

Trends for Admission, Mortality and Emergency Surgery in Upper Gastrointestinal Bleeding: A Study of Eight Years of Admissions in a Tertiary Care Hospital

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Introduction: Most studies have shown a declining incidence of upper gastrointestinal bleeding (UGIB) in recent years. Data regarding mortality were controversial; in non-variceal bleeding, the increasing age of the population, increased use of anti-thrombotic and anticoagulant therapy in patients with cardiovascular diseases, and the use of non-steroidal anti-inflammatory drugs are counter-balanced by the progress in endoscopic therapy with stable mortality.

Material and Method: We performed a retrospective, cross-sectional study that included patients admitted with UGIB in Clinical Emergency Hospital Craiova during 2013–2020.

Results: 3571 patients with UGIB were selected; a trend toward increased admission for UGIB from 2013 to 2019 was noted, with a significant decrease in 2020. Non-variceal bleeding remains the most frequent form, with a slight increase in variceal bleeding, of Mallory-Weiss syndrome and angiodysplasia, and a 3-fold decrease for unknown etiology bleeding (with no endoscopy performed) during the 2017–2020 period as compared to 2013–2016. There was a trend toward decreased mortality, with lower mortality in 2017–2020 (12.83%) compared to 2013–2016 (17.41%). The mortality for variceal bleeding and peptic ulcer bleeding has declined, but mortality for non-variceal bleeding has slightly increased during 2013–2020. Mortality has decreased in admissions during regular hours/after hours and weekdays/weekends, but the difference (off-hours and weekend effects) had increased. The percentage of endoscopies performed in the first 24 hours after admission and the rate of therapeutic endoscopy increased during 2017–2020; the median time between admission and endoscopy was 17.0 hours during 2017–2020 and 59.1 hours during 2013–2016. The proportion of patients who needed emergency surgery for uncontrolled bleeding has significantly declined since 2013–2015, with an average value of 1% in the last 5 years of the study.

Conclusion: Increased admissions for UGIB, with lower mortality, especially for peptic ulcer bleeding and variceal bleeding were noted; higher percentages of therapeutic endoscopies and endoscopies performed during the first 24 hours after admission were also recorded.

Keywords: upper gastrointestinal bleeding, peptic ulcer bleeding, endoscopy, emergency surgery

Introduction

Acute upper gastrointestinal bleeding (UGIB) represents a potentially severe complication associated with significant hospitalization, morbidity, and mortality. The etiology is dominated by peptic ulcer disease, erosive gastritis, varices (esophageal and rarely gastric), esophagitis, Mallory-Weiss syndrome, and neoplasms.^{1,2} In 3 to 19% of cases, no

apparent source of bleeding is found (obscure bleeding);^{2–4} the use of enteroscopy (capsule endoscopy, spiral, or balloon-aided endoscopy) has decreased the frequency of obscure bleeding diagnosis.^{5,6}

Non-variceal bleeding is the most frequent form of UGIB; the aging population and increased use of anti-thrombotic and non-steroidal anti-inflammatory drugs are factors that adversely affect the incidence and mortality.⁷ The progress in medical care and endoscopic therapy has counterbalanced the former factors and contributed to a stable mortality of 5 to 10% in non-variceal UGIB,^{1,8–14} although values as high as 14–15% have been estimated in some studies.^{1–19} In variceal bleeding (most frequently caused by the rupture of esophageal varices) the 6-week mortality rate is 10–20%.^{18,20} Early endoscopy may contribute to a reduction in mortality in both forms;²¹ the general recommendation is to perform endoscopy within 24 hours of admission² but in severe cases of bleeding or in variceal bleeding a very early (<12 hours of admission) or immediately after stabilization is recommended.

The selection of severe cases represents an important factor for prognostic stratification; the most used scores were the Rockall score and the Glasgow-Blatchford score^{8,18,22–24} -Tables 1 and 2, but other scores such as Baylor score (Table 3), AIM65, Cedar Sinai score, PNED, T-score, ANN score, and Cambridge score were proposed.^{10,16,23,25,26}

Several studies have shown a declining trend of incidence, hospitalization, and mortality of UGIB, and especially of peptic ulcer bleeding in recent years.^{2,4,23,27} The effect can be related to several factors: improved access to endoscopy and endoscopic treatment, reduced time to endoscopy, progress of endoscopic hemostasis procedures, improved general

Table 1 Rockall Score¹⁰

	0	1	2	3
Age	<60	60–79	≥80	–
Shock	P<100 sBP≥100	P≥100 ≥100	sBP<100	–
Comorbidities	NO major	–	Cardiac failure, coronary ischemia	Renal/liver failure Disseminated malignancy
Diagnosis	MW No lesion No stigmata	Other exc. malignancy	Malignancy	
Bleeding stigmata	No/dark spot	–	Blood, adherent clot Visible/spurting vessel	–

Abbreviations: P, pulse; sBP, systolic Blood Pressure; MW, Mallory-Weiss syndrome.

Table 2 Glasgow-Blatchford Score¹⁰

Urea (mg/dl)	39–47	2
	48–60	3
	60–149	4
	≥150	6
Hb (g/dl)	Men 12–12.99	1
	Men ≥10	3
	Woman ≥10	1
	Both sexes <10	6
sBP (mm Hg)	100–109	1
	90–99	2
	<90	3
Pulse (>100/min)		1
Melena		1
Syncope		2
Liver disease		2
Cardiac failure		2

Abbreviation: sBP, systolic blood pressure.

Table 3 Baylor Score¹⁵

	1	2	3	4	5
Age	30–49	50–59	60–69		≥70
Number of diseases	1–2			3–4	>5
Severity of diseases				Chronic	Acute
Endoscopy score					
Site of bleeding				Posterior DU	
Bleeding stigmata	IIb		IIa		I

Abbreviation: DU, duodenal ulcer.

care of patients with UGIB, increased use of proton pump inhibitors and vasoactive drugs in variceal bleeding.^{2,9,18} Significant therapeutic endoscopy advances have led to a decline in rebleeding rates and emergency surgical interventions.^{2,9}

The purpose of our study was to evaluate the temporal trend for admission rates, mortality, and etiology changes in patients with acute UGIB over a significant timeframe in a tertiary care unit.

Materials and Method

We performed a retrospective, cross-sectional study to analyze the admissions, etiology, and mortality in cases with acute UGIB admitted in Clinical Emergency County Hospital Craiova for eight years (2013–2020). In the first four years, patients with UGIB were admitted to the Surgery Departments; endoscopy was regularly available only Monday to Friday on working days from 8 to 15 and emergency endoscopy was performed outside this schedule when necessary. By 2017, the Gastroenterology Department took responsibility for UGIB management, and the endoscopy regular schedule was expanded to 8–20 during regular working days and 8–15 during weekends and holidays.

The trend for admissions, etiology, total mortality, case-fatality (nonvariceal, peptic ulcer bleeding, variceal bleeding, UGIB with no endoscopy performed), the timing of endoscopy, the need for emergency surgery, and the influence of admission time were assessed. We quantified admissions as PROGRAMME IN/OUT (IN=admissions during regular hours, OUT=admissions after regular hours schedule) and also as WEEK IN/OFF (IN=admissions during working days, OFF=admissions during weekends and holidays) and stratified patients regarding risk factors for mortality (age, pre-endoscopic and after endoscopy Baylor bleeding score, Forrest score, Charlson comorbidity index) in non-variceal and variceal bleeding (Table 4 and Table 5). Charlson comorbidity index (CCI) was developed as a method for the estimation of mortality risk by weighing associated diseases with 1.2 and 6 points and also by adding supplemental points in patients at advanced age;²⁸ however, the accuracy in the prognosis of peptic ulcer bleeding is inferior to specific bleeding scores. The intervals between the onset of bleeding and endoscopy and between admission and endoscopy were estimated.

Inclusion and Exclusion Criteria

All patients admitted with UGIB in the Clinical Emergency County Hospital Craiova were included. The diagnosis was based on hematemesis, melena, or hematochezia and confirmed by endoscopy; in patients with melena or

Table 4 Forrest Classification¹⁰

		Prevalence (%)	Rebleeding Rate (%)
Active bleeding	IA (spurting bleeding)	10	90
	IB (oozing bleeding)	10	10–20
Bleeding stigmata, no active bleeding	IIA (visible vessel)	25	50
	IIB (adherent clot)	10	25–50
	IIC (hematin spot)	10	7–10
No bleeding stigmata	III (clean base)	35	3–5

Table 5 Charlson Comorbidity Index²⁸

	Points
Age >40	1
>50	2
>60	3
>70	4
Chronic pulmonary disease	1
Myocardial infarction	1
Peripheral vascular disease	1
Chronic Heart Failure	1
Peptic ulcer disease	1
Mild Liver Disease	1
Rheumatological disease	1
Dementia	1
Diabetes without chronic complications	1
Diabetes with chronic complications	2
Hemiplegia or paraplegia	2
Renal disease	2
Solid tumors	2
Leukemia/lymphoma	2
Moderate/severe liver disease	3
HIV/AIDS	6
Metastatic solid tumors	6

hematochezia and no endoscopy performed, the nazo-gastric tube has confirmed upper digestive source of bleeding. The study was conducted following the Declaration of Helsinki. Informed consent was obtained from all admitted patients and approval by the Local Ethics Committee of the Emergency Clinical County Hospital of Craiova was also obtained. Patients under 18 years of age, those who denied consent for data usage, and those with missing data were excluded.

In non-variceal bleeding, proton pump inhibitor therapy (80 mg iv bolus followed by 8 mg/hour 72 hours) was initiated before endoscopy; blood transfusions were recommended if the hemoglobin value was below 8 g/dl. Vitamin K or plasma concentrate was used in cases with over-dosage of vitamin K antagonists, and thrombocyte concentrate was used in cases with thrombocyte counts below 50.000/dl. In case of possible variceal bleeding (patients with known cirrhosis or previous variceal bleeding), the treatment with Terlipressin was initiated before endoscopy and was continued 3–5 days after endoscopy, antibiotics for prevention of infections, and corrective measures for coagulation disturbances were used; Sengstaken-Blakemore tube was used in unstable cases before endoscopy to help stabilize the patients.

Endoscopic therapy was performed in cases with active bleeding (Forrest Ia, Ib) and cases with a high risk of rebleeding (Forrest IIa, IIb); adrenaline injection combined with either clip placement or electrocoagulation was used for non-variceal bleeding, while in variceal bleeding EVL (endoscopic variceal ligation) procedure was used for esophageal varices or type I or II of GOV (gastro-esophageal varices) with active bleeding, with stigmata of recent bleeding or in case of high-risk varices (large, red signs present). Surgery was imposed in life-threatening non-variceal bleeding cases and cases with repeated endoscopic hemostatic failure with continued bleeding, whereas Sengstaken-Blakemore was used in variceal bleeding with persistent bleeding.

Statistical data were analyzed and provided using MedCalc version 22.009. Continuous variables were compared using the Student test; the Chi-square or the Fisher test were used for categorical variables. The received operating area under the curve (AUROC) was used to assess the predictive value of the Baylor bleeding score and the Charlson comorbidity index for mortality prediction.

Results

3571 patients with UGIB were selected during the analyzed period. The median age was 62.6 years in 2013–2016 and 62.9 years in 2017–2020. 19.1% were variceal bleeding (681 cases) and 58.3% were non-variceal bleeding (2081 cases); 226 cases had no known cause (obscure bleeding) and in 583 cases endoscopy was not performed during the bleeding episode (patient refusal, dementia, immediate death, alcohol withdrawal, other contraindications). Characteristics of the patients are illustrated in Table 6.

Admission Rate and Etiology of Bleeding

During the 2013–2020 interval, we noted a trend toward increased admission for UGIB from 2013 to 2019, with a decrease in 2020 (the first pandemic year) - Figure 1. The etiology was similar, with the ratio between non-variceal and variceal bleeding being 3.04 during 2013–2016 and 3.08 in 2017–2020; an increased frequency of Mallory-Weiss bleeding and a decreased frequency of tumoral bleeding was seen. A 3-fold reduction for unknown etiology bleeding (with no endoscopy performed) and a 2-fold reduction of obscure bleeding were observed during 2017–2020 period, as compared with 2013–2016 period (8.4 versus 26.9%, OR=0.2490, 95% CI 0.2052–0.3021, $P<0.0001$, and 5.3 versus 11.1%, OR=0.4465, 95% CI 0.3393 to 0.5875, $P<0.0001$). The reduction of bleeding with no endoscopy was related to the improvement of the permanent endoscopy schedule, whereas the lower rate of obscure bleeding can be related to a more accurate endoscopy.

Mortality

During the analyzed period of 8 years, there was a trend toward decreased mortality (Figure 2) with lower mortality in the 2017–2020 period (12.8%) as compared with the 2013–2016 period (17.4%, OR=0.6988, 95% CI 0.5806 to 0.8410,

Table 6 Characteristics of Patients with UGIB

Characteristics	2013–2016 -1585 Patients-	2017–2020 -1986 Patients-	P-value
Age yrs±STD (Minimum-maximum)	62.6±13.9 (18–94)	62.9±13.9 (16–99)	0.5724
<60/60-79/>80 (%)	39.6/50.8/9.6	37.5/50.5/13	0.0593
M/F (%M)	64.9	63.3	0.8099
Etiology (endoscopy performed)			
Ulcer	39.1	36.9	0.6373
Gastric/duodenal/esophageal erosions	12.9	15.4	0.0049
MW/Boerhaave syndrome	3.3	6.8	<0.0001
Esophageal/gastric/jejunal varices	21.8	23.6	0.0189
Angiodysplasia/Dieulafoy/GAVE	0.7	3.5	0.0006
Tumors	5.8	5.8	0.6106
Anticoagulants/antithrombotic	5.1	3.5	0.0995
Other	0.3	0.2	0.9119
Obscure	11.1	5.3	<0.0001
Unknown (endoscopy not done)	26.9	8.4	<0.0001
Mortality (%) -all patients	12.8	7.4	0.0001
- Patients with endoscopy (%)	6.5	7.9	0.1743
- Patients without endoscopy (%)	36.8	35.9	0.8467
- Variceal bleeding	23.4	22.1	0.7025
- Non-variceal bleeding	6.6	7.0	0.7166
- Cirrhosis with non-variceal bleeding	12.5	10.8	0.7218
Cirrhosis (%)	27.6	32.0	0.0056
Endoscopy <6h/<12h/<24h	6.5/14.5/38.5	40.3/57.8/83.1	<0.0001
Endoscopic therapy (%)	7.3	23.7	<0.0001
Emergency surgery (%)	3.7	0.8	<0.0001
Mean hospital stay (days)	7.9	7.4	0.0401

Note: Statistically significant P-values are marked with italicized fonts.

Abbreviations: STD, standard deviation; GAVE, Gastric antral vascular ectasia.

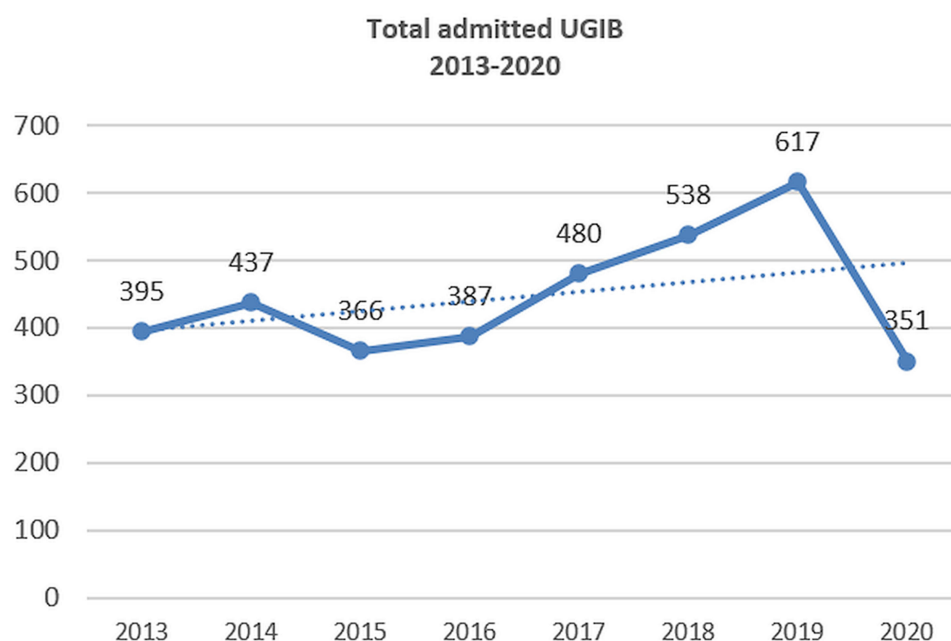


Figure 1 Admissions for UGIB (2013–2020).

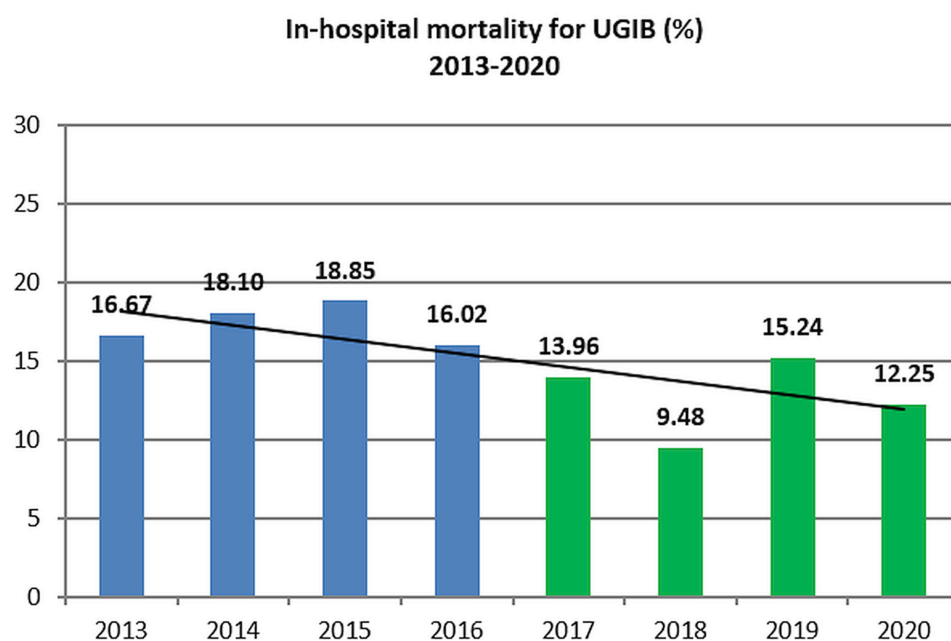


Figure 2 In-hospital mortality for UGIB (2013–2020).

$P=0.0001$). The mortality in 2019 (15.2%) was higher than in 2017–2018 (11.6%, $OR=1.3708$, 95% CI 1.0241 to 1.8350, $P=0.0340$). The appearance of the COVID-19 pandemic may have altered admission and possibly mortality in UGIB,^{28,29} although our study has included only the first year of the pandemic.

Associated Comorbidities

The percentage of patients with cirrhosis and the mean values of CCI have no significant variations during the analyzed period; however, a slight increase for pre- and after-endoscopy BBS was recorded (Figures 3–4).

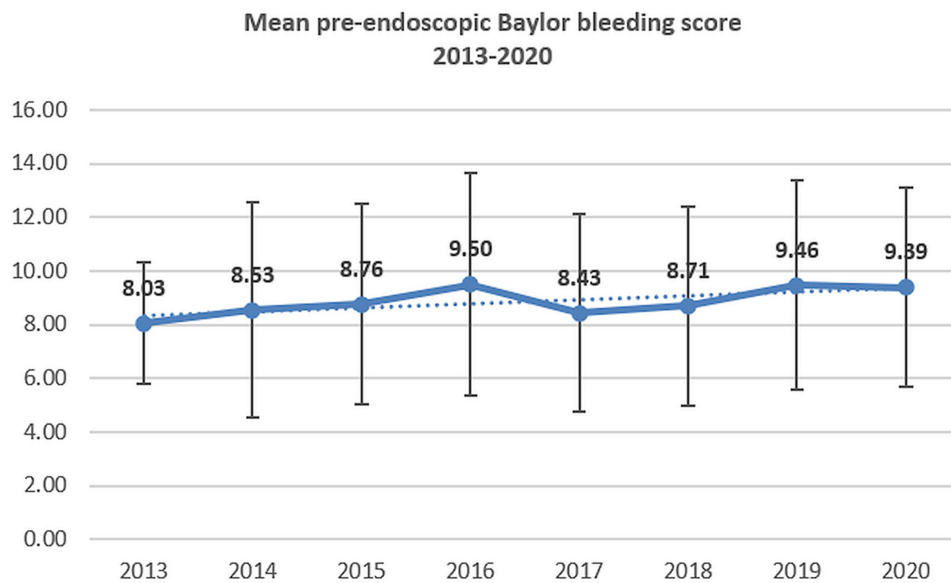


Figure 3 The mean value of pre-endoscopic Baylor bleeding score in UGIB (2013–2020).

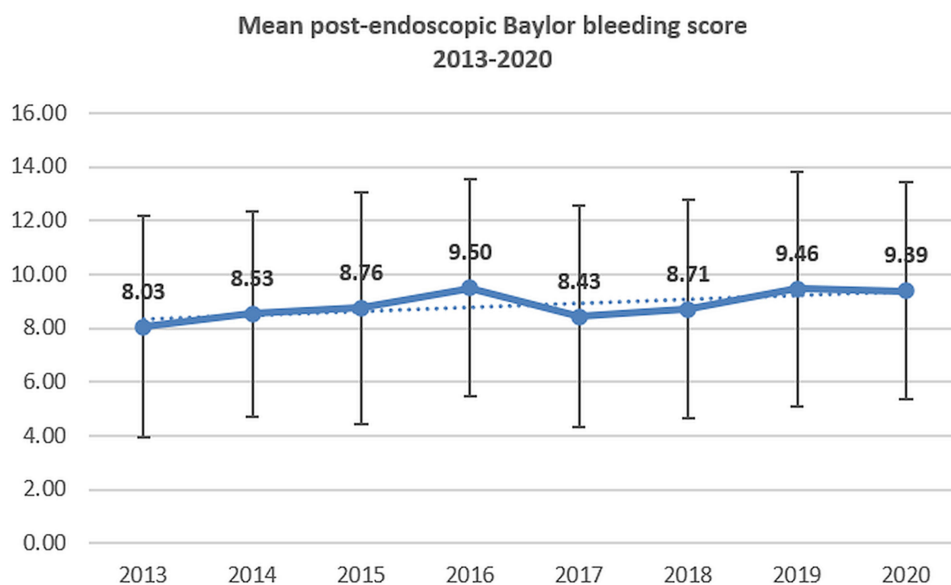


Figure 4 The mean value of after-endoscopic Baylor bleeding score in UGIB (2013–2020).

Case Fatality Rate Related to the Type of Bleeding

Case fatality ratios for variceal bleeding and peptic ulcer bleeding have declined; however, the mortality for non-variceal bleeding has slightly increased during 2013–2020 (Figures 5–8).

The Effect of Admission Time

Several studies in the literature have analyzed the potential increased mortality in patients admitted after-hours (off-hours or after-hours effect) and during weekends; the possible explanations were a lower rate of endoscopy after-hours or during weekends because of schedule, decreased quality of medical care because less staff or less experienced staff involved during after-hours and weekends, or more severe cases admitted.²⁸ In our study, we noted decreasing mortality

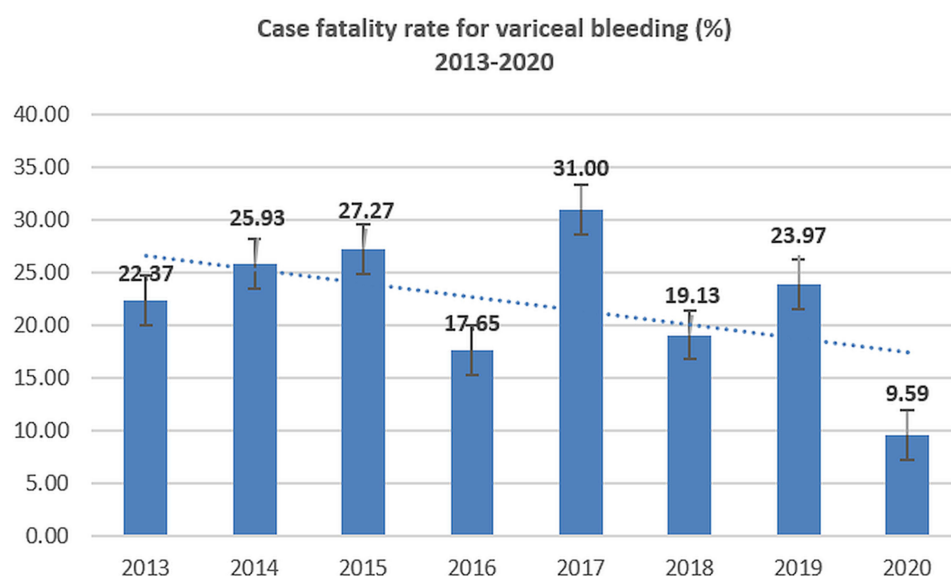


Figure 5 Case-fatality rate for variceal bleeding (2013–2020).

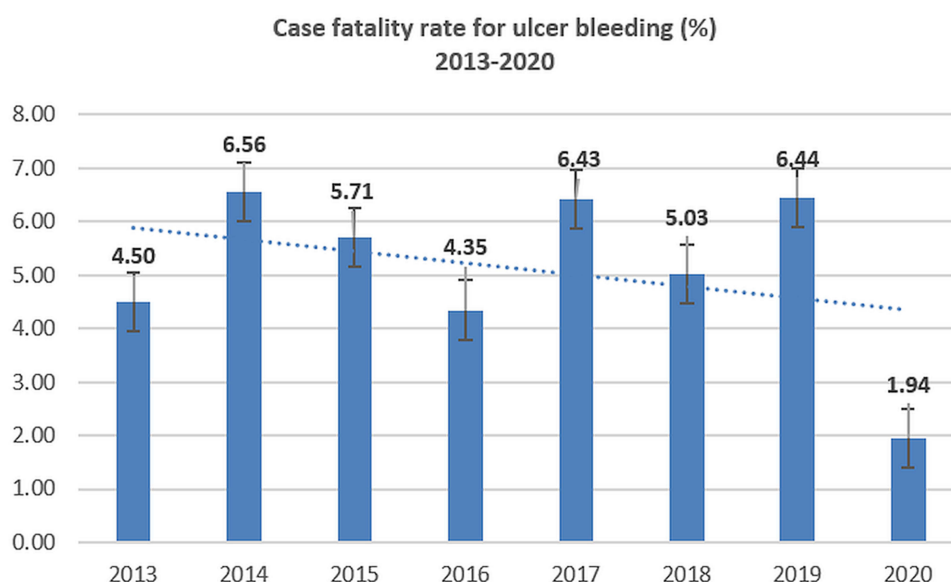


Figure 6 Case-fatality rate for peptic ulcer bleeding (2013–2020).

in admissions during both regular hours/after-hours and weekdays/weekends, nevertheless, the differences (off-hours and weekend effects) have increased from 2013 to 2020 (Figures 9–10).

Endoscopy-Timing, Percentage, Therapy

41.6% of patients admitted from 2013 to 2016 have performed endoscopy during the first 24 hours compared with 84.7% for those during the 2017–2020 period. The median time between admission and endoscopy was 17.0 hours during 2017–2020 compared to 59.1 hours during 2013–2016 ($P<0.0001$). The percentage of therapeutic endoscopy has also increased during the 2017–2020 period (23.7% versus 7.3% during the 2013–2016 period, $P<0.0001$).

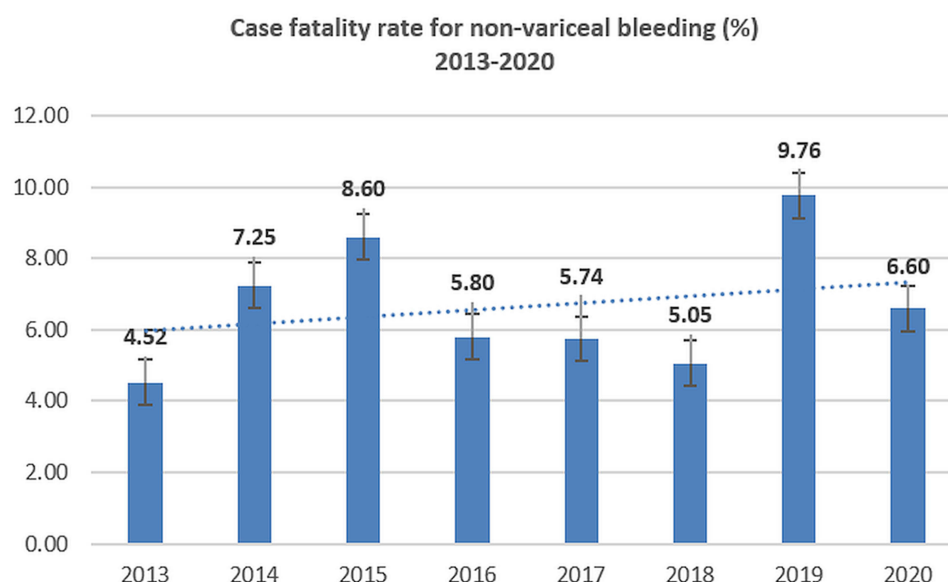


Figure 7 Case-fatality rate for non-variceal UGIB (2013–2020).

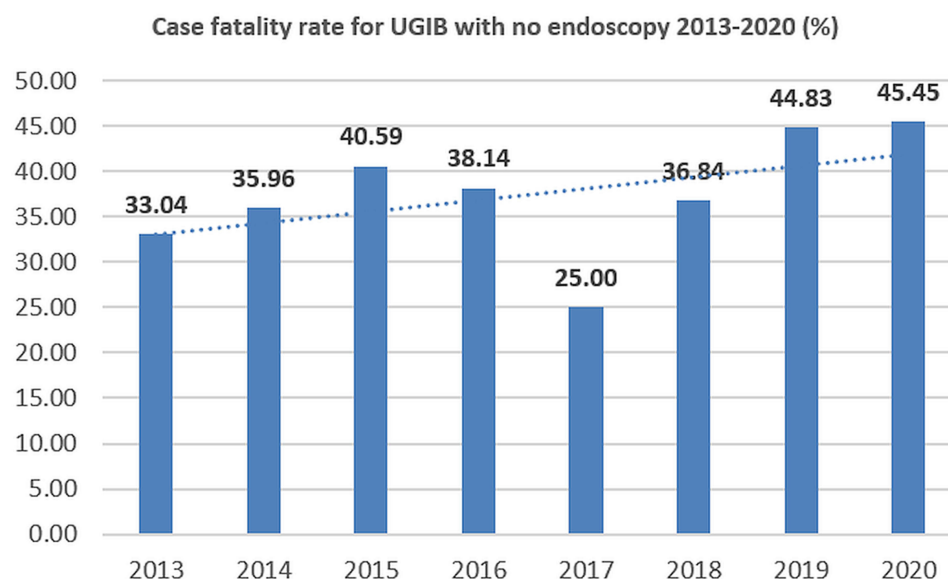


Figure 8 Case-fatality rate for UGIB with no endoscopy (2013–2020).

Surgery

The proportion of patients who needed emergency surgery for uncontrolled bleeding has declined since 2016, with an average value of 1% in the last 5 years of the study. The extension of endoscopy availability to 8–20 during weekdays and 8–15 during weekends, the possibility of emergency endoscopy until midnight, together with admission of UGIB to Gastroenterology instead of the Surgery Department may have contributed to this decline.

Discussions

Admissions for UGIB have increased from 2013 to 2019, mostly related to the increased availability of emergency endoscopy in our center. In 2020 a decreased admission for UGIB was attributed to the beginning of the COVID-19

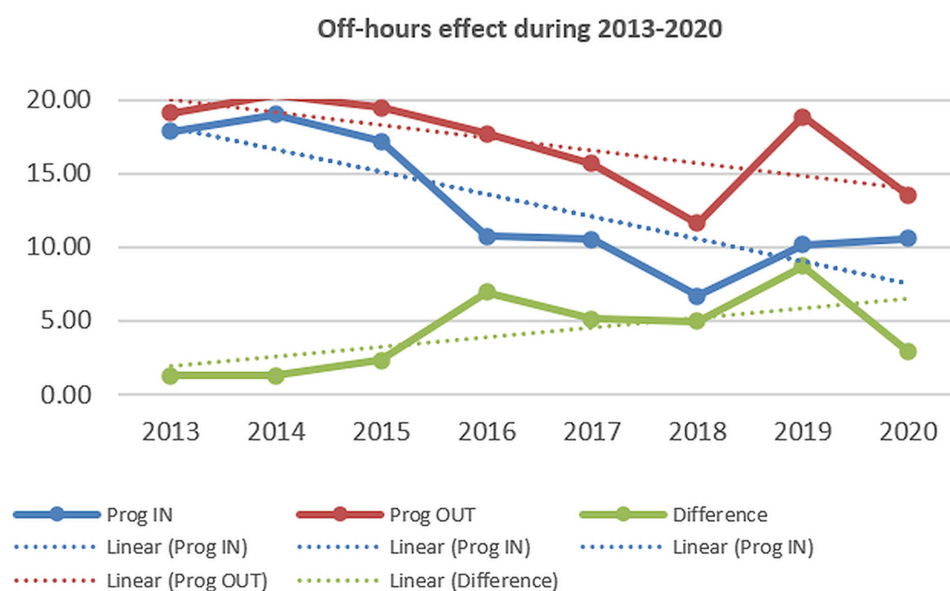


Figure 9 Mortality in UGIB adjusted by admission during regular hours/after hours (2013–2020).

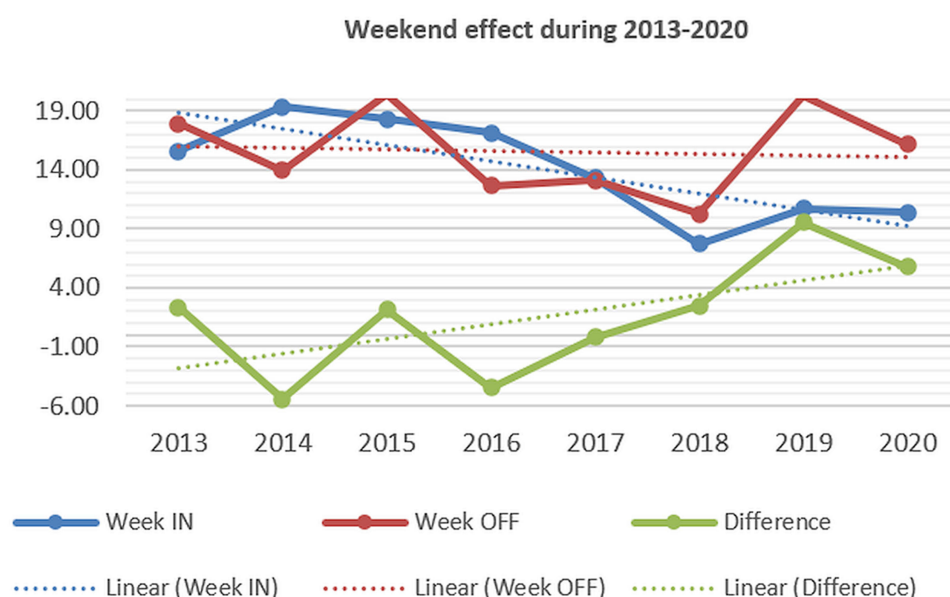


Figure 10 Mortality in UGIB adjusted by admission during weekdays/weekends (2013–2020).

pandemic, with multiple causes (lockdown imposed during March-May 2020, “fear effect” related to the hospital visits and admissions, the need for triage and dedicated spaces).^{29–32}

The etiology of UGIB has only limited changes during the 2013–2020 period, mainly related to an increased proportion of angiodysplasia and Mallory-Weiss syndrome. Non-variceal bleeding was the most frequent form, and peptic ulcer represented the first cause of non-variceal bleeding during the analyzed period, with no significant variation during 2013–2020. Although the prevalence of peptic ulcer has decreased during the last decades as a result of proton pump inhibitor treatment and *H. pylori* eradication; the prevalence of peptic ulcer bleeding was stable because of the aging population, frequent use of NSAID and also antithrombotic therapy.^{29,31,33} Erosive diseases (esophagitis, gastritis, and duodenitis) accounted for 12.9% of UGIB during 2013–2016 and 15.4% during 2017–2020; tumors represent the third cause of non-variceal bleeding, with 5.8% of UGIB during both the 2013–2016 and 2017–2020 period; most cases

were gastric adenocarcinoma, but esophageal carcinoma, GIST, or gastric polyps can also be associated with a risk of UGIB.³⁴ Mallory-Weiss syndrome has increased during 2017–2020, while antithrombotic therapy and angiodysplasia/Dieulafoy lesions have represented the fifth and sixth cause of UGIB. We noted a 3-fold reduction in unknown etiology bleeding and a 2-fold reduction in obscure bleeding; the main explanation was related to the increased accessibility to endoscopy during after-hours and weekends and better investigation of obscure cases of UGIB including colonoscopy, capsule or balloon-aided enteroscopy. UGIB with no endoscopy performed has a higher mortality rate compared to both variceal and non-variceal bleeding with endoscopy performed,³⁰ because of the lack of endoscopic therapy.

Mortality rates progressively decreased during 2013–2020, with lower mortality in the second half. The reduction was mainly induced by a reduction in case fatality rate for variceal bleeding and PUB, while for patients with no endoscopy performed a slightly increased mortality trend was counterbalanced by a superior decrease in the number of cases (because of higher accessibility at emergency endoscopy). Studies in the literature are contradictory; a study in Canada from 1993–2003 found a stable mortality of 3–3.5% during the period,³⁵ while a decrease was noted in several studies in the UK,^{36–39} and also in Scotland.⁴⁰ A study in Turkey found that mortality for nonvariceal UGIB doubled in 2015–2016 as compared with 1993–1995 (6% versus 3% during 1993–1995, $P=0.06$).⁴¹ Some longitudinal studies have shown that the mortality rate has decreased,^{42,43} with an increased proportion of neoplasms, angiodysplasia, Dieulafoy lesions, and esophagitis as the causes of UGIB.⁴² In the USA, a longitudinal study from 2012 to 2021 has shown a slightly increased mortality over time, partially explained by the Covid-19 pandemic;⁴⁴ another study in Finland has shown a declining trend for mortality in men (which remains between 5–10%) and a stable trend of fatality in women.⁴⁵

Despite significant progress in the endoscopic and pharmacological management of UGIB during the last decades, the downward trend for mortality in UGIB was very slow. Age and comorbidities represent the main factors for mortality, and increasing the use of anti-thrombotic therapy can be a significant factor in increasing the prevalence of UGIB. Aging population together with increased consumption of NSAID and anti-thrombotic drugs can slow down or even stop the decline of mortality in UGIB. In our study, the mean age was similar during 2017–2020 compared to 2013–2016 (62.6 ± 13.9 versus 62.9 ± 13.9 years, $P\text{-value}=0.5724$). Data for NSAID and AT use was available only for the 2017–2020 period and was published in one of our previously published papers;²⁹ no differences were seen between NSAID use but a significant increase in AT drugs was noted, which may be an explanation for increased admissions during the 2017–2020 period.

The assessment of severity variations during 2013–2020 was contradictory; the Charlson comorbidity index was not significantly changed during the whole analyzed periods, but a slightly increasing trend for both pre-endoscopic and after-endoscopy Baylor scores was recorded, which may suggest a potential trend toward more severe UGIB admitted cases.

The “weekend effect” (increased mortality in patients admitted during weekends) was noted in patients with UGIB in several studies,^{39,40,46–49} although other studies have shown no difference.^{50–52} Some meta-analyses were available; higher mortality was noted for weekend admissions,^{53–56} but only non-variceal UGIB had a significant weekend effect in some meta-analyses.^{53–55} Some studies have shown a more pronounced effect in European hospitals.⁵⁶ For off-hours admissions, higher mortality was also noted in a systematic review and meta-analysis in non-variceal UGIB.⁵⁷ In our study both off-hours and weekend effects were observed; although the mortality has decreased in both after-hours/regular hours and weekdays/weekend admitted patients, the intensity of off-hour and weekend effects have increased, which suggests that medical care and endoscopic therapy improvements were more significant during regular hours and weekdays.

A significant improvement in endoscopy and endoscopic therapy was noted during the 2017–2020 period, with an increasing percentage of total and therapeutic endoscopies, procedures performed during the first 24 hours, and the median time between admission and endoscopy. The improvement in endoscopy may represent the main reason for improved mortality, although improved care of patients with UGIB may also have an important role. A significantly lower percentage of patients needed surgery for uncontrollable UGIB during 2017–2020 compared to 2013–2016 ($OR=5.0803$, 95% CI 2.8711 to 8.9896, $P<0.0001$). This finding was consistent with international data^{35,49–61} and studies from Romania.⁵⁹ Mortality rates of 10–30% in patients with emergency surgery for UGIB have been noted,^{62–64} improvements in mortality for surgical cases were however observed.^{63,65}

Conclusions

The temporal trend for UGIB was marked by increased admissions between 2013 and 2019, with a decrease in 2020. The etiology of UGIB was stable, but the mortality rates progressively decreased, with a decreasing case fatality for variceal bleeding and PUB. Significant improvements in endoscopy and endoscopic therapy were noted during 2017–2020. Less than 1% of patients needed surgery for uncontrollable UGIB during 2017–2020.

Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) of the EMERGENCY HOSPITAL OF CRAIOVA (protocol code 11977/24.03.2020).

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Data Sharing Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

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