal kanama, endoskopi, proton pompa inhibitörü, kanama, mortalite

INTRODUCTION

Non-variceal upper gastrointestinal bleeding (NVUGIB), due to erosions of the esophagus, stomach and duodenum, has been ranked as the most common medical emergency managed by gastroenterologists. It occurs with an incidence of 50–150 per 100,000 of the population each year and with associated mortality rates of approximately 11–14% (1-4).

Major advances over recent decades in the treatment of acute upper GI hemorrhage (5,6), such as the advent of therapeutic endoscopy and the widespread use of proton pump inhibitors (PPIs) to promote hemostasis and healing of bleeding lesions, have not been reflected by improvements in mortality rates associated with the disease (7,8).

The ageing of the population as well as associated increases in comorbidity have been cited for this lack of significant improvement in associated mortality rates in spite of advances in the medical and endoscopic treatment of upper GI hemorrhage (7-9). Subsequently, considerable effort has been made to identify the risk factors that may indicate those whose mortality rates may be higher (10).

The management of NVUGIB varies internationally, not just from one country to another but also between academic centers and district hospitals. While randomized clinical trials have been considered to be the gold standard for determining the efficacy of disease management, the outcomes obtained in clinical studies may be far from those of daily clinical practice (11).

Therefore, the ENERGIB (European Survey of Non-Variceal Upper Gastro Intestinal Bleeding) Study (NCT00797641) aimed to assess the current management strategies in a pan-European "real-life" setting and to uncover unmet needs concerning NVUGIB. It was designed to describe the clinical outcomes with current endoscopic and pharmacological treatment strategies in the management of NVUGIB in relation to bleeding continuation, re-bleeding and mortality and to assess the predictive factors associated with the clinical outcome (12). Data obtained from patients included in the study in Turkey are presented herein.

MATERIALS AND METHODS

Patient Population and Study Design

The ENERGIB survey is an observational, international, multicenter retrospective cohort study involving 2660 patients at 123 centers across seven countries including Belgium, Greece, Italy, Norway, Portugal, Spain, and Turkey (NCT00797641); the study was conducted in Turkey with 423 eligible patients selected according to codes from ICD9/ICD10 registered at 23 different hospitals across Turkey between January 6 and March 10, 2009.

In order to obtain an accurate estimate of the proportion of patients with continued and/or re-bleeding during the same hospitalization or up to 30 days from the NVUGIB episode, when the sample size was 400 patients, a two-sided 95.0% confiden-

ce interval for a single proportion using the large sample normal approximation extended less than 3.5% from the observed proportion, for an expected proportion of 14.1% (13). The study investigators were specialists from a representative sample of hospitals and were selected by the Project Advisory Board of the study and AstraZeneca authorities according to their geographical distribution and the local incidence of NVUGIB in Turkey in order to achieve the expected sample size according to the proposed timelines.

Adult patients (≥18 years) admitted to hospital or inpatients admitted for another reason, presenting overt NVUGIB manifestations as hematemesis/coffee ground vomiting, melena, hematochezia, and other clinical or laboratory evidence of acute blood loss from the upper GI tract over the selection period were included in the study, provided that an upper GI endoscopy was performed and complete medical records related to hospitalization were available for the study. Data concerning the NVUGIB episode and up to 30 days afterwards were retrospectively collected from medical records of each patient. The assignment of a patient to a particular therapeutic strategy was not decided in advance by a protocol but fell within current practice in each hospital. Neither visits nor interventions were carried out in order to maintain the non-interventional study design.

The study was conducted in accordance with ethical principles that are consistent with the Declaration of Helsinki and legislation applicable to non-interventional studies as well as to national regulations and guidelines governing medical practice and ethics.

Primary Study Variables

Bleeding continuation after treatment, re-bleeding, surgery, and mortality were the primary endpoints of the study. Management strategy and therapies during hospitalization were also recorded.

Continued bleeding was defined as spurting from an artery at the initial endoscopic examination, which did not respond to endoscopic therapy, or persistence following initial endoscopy; and/or the presence of a red bloody nasogastric aspirate; and/or shock with a pulse greater than 100 beats/min, a systolic blood pressure of under 100 mmHg, or both; and/or the need for substantial replacement of blood and fluid volume (transfusion of more than 3 units of blood within 4 hour [h]) following endoscopic therapy.

Re-bleeding was defined as recurrent vomiting of fresh blood, melena, or both, with either shock or a decrease in hemoglobin concentration of at least 20 g/L following initial successful treatment including resuscitation and endoscopic therapy, if indicated, during the same hospitalization (up to 30 days from the NVUGIB episode) or after discharge (up to 30 days from the NVUGIB episode).

Surgery (except endoscopic treatment) was evaluated during the same hospitalization (up to 30 days from the NVUGIB episode) or after discharge (up to 30 days from the NVUGIB episode).

Mortality was evaluated as in-hospital mortality, i.e. during hospitalization (up to 30 days from the NVUGIB episode) or after discharge (up to 30 days from the NVUGIB episode). Mortality cases were classified into bleeding-related and non-bleeding-related deaths. Bleeding-related death included deaths from uncontrolled bleeding, within 48 h of endoscopy, during surgery for uncontrolled bleeding, from surgical complications, or within one month of surgery, and from endoscopic-related mortality. Non- bleeding-related death included deaths due to cardiac, pulmonary, or cerebrovascular diseases, multi-organ failure including liver and kidney failure, and terminal malignant diseases.

Secondary Study Variables

Secondary variables included patient characteristics, bleeding characteristics, hospitalization, diagnostic tests, therapeutic strategy, and the assessment of predictive factors associated with clinical outcomes.

Factors related to patient characteristics were gender, age, alcohol use, underlying hematological condition, source of admission, clinical risk assessment (≥65 years, shock, comorbidities, fresh red blood on rectal examination/emesis, or nasogastric tube aspirate), Rockall and/or American Society of Anesthesiologists (ASA) and/or Blatchford scoring, previous treatment (empirical therapy with high-dose PPI from admission until endoscopy), time to endoscopy from admission, Forrest classification or endoscopic stigmata of high risk (active bleeding and visible vessel) or low risk (protuberant pigmented clot and clean-based ulcer), and treatment (administration route, dosing, onset date, and the length of treatment).

Bleeding characteristics were evaluated in terms of complications, final diagnosis and stigmata. Hospital admission included duration, causes,

unit, and the type of monitoring, while causes of second-look endoscopy, discharge date and outpatient care (treatment, *Helicobacter pylori* after treatment, *H. pylori* eradication) were evaluated for hospital follow-up.

Endoscopic re-treatment within 30 days due to re-bleeding from the NVUGIB episode, number of blood units transfused within 30 days from the NVUGIB episode, number of days hospitalized due to bleeding and/or re-bleeding within 30 days from the NVUGIB episode, and number of hospitalizations due to bleeding and/or re-bleeding within 30 days from the NVUGIB episode were also evaluated.

Statistical Analysis

Due to the study design, variables were presented as descriptive statistics. Categorical data were reported as frequencies and proportions. Continuous data were reported as means and standard deviations. Where appropriate, alternate descriptive statistics such as quartile ranges for categorical data and medians for continuous data were reported. Multivariable analyses were performed using random-intercept mixed model logistic regression to account for clustering by study center. Model creation and selection was based on a priori clinical and biological considerations. Raw (univariate) and multivariable adjusted odds ratios (OR) and 95% confidence intervals (CI) were calculated from the logistic regression coefficients and standard errors. The significance level was 5% for keeping independent predictors in the models.

RESULTS

Demographic and Baseline Patient Characteristics

The mean age of the 423 patients enrolled in the Turkish arm of the study was 57.8±18.9 years and the majority of patients were male (67.4%). Patient characteristics such as history of alcohol abuse (5.4%), smoking, comorbidities, underlying hematological condition (6.2%), and previous history of NVUGIB (18.4%) are presented in Table 1.

Table 1. Description of patient characteristics in ENERGIB-Turkey (n=423)

Age (years; mean±SD)	57.75±18.85
Gender (male, %)	67.38
History of alcohol abuse (%)	5.44
Smoking habit (%)	
Current smoker	20.33
Ex-smoker	14.42
Non-smoker	48.94
Unknown	16.31
Comorbidities (%, ≥1)	60.76
Comorbidities (number; mean±SD)	0.91±0.92
Comorbidities [multiple response] (%)	
Ischemic heart disease	20.09
Cardiac failure	7.57
Respiratory disease	5.67
Cancer/malignancy	5.44
Stroke	4.73
Dementia	0.95
Documented cirrhosis	0.95
Renal disease	6.62
Other significant disease	39.24
Presence of hematological condition (%)	6.15
History of NVUGIB (%)	18.44

NVUGIB: Non-variceal upper gastrointestinal bleeding

Hospital Admission Characteristics (Table 2)

With respect to hospital admission characteristics, the majority of NVUGIB admissions were acute (96.2%), and most patients were admitted directly from their own home (76.4%). On admission, the most common symptom was melena (76.1%), followed by fresh blood hematemesis (27.2%), coffee ground vomiting (13.2%), and shock/syncope (5.0%). Most patients were hemodynamically stable, although 18.0% of the patients had tachycardia (heart rate >100), and 13.5% of the patients had systolic blood pressure <100 mmHg. One-third (32.6%) of the patients were not taking any medication, 28.6% were taking aspirin, 19.9% were taking non-steroidal anti-inflammatory drugs (NSAIDs), and 7.3% were taking PPIs.

Most patients were discharged from the hospital (96.9%) within one month after the NVUGIB admission, and the average hospital stay was 5.36±4.91 days. The percentage of admission to large hospitals, i.e. equal or more than 500 beds, was 70.0%.

Underlying Causes (Table 3) and Management (Table 4a, 4b) of the Bleeding Episode

The most common endoscopic diagnoses underlying NVUGIB episodes were duodenal ulcer (45.2%), gastric ulcer (27.7%), gastritis/gastric erosions (26.2%), and esophagitis (9.9%).

Almost half of the NVUGIB episodes were managed in general medical wards (45.4%). GI teams were in charge of management for most patients (64.8%), while 22.9% of the patients were transferred to another unit after the initial hospital assessment.

Table 2. Description of hospital admission characteristics in ENERGIB-Turkey (n=423)

Presentation to Hospital (%)	
Acute admission with NVUGIB	96.22
NVUGIB in established inpatient	3.78
NVUGIB clinical signs (%)	
Fresh blood hematemesis	27.19
Melena	76.12
Shock/syncope	4.96
Coffee ground vomiting	13.24
Blood in nasogastric tube	1.65
Other	5.67
Admission source (%)	
Own home	76.36
Residential/nursing	0.47
Transfer from acute hospital	15.37
Transfer from other hospital	4.26
Established inpatient	1.65
Unknown	0.71
Other	1.18
Hemodynamic status (%)	
Not in shock state	65.25
Tachycardia	17.97
Systolic blood pressure <100	13.48
Systolic blood pressure <70	0.71
Systolic blood pressure <50	0.00
Not available	2.60
Current medication at admission [MR] (%)	
No medication	32.62
Aspirin ≤100 mg/d	16.78
Aspirin >100 mg/d	11.82
Warfarin	9.22
Selective serotonin reuptake inhibitor	0.47
Non-steroidal anti-inflammatory drug	19.86
Fibrinolytic	0.70
Glycoprotein IIb/IIIa inhibitor	1.65
Proton pump inhibitor	7.33
H_2 receptor inhibitor	1.65
LMW heparin	0.95
Unfractionated heparin	0.47
Other	29.55
Admission to large hospital (≥500 beds; %)	69.98
Discharge (% discharged at 1 month)	96.93
Days hospitalized (mean±SD)	5.36±4.91

LMW: Low molecular weight. MR: Multiple response. NVUGIB: Non-variceal upper gastrointestinal bleeding.

Table 3. Description of bleeding episode characteristics in ENERGIB–Turkey (n=423)

Helicobacter pylori test (% performed)	26.95
Rockall risk score (% available)	38.53
Blatchford risk score (% available)	16.55
ASA score (% available)	27.42
Diagnosis – Esophagus (%)	
Varices	0.95
Esophagitis	9.93
Ulcer	4.73
Mallory-Weiss syndrome	2.6
Diagnosis – Stomach (%)	
Gastritis/erosions	26.24
Ulcer	27.66
Malignancy	2.6
Vascular ectasia	0.71
Angiodysplasia with hemorrhage	0.47
Dieulafoy lesion	0.71
Diagnosis – Duodenum (%)	
Erosive duodenitis	9.93
Ulcer	45.15
Malignancy	0.47
Vascular ectasia	0.24
Ulcer size (cm; mean ±SD)	1.85±2.32

ASA: American Society of Anesthesiologists.

A total of 88.7% of the patients received empirical treatment prior to endoscopy, most commonly a PPI (87.7%). Pantoprazole (36.4%), omeprazole (28.4%), and esomeprazole (21.3%) were the most commonly prescribed PPIs. Most of the endoscopies (92.2%) were performed in the Endoscopy Department, and for 32.4%, therapeutic procedures were performed during the endoscopy. Most patients (94.6%) received a PPI post-endoscopy.

Prognosis: Continuous Bleeding, Re-Bleeding, Other Complications, and Deaths (Tables 5 and 6)

The proportions of patients with continued bleeding and re-bleeding after the first endoscopy were 7.1% and 6.6%, respectively, and the cumulative proportion of continued bleeding or re-bleeding during the first 30 days was 9.0%. Only 38 patients were identified as receiving various medications when re-bleeding occurred. Most patients (87.4%) with NVUGIB received a transfusion (any intravenous [IV] fluid) during their hospitalization for the management of continued or re-bleeding; 12.6% of the patients received additional endoscopies. The proportions of patients undergoing angiographic coiling or surgery within 30 days of the NVUGIB episode were 0.2% and 2.6%, respectively. The proportions of patients with NVUGIB complications or death within 30 days of the NVUGIB episode were 5.7% and 2.8%, respectively.

Based on multivariate analysis, hospital size, presence of comorbidities, fresh red blood hematemesis, and prior history of NVUGIB were signifi-

Table 4a. Management of bleeding episode characteristics before endoscopy in ENERGIB-Turkey (n=423)

Intra-hospital management – Area (%)	
General medical ward	45.39
Medical assessment	1.65
General surgical ward	5.2
Gastrointestinal bleeding unit	0.24
High dependency unit	3.78
Intensive care unit	7.33
Emergency observation	31.91
Other	4.26
Unknown	0.24
Intra-hospital management – Team (%)	
GI bleeding team/gastroenterology	64.78
General medical	17.49
General surgical	4.96
Intensive and Critical Care Unit/Anesthetics	1.65
Other	11.1
Patient transferred to another team for the management of the NVUGIB [MR] (%)	22.93
Blood coagulation treatment before endoscopy [MR] (%)	
Any	13.95
Vitamin K	6.38
Cryoprecipitate	5.2
Prothrombin complex	1.42
Other	6.15
NVUGIB treatment before endoscopy [MR] (%)	
Any	88.65
Proton pump inhibitor (PPI)	87.71
Omeprazole	28.37
Esomeprazole	21.28
Pantoprazole	36.41
Lansoprazole	1.65
H_2 receptor inhibitor	1.18
Vasopressin or analogue	1.18
Other	1.42
Route of administration of PPI before endoscopy [MR] (%)	
Oral	1.42
IV boluses	47.52
IV infusion	48.94

IV: Intravenous. MR: Multiple response.

cantly and positively associated with the likelihood of receiving treatment prior to endoscopy. Patients older than 65 years with a diagnosis of duodenal ulcer were significantly more likely to receive additional endoscopies, which were shown to be less likely to be performed among patients presenting with melena (Table 7).

The presence of duodenal ulcer was positively associated, while the diagnosis of esophagitis was negatively associated, with the performance of therapeutic procedures. The risk of performance of surgery within 30 days after NVUGIB was significantly and positively associated with the diagnosis of duodenal ulcer and time to endoscopy (Table 8).

In the Turkish sub-group of patients, significant risk factors for bleeding continuation or re-bleeding included age >65 years, presentation with fresh red blood hematemesis or shock/syncope, and the diagnosis of duodenal ulcer. The risk of bleeding continuation was more prominent in large hospitals. Use of aspirin, NSAIDs or warfarin at baseline was determined to be negatively associated with bleeding continuation or re-bleeding (Table 9).

Table 4b. Management of bleeding episode characteristics during/after endoscopy in ENERGIB-Turkey (n=423)

Location of endoscopy (%)	
Endoscopy department	92.2
Intensive or critical care unit	0.7
GI bleeding unit	1.2
Medical ward	0.5
Surgical ward	0.5
Other	4.7
Unknown	0.2
Stigmata of recent hemorrhage [MR] (%)	
Any	48.7
Blood in upper GI tract	10.17
Visible vessel	16.55
Spurting vessel	2.6
Dark spot in ulcer base	4.96
Red spot/wheal markings	4.26
Adherent clot	8.75
Oozing bleeding	13.48
Therapeutic procedures during endoscopy [MR] (%)	
Any	32.39
Ulcer base injection sclerotherapy	17.26
Epinephrine injection	20.09
BICAP/heater probe	1.42
Endoclip(s) applied	1.42
Variceal injection/sclerotherapy	0.47
Variceal banding	0.24
Argon plasma coagulation	5.91
Other	0.47
NVUGIB treatment after endoscopy [MR] (%)	
Any	95.98
Proton pump inhibitor (PPI)	94.56
Omeprazole	28.37
Esomeprazole	22.22
Pantoprazole	41.61
Lansoprazole	2.6
H_2 receptor inhibitor	1.18
Vasopressin or analog	0.47
Other	4.02
Route of administration of PPI after endoscopy (%)	
Oral	12.53
IV boluses	26.71
IV infusion	56.97
Other	0.47
Time from admission to endoscopy (mean±SD)	
Days	1.03±2.14
Hours	23.76±36.00

BICAP: Bipolar circumactive probe. MR: Multiple response.

The risk of clinical complications after NVUGIB was higher in female patients ≥65 years, in patients with comorbidities, and in patients presenting with shock/syncope. Time to endoscopy was positively associated with the development of clinical complications. The use of aspirin, NSAIDs or warfarin at baseline was negatively associated with the development of clinical complications. The risk of death within 30 days after NVUGIB was significantly higher in patients ≥65 years and in patients receiving transfusions other than IV fluid or red blood cell within 12 h of presentation (Table 10).

Table 5. Description of continued bleeding/re-bleeding and related procedures in ENERGIB-Turkey (n=423)

Continued bleeding after first endoscopy (%)	7.09
Re-bleeding during hospitalization (%)	6.62
Re-bleeding after discharge (%)	2.13
Continued bleeding or re-bleeding (%)	8.98
Current medication in re-bleeding* [MR] (n=38) (%)	
Aspirin >100 mg/d	2.63
Proton pump inhibitor	57.89
Helicobacter pylori eradication	2.63
Low molecular weight heparin	5.26
Other	31.58
Transfusions within 12 hours (%)	87.44
IV fluid (units)	2.27±3.48
Red blood cell (units)	1.18±1.48
Other fluid (units)	0.52±1.00
Transfusions within 30 days (%)	86.49
IV fluid (units; mean±SD)	8.24±10.54
Red blood cell (units; mean±SD)	2.34±3.31
Other fluid (units; mean±SD)	2.15±4.79
Angiographic coiling during hospitalization (%)	0.24
Surgery except endoscopy (%)	
During hospitalization	2.13
After discharge	0.47
Any	2.61
Additional endoscopies (%)	12.56
Reasons for additional endoscopy [MR] (%)	
Check/repeat therapeutic procedure	5.69
For further bleeding (continued or re-bleeding)	4.27
Patient unstable	0.24
Technical/equipment failure	0
Inadequate view	1.9
Other	0.24
Total number of endoscopies	
During hospitalization (mean±SD)	1.14±0.40
Within 30 days (mean±SD)	1.27± 0.53

MR: Multiple response. *Any continued bleeding or re-bleeding.

Table 6. Description of NVUGIB complications and deaths in ENERGIB-Turkey (n=423)

Complications [MR] (%)	5.67	**Cause of death (n)**	
Pneumonia	1.18	Bleeding-related	3
Renal failure	1.18	Uncontrolled bleeding	2
Deep vein thrombosis	0.95	Within 48h after endoscopy	1
Pulmonary embolism	0.24	Non-bleeding-related	9
Perforation	0.24	Cardiac causes	5
Cardiac event	2.6	Pulmonary causes	1
Other	2.13	Multi-organ failure	2
Death (%)		Terminal malignant diseases	1
During hospital	2.36		
After discharge	0.47		
Any	2.84		

Table 7. Determinants of PPI of any drug as a treatment for NVUGIB before endoscopy and additional endoscopies within 30 days of NVUGIB episode (n=371) in ENERGIB-Turkey

Characteristics	Univariate analysis OR (95%CI)	p	Multivariate analysis* OR (95%CI)	p
PPI of any drug as a treatment for NVUGIB before endoscopy				
Hospital size (large vs. small)	14.96 (2.58 – 86.75)	0.006	12.97 (2.20 – 76.31)	**0.01**
Sex (male vs. female)	0.87 (0.52 – 1.47)	0.62	0.78 (0.43 – 1.42)	0.42
Age (>65 vs. ≤65 y)	1.76 (1.04 – 3.00)	0.04	1.19 (0.61 – 2.31)	0.61
Comorbidities (≥1 vs. none)	2.66 (1.56 – 4.53)	<0.001	2.30 (1.13 – 4.67)	**0.02**
History of NVUGIB (yes vs. no)	3.61 (1.34 – 9.72)	0.01	3.56 (1.26 – 10.02)	**0.02**
Admission (acute vs. no)	1.40 (0.40 – 4.87)	0.59	1.95 (0.43 – 8.87)	0.40
Symptoms				
Fresh red blood hematemesis (yes vs. no)	1.95 (1.07 – 3.58)	0.03	3.19 (1.29 – 7.85)	0.01
Melena (yes vs. no)	1.34 (0.78 – 2.30)	0.28	2.09 (0.95 – 4.61)	0.07
Shock/syncope	0.55 (0.18 – 1.67)	0.29	0.95 (0.25 – 3.56)	0.94
Coffee ground vomit (yes vs. no)	0.56 (0.28 – 1.11)	0.10	0.80 (0.33 – 1.94)	0.63
Blood up nasogastric tube (yes vs. no)	-	-	-	-
Use of aspirin, NSAIDs or warfarin at baseline (yes vs. no)	1.58 (0.90 – 2.77)	0.11	0.96 (0.48 – 1.93)	0.91
Additional endoscopies within 30 days of NVUGIB episode				
Hospital size (large vs. small)	1.33 (0.59 – 2.98)	0.50	1.74 (0.67 – 4.54)	0.28
Sex (male vs. female)	1.55 (0.82 – 2.90)	0.18	1.57 (0.78 – 3.13)	0.21
Age (>65 vs. ≤65 y)	1.49 (0.85 – 2.62)	0.17	2.32 (1.18 – 4.53)	**0.02**
Comorbidities (≥1 vs. none)	0.86 (0.49 – 1.51)	0.59	0.59 (0.30 – 1.18)	0.15
History of NVUGIB (yes vs. no)	0.93 (0.44 – 1.95)	0.85	1.14 (0.52 – 2.50)	0.74
Admission (acute vs. no)	1.09 (0.25 – 4.69)	0.91	0.62 (0.13 – 2.98)	0.56
Symptoms				
Fresh red blood hematemesis (yes vs. no)	1.80 (1.01 – 3.22)	0.005	1.31 (0.60 – 2.86)	0.51
Melena (yes vs. no)	0.49 (0.27 – 0.89)	0.02	0.36 (0.16 – 0.82)	**0.02**
Shock/syncope	1.49 (0.44 – 5.06)	0.52	1.16 (0.30 – 4.50)	0.83
Coffee ground vomit	0.56 (0.20 – 1.56)	0.27	0.56 (0.18 – 1.72)	0.32
Blood up nasogastric tube (yes vs. no)	0.94 (0.12 – 7.46)	0.95	1.00 (0.11 – 8.88)	1.00
Use of aspirin, NSAIDs or warfarin at baseline (yes vs. no)	1.41 (0.80 – 2.49)	0.24	1.76 (0.94 – 3.30)	0.09
Lack of risk score (lacking vs. present)	0.82 (0.40 – 1.69)	0.60	0.83 (0.36 – 1.95)	0.68
Time to endoscopy (days)	1.04 (0.91 – 1.18)	0.57	1.04 (0.91 – 1.19)	0.60
Endoscopic diagnosis				
Esophagitis (yes vs. no)	0.76 (0.27 – 2.13)	0.60	0.70 (0.24 – 2.06)	0.53
Gastric ulcer (yes vs. no)	1.38 (0.75 – 2.53)	0.30	1.72 (0.87 – 3.40)	0.13
Duodenal ulcer (yes vs. no)	1.63 (0.93 – 2.87)	0.09	2.35 (1.21 – 4.56)	**0.01**

NSAID: Non-steroidal anti-inflammatory drug. OR. Odds ratio. CI: Confidence interval. All models are random intercept logistic regression models with centers as random effects. *Multivariable adjusted: adjusted for other variables in the Table. The effects for the presence of blood up the nasogastric tube could not be estimated.

DISCUSSION

Overall, our findings related to the clinical management of NVUGIB across Turkey revealed low-to-moderate rates for mortality, continued bleeding, re-bleeding, and surgery, which probably reflect the high proportion of patients receiving both combined endoscopic therapy and PPI.

Apart from the predominance of younger patients (57.8 vs. 67.7 years) and rare history of alcohol abuse (5.4 vs. 13.7), our patient population was compatible with the overall population in the ENERGIB Study in terms of gender distribution, types of comorbidities, prior history of NVUGIB, admission type, symptoms at admission, and primary diagnosis underlying the current NVUBIG episode (12).

When compared to other countries included in the pan-European ENERGIB Study, the leading characteristics concerning management of NVUGIB episodes among Turkish patients included a hig-

Table 8. Determinants of performance of therapeutic procedures during endoscopy for NVUGIB (n=137) and surgery (n=11) within 30 days of NVUGIB episode in ENERGIB-Turkey (n=423)

Characteristics	Univariate analysis OR (95%CI)	p	Multivariate analysis* OR (95%CI)	p
Performance of therapeutic procedures during endoscopy for NVUGIB				
Hospital size (large vs. small)	0.60 (0.27 – 1.34)	0.23	0.56 (0.22 – 1.40)	0.24
Sex (male vs. female)	1.76 (1.11 – 2.80)	0.02	1.61 (0.96 -2.70)	0.08
Age (>65 vs. ≤65 y)	0.81 (0.53 – 1.25)	0.35	1.15 (0.69 – 1.92)	0.60
Comorbidities (≥1 vs. none)	0.87 (0.56 – 1.33)	0.52	1.06 (0.62 – 1.82)	0.84
History of NVUGIB (yes vs. no)	0.72 (0.41 -1.26)	0.26	0.79 (0.43 -1.44)	0.45
Admission (acute vs. no)	2.21 (0.61 – 8.04)	0.23	1.08 (0.27 – 4.36)	0.91
Symptoms				
Fresh red blood hematemesis (yes vs. no)	1.60 (1.01 - 2.54)	0.05	1.84 (1.00 – 3.41)	0.06
Melena (yes vs. no)	0.84 (0.51 – 1.37)	0.49	0.93 (0.48 – 1.80)	0.82
Shock/syncope	1.83 (0.71 – 4.74)	0.22	1.84 (0.63 – 5.36)	0.28
Coffee ground vomit	0.99 (0.52 – 1.88)	0.98	0.96 (0.46 – 2.03)	0.93
Blood up nasogastric tube (yes vs. no)	1.66 (0.36 – 7.71)	0.52	1.40 (0.27 – 7.31)	0.70
Use of aspirin, NSAIDs or warfarin at baseline (yes vs. no)	1.15 (0.75 – 1.76)	0.52	1.10 (0.67 – 1.82)	0.71
Lack of risk score (lacking vs. present)	0.96 (0.48 – 1.92)	0.90	1.43 (0.64 – 3.21)	0.40
Time to endoscopy (days)	0.96 (0.86 – 1.07)	0.48	0.97 (0.862 – 1.10)	0.69
Endoscopic diagnosis				
Esophagitis (yes vs. no)	0.32 (0.13 – 0.79)	0.01	0.32 (0.12 – 0.83)	**0.02**
Gastric ulcer (yes vs. no)	0.84 (0.53 – 1.36)	0.49	1.12 (0.65 – 1.92)	0.69
Duodenal ulcer (yes vs. no)	2.98 (1.92 – 4.62)	<0.001	3.23 (1.93 – 5.38)	**<0.001**
Performance of surgery within 30 days of NVUGIB episode				
Hospital size (large vs. small)	1.94 (0.42 – 8.85)	0.40	1.62 (0.29 – 8.90)	0.60
Sex (male vs. female)	2.69 (0.75 – 9.66)	0.13	1.49 (0.29 – 7.58)	0.64
Age (>65 vs. ≤65 y)	1.27 (0.44 – 3.67)	0.66	3.09 (0.77 – 12.44)	0.12
Comorbidities (≥1 vs. none)	0.34 (0.11 – 1.01)	0.05	0.37 (0.09 – 1.46)	0.16
History of NVUGIB (yes vs. no)	0.93 (0.24 – 3.66)	0.92	1.34 (0.28 – 6.42)	0.72
Admission (acute vs. no)	-	-	-	-
Symptoms				
Fresh red blood hematemesis (yes vs. no)	2.28 (0.68 – 7.62)	0.18	1.51 (0.31 – 7.31)	0.62
Melena (yes vs. no)	0.52 (0.18 – 1.54)	0.24	4.10 (0.07 – 2.25)	0.32
Shock/syncope	2.23 (0.36 – 13.97)	0.39	1.10 (0.10 – 11.95)	0.94
Coffee ground vomit	-	-	-	-
Blood up nasogastric tube (yes vs. no)	6.75 (0.74 – 61.41)	0.09	7.26 (0.55 – 96.65)	0.14
Use of aspirin, NSAIDs or warfarin at baseline (yes vs. no)	0.24 (0.05 – 1.07)	0.06	0.31 (0.07 – 1.44)	0.14
Lack of risk score (lacking vs. present)	1.38 (0.42 – 4.60)	0.60	1.27 (0.33 – 4.82)	0.73
Time to endoscopy (days)	1.17 (1.01 – 1.35)	0.03	1.16 (0.98 – 1.36)	**0.09**
Endoscopic diagnosis				
Esophagitis (yes vs. no)	-	-	-	-
Gastric ulcer (yes vs. no)	1.47 (0.47 – 4.55)	0.51	2.34 (0.60 – 9.07)	0.23
Duodenal ulcer (yes vs. no)	2.34 (0.84 – 6.57)	0.11	4.07 (1.02 – 16.18)	**0.05**

NSAID: Non-steroidal anti-inflammatory drug. OR. Odds ratio. CI: Confidence interval. All models are random intercept logistic regression models with centers as random effects. *Multivariable adjusted: adjusted for other variables in the Table. The effects for the type of admission, the presence of coffee ground vomit, and the presence of esophagitis could not be estimated for surgery.

her rate of admission to a large hospital, more frequent use of empirical pre-endoscopy PPI treatment, higher prevalence of duodenal ulcer as the cause of bleeding, lower cumulative proportion of continued bleeding or re-bleeding, and lower incidence of additional endoscopies, complications and mortality within 30 days of initial NVUGIB episode.

In line with previous studies ranking peptic ulcer first among the causes of NVUGIB and indicating

Table 9. Determinants of bleeding continuation (n=30) or re-bleeding (n=31) after initial NVUGIB episode in ENERGIB-Turkey (n=423)

Characteristics	Univariate analysis		Multivariate analysis*	
	OR (95%CI)	p	OR (95%CI)	p
Bleeding continuation after initial episode				
Hospital size (large vs. small)	3.76 (1.07 – 13.26)	0.05	7.26 (1.31 – 40.16)	**0.04**
Sex (male vs. female)	1.71 (0.80 – 3.64)	0.17	2.02 (0.95 – 4.29)	0.07
Age (>65 vs. ≤65 y)	1.48 (0.76 – 2.89)	0.25	3.79 (1.84 – 7.83)	**<0.001**
Comorbidities (≥1 vs. none)	0.77 (0.39 – 1.52)	0.46	0.75 (0.38 – 1.48)	0.42
History of NVUGIB (yes vs. no)	0.78 (0.32 -1.89)	0.58	0.63 (0.27 – 1.44)	0.28
Admission (acute vs. no)	-	-	-	-
Symptoms				
Fresh red blood hematemesis (yes vs. no)	1.92 (0.98 – 3.80)	0.06	2.46 (1.14 – 5.27)	**0.02**
Melena (yes vs. no)	0.70 (0.32 – 1.52)	0.37	0.85 (0.34 – 2.14)	0.74
Shock/syncope	3.73 (1.15 – 12.16)	0.03	8.78 (2.57 – 29.94)	**0.001**
Coffee ground vomit	0.24 (0.04 – 1.45)	0.12	0.31 (0.07 – 1.42)	0.14
Blood up nasogastric tube (yes vs. no)	1.14 (0.16 – 8.02)	0.89	0.28 (0.05 – 1.60)	0.16
Use of aspirin, NSAIDs or warfarin at baseline (yes vs. no)	0.58 (0.29 – 1.17)	0.13	0.49 (0.25 – 0.98)	**0.05**
Lack of risk score (lacking vs. present)	1.57 (0.64 – 3.87)	0.33	1.16 (0.38 – 3.50)	0.80
Time to endoscopy (days)	0.95 (0.80 – 1.13)	0.55	0.92 (0.76 – 1.10)	0.35
Endoscopic diagnosis				
Esophagitis (yes vs. no)	-	-	-	-
Gastric ulcer (yes vs. no)	0.59 (0.26 – 1.35)	0.22	0.59 (0.27 – 1.29)	0.19
Duodenal ulcer (yes vs. no)	3.22 (1.57 – 6.60)	0.002	4.77 (2.40 – 9.48)	**<0.001**
Re-bleeding after initial episode				
Hospital size (large vs. small)	1.86 (0.74 – 4.65)	0.20	1.88 (0.63 – 5.60)	0.28
Sex (male vs. female)	1.46 (0.64 – 3.30)	0.37	1.42 (0.63 – 3.21)	0.41
Age (>65 vs. ≤65 y)	1.69 (0.81 – 3.50)	0.16	3.65 (1.67 – 8.00)	**0.002**
Comorbidities (≥1 vs. none)	0.77 (0.37 – 1.60)	0.48	0.75 (0.33 – 1.69)	0.50
History of NVUGIB (yes vs. no)	1.07 (0.42 – 2.70)	0.89	1.04 (0.43 – 2.55)	0.93
Admission (acute vs. no)	-	-	-	-
Symptoms				
Fresh red blood hematemesis (yes vs. no)	2.05 (0.97 – 4.34)	0.06	3.24 (1.33 – 7.91)	0.01
Melena (yes vs. no)	0.74 (0.33 – 1.66)	0.47	1.18 (0.45 – 3.09)	0.74
Shock/syncope	3.49 (1.13 – 10.82)	0.03	6.65 (1.95 – 22.65)	**0.003**
Coffee ground vomit	0.97 (0.33 – 2.88)	0.95	1.43 (0.48 – 4.25)	0.53
Blood up nasogastric tube (yes vs. no)	2.14 (0.25 – 18.40)	0.49	0.75 (0.09 – 6.64)	0.80
Use of aspirin, NSAIDs or warfarin at baseline (yes vs. no)	0.42 (0.19 – 0.94)	0.04	0.37 (0.16 – 0.83)	**0.02**
Lack of risk score (lacking vs. present)	1.65 (0.79 – 3.46)	0.19	1.47 (0.60 – 3.60)	0.42
Time to endoscopy (days)	0.95 (0.80 – 1.12)	0.53	0.92 (0.77 – 1.11)	0.40
Endoscopic diagnosis				
Esophagitis (yes vs. no)	0.61 (0.14 – 2.64)	0.51	0.49 (0.12 – 1.97)	0.33
Gastric ulcer (yes vs. no)	0.61 (0.24 – 1.50)	0.28	0.58 (0.23 – 1.43)	0.24
Duodenal ulcer (yes vs. no)	2.82 (1.32 – 6.03)	0.008	3.42 (1.57 – 7.45)	**0.003**

NSAID: Non-steroidal anti-inflammatory drug. OR. Odds ratio. CI: Confidence interval. All models are random intercept logistic regression models with centers as random effects. * Multivariable adjusted: adjusted for other variables in the Table. The effects for the type of admission in continuation of bleeding and re-bleeding and the presence of esophagitis in re-bleeding could not be estimated.

an increase in prevalence of erosive esophagitis and gastritis (13,14), duodenal ulcer (45.2%) was the major cause of bleeding in the Turkish study population, followed by gastric ulcer, gastritis/gastric erosions and esophagitis. On the other hand, the high prevalence of duodenal ulcer as the cause of bleeding in our population compared with other countries involved in the ENERGIB Study seems to indicate failure to eradicate *H. pylori* infection in Turkey, since eradication of *H. pylori* has been

Table 10. Determinants of development of clinical complications (n=24) during and mortality (n=12) within 30 days of NVUGIB episode in ENERGIB-Turkey (n=423)

Characteristics	Univariate analysis OR (95%CI)	p	Multivariate analysis* OR (95%CI)	p
Development of clinical complications during NVUGIB episode				
Hospital size (large vs. small)	1.03 (0.33 – 3.21)	0.96	0.77 (0.14 – 4.09)	0.76
Sex (male vs. female)	0.40 (0.19 – 0.85)	0.02	0.28 (0.13 – 0.60)	**0.001**
Age (>65 vs. ≤65 y)	2.56 (1.23 – 5.32)	0.01	2.60 (1.22 – 5.51)	**0.02**
Comorbidities (≥1 vs. none)	2.01 (0.90 – 4.48)	0.09	3.28 (1.32 – 8.15)	**0.01**
History of NVUGIB (yes vs. no)	1.24 (0.52 – 2.98)	0.63	1.32 (0.55 – 3.14)	0.55
Admission (acute vs. no)	-	-	-	-
Symptoms				
Fresh red blood hematemesis (yes vs. no)	1.22 (0.57 – 2.64)	0.61	1.44 (0.56 – 3.69)	0.45
Melena (yes vs. no)	0.69 (0.31 – 1.56)	0.38	1.28 (0.47 – 3.44)	0.64
Shock/syncope	4.45 (1.55 – 12.76)	0.006	5.28 (1.63 – 17.17)	**0.007**
Coffee ground vomit	0.98 (0.33 – 2.91)	0.98	0.76 (0.24 – 2.39)	0.65
Blood up nasogastric tube (yes vs. no)	2.05 (0.29 – 14.48)	0.47	1.14 (0.15 – 8.95)	0.90
Use of aspirin, NSAIDs or warfarin at baseline (yes vs. no)	0.45 (0.21 – 0.97)	0.04	0.20 (0.08 – 0.47)	**<0.001**
Lack of risk score (lacking vs. present)	1.10 (0.40 – 3.02)	0.86	0.96 (0.26 – 3.58)	0.95
Time to endoscopy (days)	1.14 (1.00 – 1.29)	0.05	1.22 (1.05 – 1.41)	**0.009**
Endoscopic diagnosis				
Esophagitis (yes vs. no)	0.96 (0.26 – 3.45)	0.94	0.95 (0.28 – 3.20)	0.93
Gastric ulcer (yes vs. no)	1.12 (0.51 – 2.47)	0.77	1.23 (0.52 – 2.89)	0.64
Duodenal ulcer (yes vs. no)	2.29 (1.09 – 4.80)	0.03	4.94 (2.15 – 11.39)	**<0.001**
Development of mortality within 30 days of NVUGIB episode				
Hospital size (large vs. small)	1.30 (0.35 – 4.87)	0.71	1.10 (0.12 – 9.79)	0.93
Sex (male vs. female)	0.47 (0.15 – 1.49)	0.20	0.63 (0.21 – 1.95)	0.44
Age (>65 vs. ≤65 y)	3.14 (0.93 – 10.59)	0.07	3.31 (1.01 – 10.87)	**0.05**
Comorbidities (≥1 vs. none)	3.32 (0.72 – 15.35	0.13	3.85 (0.88 – 16.87)	0.08
History of NVUGIB (yes vs. no)	0.88 (0.19 – 4.11)	0.87	0.88 (0.22 – 3.57)	0.86
Admission (acute vs. no)	-	-	-	-
Symptoms				
Fresh red blood hematemesis (yes vs. no)	1.35 (0.40 – 4.58)	0.63	1.72 (0.46 – 6.44)	0.43
Melena (yes vs. no)	0.94 (0.25 – 3.54)	0.93	1.67 (0.38 – 7.32)	0.51
Shock/syncope	7.28 (1.81 – 29.20)	0.005	-	-
Coffee ground vomit	0.59 (0.07 – 4.65)	0.62	0.67 (0.09 – 4.82)	0.70
Blood up nasogastric tube (yes vs. no)	-	-	-	-
Use of aspirin, NSAIDs or warfarin at baseline (yes vs. no)	0.78 (0.24 – 2.48)	0.67	0.41 (0.11 – 1.49)	0.19
Lack of risk score (lacking vs. present)	1.63 (0.51 – 5.21)	0.41	3.41 (0.67 – 17.37)	0.15
Time to endoscopy (days)	0.99 (0.76 – 1.30)	0.96	0.92 (0.75 – 1.13)	0.44
Endoscopic diagnosis				
Esophagitis (yes vs. no)	0.82 (0.10 – 6.52)	0.85	1.39 (0.22 – 8.75)	0.74
Gastric ulcer (yes vs. no)	1.91 (0.59 – 6.13)	0.28	2.04 (0.67 – 6.23)	0.22
Duodenal ulcer (yes vs. no)	1.22 (0.39 – 3.85)	0.73	2.97 (0.96 – 9.19)	0.07
Transfusion within 12 h of presentation				
Intravenous fluid (yes vs. no)	4.34 (0.55 – 34.00	0.16	6.88 (0.79 – 59.71)	0.09
Red blood cell (yes vs. no)	3.87 (0.84 – 17.91)	0.08	2.98 (0.71 – 12.47)	0.15
Other (yes vs. no)	4.55 (1.56 – 13.28)	0.006	6.41 (1.72 – 23.86)	**0.007**

All models are random intercept logistic regression models with centers as random effects. * Multivariable adjusted: adjusted for other variables in the Table. The effects for the type of admission could not be estimated in complications. The effects for the type of admission, presence of blood up the nasogastric tube, and presence of shock/syncope in multivariate models could not be estimated in mortality.

reported to be responsible for the recent decline in the risk of developing peptic ulcer disease and its complications in the general population (16,17).

The most obvious and widely used medications that have an adjunctive role in preparation of patients for endoscopy have been documented to be

the PPIs, which through raising intra-gastric pH, were reported to stabilize clotting in the upper tract and decrease the risk of re-bleeding (6). Considering the association between empirical PPI treatment before endoscopy and reduction in recurrent bleeding (18) and a higher incidence of empirical pre-endoscopy PPI treatment in our population compared to other participants of ENERGIB Study, PPI may have a prominent influence on low-to-moderate level of bleeding continuation, re-bleeding, complications, and mortality specific to the Turkish population sample.

The low rate of surgery in the management of NVUGIB in the Turkish study population indicates the success of endoscopic and medical management of the disease (18,19) reflected by a reduction in re-bleeding rates obviating the need for surgical management (20). It is also compatible with the gradual and significant decrease in the proportion of patients requiring surgical management for the control of NVUGIB seen in the literature (4,18,19).

The mortality rate associated with NVUGIB has been reported to be approximately 5–10% (3,9). In an attempt to identify those NVUGIB patients with higher mortality rates, significant markers for re-bleeding and poor outcome were reported in the literature as age, comorbidity, shock, diagnosis, admission hemoglobin values, mode of presentation, and blood transfusion requirements (7). Accordingly, in the present study, presence of comorbidities, fresh red blood hematemesis and a prior history of NVUGIB were significantly and positively associated with the likelihood of receiving treatment prior to endoscopy.

Patients older than 65 years with a diagnosis of duodenal ulcer without use of aspirin, NSAIDs or warfarin at baseline in the present study were determined to be more likely to receive additional endoscopies and to experience more frequent bleeding continuation or re-bleeding within 30 days of the initial episode. Age older than 65 years was also positively associated with increased risk of complications and mortality *per se.* Likewise, having duodenal ulcer was associated with the increased likelihood of therapeutic procedures during endoscopy as well as a higher need for surgery within 30 days of the episode.

While the percentage of patients diagnosed with duodenal ulcer as the cause of bleeding was high compared with other countries involved in the ENERGIB Study, the presence of factors positively associated with the presence of duodenal ulcer, such as incidence of bleeding continuation or re-bleeding within 30 days of the initial episode, was low.

Profound acid suppression with an IV PPI improves outcomes in high-risk patients with peptic ulcer bleeding (21), and the combination of endoscopic therapy with PPIs was documented to be superior to either alone (5,18), indicating the prognostic value of empirical treatment with PPIs prior to endoscopy.

The mortality rate in elderly patients with UGIB was reported to be higher than in younger patients. Also, comorbidity in the elderly, such as cardiac or pulmonary disease, was indicated to significantly affect the clinical outcome (22), and mortality due to NVUGIB was associated predominantly with decompensation of concurrent medical illnesses (3,4,9). Likewise, among our population, the presence of comorbidities and presentation with fresh red blood hematemesis or shock/syncope were the leading predictive factors for receiving treatment prior to endoscopy and the likelihood of bleeding continuation or re-bleeding as well as complications after endoscopy. Therefore, based on its relation to empirical treatment and the prognosis of the disease, proper and accurate evaluation of initial symptoms and rapid recognition and intensive treatment of comorbidities diagnosed on admission seem to be crucial in the effective management of NVUGIB.

Early discharge of those GIB patients who are at low risk of significant complications for outpatient medical or even endoscopic management has been consistently advised due to the current economic climate, though this puts considerable pressure upon acute care physicians and gastroenterologists (10). Since endoscopy improves outcomes for patients at low and high risk for re-bleeding and death (6,23,24), the decision to proceed with early endoscopy becomes critical in the early management of patients with NVUGIB. Likewise, in the present study, time to endoscopy was found to be associated with increased likelihood of surgery and complications after the initial NVUGIB episode. In this sense, prompt evaluation of patient status in relation to associated risk factors as well as protective factors may have a role in the reduction of complications and mortality risk, particularly in older duodenal ulcer patients needing transfusions within 12 h of their admission to hospital.

Early endoscopic hemostasis carried out within 24 h of hospital admission has consistently been shown to reduce the length of hospital stay with a trend towards a lower risk for re-bleeding (25-27) and the subsequent need for surgery (25,28). Nevertheless, reductions in re-bleeding rates and mortality have been the main factors documented to trigger therapeutic advances in endoscopy (28).

While there was no difference in mortality rates between the NSAID and the non-NSAID group, higher re-bleeding rates observed in acute peptic ulcer bleeding patients with recent NSAID use in a recent, prospective cohort study was reported to be related to the effect of NSAIDs on platelet function, mucosal prostaglandins and ulcer healing (29). The fairly stable incidence of NVUGIB in recent decades has been associated with the advanced age of the patients with UGIB (9). In this context, based on the young patient distribution, a gradual increase in the incidence and risk of UGIBs seems inevitable in Turkey in the coming years.

In conclusion, the global results of the ENERGIB Study have shown substantial and significant differences in patient management and clinical outcomes across countries. In our study, we concluded that the presence of comorbidities, presentation with fresh red blood hematemesis or shock/syncope, and a prior history of NVUGIB are the predictors of patient management and clinical outcomes of NVUGIB, which may affect bleeding continuation or re-bleeding as well as complications after endoscopy among our population.

Despite the diminishing need for surgical intervention and mortality rates for NVUGIB in Turkey, as is the case in other European countries, NVUGIB remains a serious problem.

Acknowledgement: *This study was funded by AstraZeneca Turkey. The authors would like to thank Prof. Sule Oktay, MD, PhD and Cagla Isman, MD from KAPPA Consultancy Training Research Ltd (Istanbul, Turkey), for providing medical writing support funded by AstraZeneca Turkey.*

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