Timing of Endoscopy and Clinical Outcomes in Patients Presenting with Acute Upper Gastrointestinal Bleeding in a Tertiary Hospital in Davao City, Philippines: A Retrospective Cohort Study

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Abstract

Background. Upper gastrointestinal bleeding (UGIB) is a common cause of

hospitalizations in adult Filipinos. Upper endoscopy is the cornerstone of diagnosis and therapy with guidelines recommending endoscopy within 24 hours of hospital admission. However, data on the clinical outcomes in relation to the optimal timing of endoscopy remains limited in Davao City.

Methods. A retrospective cohort study of adult patients (age ≥19) with a primary or secondary diagnosis of UGIB who underwent an upper endoscopy was conducted in a tertiary hospital in Davao City, Philippines from January 2019 to December 2022. Patient demographics and clinical data were analyzed by chart review. Patients were categorized based on the timing of endoscopy from admission or from the presentation of UGIB symptoms in patients previously admitted for other complaints: urgent (t ≤6 hours), early (t >6-24 hours), late (t >24-48 hours), and very late (t >48 hours). The 30-day all-cause in-hospital mortality, and the rates for further bleeding, endoscopic treatment, average units of blood transfused, intensive care unit admission, and duration of hospitalization within 30 days were compared. Statistical analyses were performed using the JASP software, and a *P* value <0.05 was considered as statistically significant.

Results. A total of 142 patients were included in the study. Mean age was 62 years, with more males (66.2%) than females (33.8%). Non-variceal causes, particularly erosive diseases (53.7%), were the most common endoscopy findings in our center. Endoscopic treatments were only performed in 26 patients (18.3%). The 30-day all-cause in-hospital mortality rate did not differ between the urgent, early, late and very late elective endoscopy groups (25% vs 2.6% vs 9.3% vs 13%; p=0.26). Although it did not reach statistical significance, urgent timing (n=4) was associated with a higher further bleeding rate (25%), and the need for endoscopic intervention (50%). A significant association between early and late endoscopy groups in the duration of hospitalization of only one week was demonstrated (p=0.032). There was no difference regarding the rate of ICU admissions and mean number of blood transfused among the four groups.

Conclusion. There were no significant differences in mortality and other clinical outcomes between all four endoscopy groups except for the duration of hospitalization. Among admitted UGIB patients, optimal medical management is still emphasized and elective endoscopy within 24 hours or until the patient is stabilized can be safely performed in most acute UGIB patients.

Keywords. Upper gastrointestinal bleeding, endoscopy, timing, clinical outcome

Introduction

Gastrointestinal bleeding (GIB) is the most common gastrointestinal condition leading to hospitalization in adults.[1] It is commonly categorized based on the bleeding site, separated anatomically by the ligament of Treitz: Upper and Lower GIB.[1,2] Seventy-five percent of acute GIB cases are due to upper gastrointestinal bleeding (UGIB), which is mostly caused by peptic ulcer disease (PUD).[3,4] In the Philippines, PUD accounted for 80% of total Daily Adjusted Life Years (DALY) lost.[5] PUD-associated deaths reached 6,865 or 1.02% of total deaths, while the age-adjusted death rate was 9.95 per

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100,000 population, making the Philippines rank 12th in the world.[5]

Risk factors for UGIB include the use of nonsteroidal anti-inflammatory drugs (NSAIDs), antiplatelets, anticoagulants, history of alcohol abuse, prior GIB, and liver disease.[6,7] In patients with liver cirrhosis, UGIB can arise as a consequence of portal hypertension, particularly from gastroesophageal varices and portal hypertensive gastropathy.[8] Variceal bleeding accounts for 60–65% of bleeding episodes in patients with liver cirrhosis and remains one of the major causes of death in cirrhotic patients.[8,9] The outcome for variceal bleeding depends on the severity of the underlying liver disease.[8]

Initial assessment of patients presenting with upper GIB consists of measuring vital signs and differentiation between upper and lower GIB.[1] Available risk assessment tools are the Glasgow-Blatchford and the Rockall scoring systems which may stratify patients into low risk or high risk.[1,10-13] Adequate intravenous fluid resuscitation is administered to maintain hemodynamic stability prior to endoscopy, with some cases necessitating packed red cell transfusion to maintain adequate tissue perfusion and oxygenation.[3,6,10] Medications include proton pump inhibitors (PPI) for non-variceal UGIB and vasoactive agents, such as Ocreotide for patients with variceal bleeding and cirrhosis.[1,3,9]

Endoscopy is the cornerstone of diagnosis and therapy in GIB.[14] It is a diagnostic endoscopic procedure in which a flexible endoscope is passed through the mouth to visualize the esophagus, stomach, and proximal duodenum.[1,15] National guidelines recommend performing upper endoscopy in most patients hospitalized with UGIB within 24 hours of presentation to the hospital to identify source of bleeding, risk-stratify patients, and provide potential endoscopic treatments.[1,10,16] However, there is still an ongoing debate and conflict regarding the optimal timing of endoscopy and its association with better or worse clinical outcomes.[6] A consensus of international trials showed no significant difference in patient outcomes in terms of reduction in rebleeding, need for surgical intervention, and mortality rates between urgent endoscopy (<12 hours) and early endoscopy (>12 - 24 hours).[17]

Despite conflicting findings from previous international studies, the impact of the timing of endoscopy on clinical outcomes remains limited, particularly in the local context.

Thus, this study aimed to investigate whether significant differences exist in clinical outcomes based on the timing of endoscopy in patients with UGIB. The findings may identify the optimal timing for endoscopy, potentially reducing complications, shortening hospital stays, improving overall patient care, and encouraging further research into other factors affecting the timing of endoscopy in UGIB patients.

Methodology

Research Design

This study is a retrospective cohort study that included a heterogeneous population of adult patients (≥19 years old) clinically diagnosed with UGIB in a tertiary hospital in Davao City, Philippines from January 1, 2019 to December 31, 2022.

Data gathering was done by reviewing the charts from the medical records section. The patients' demographic information, clinical history, laboratory results, timing of endoscopy, endoscopy findings, treatment interventions, and outcomes of the interventions were recorded using the information in the chart review.

General Objective

To determine the clinical outcomes associated with the timing of endoscopy, categorized into four groups (urgent endoscopy *t ≤ 6 hours*, early endoscopy *t > 6-24 hours*, late endoscopy *t > 24-48 hours*, and very late endoscopy *t > 48 hours*), in patients with acute UGIB admitted in a tertiary hospital in Davao City from January 1, 2019 to December 31, 2022.

Specific Objectives

1. To describe the demographic and clinical profile of patients in the four endoscopy groups in terms of age, sex, comorbidities, history of bleeding peptic ulcers, risk factors for PUD, hemoglobin level on admission, systolic blood pressure, heart rate, Glasgow-Blatchford score, Rockall score, and bleeding during hospitalization;
2. To describe the endoscopic findings among the four endoscopy groups;
3. To determine the distribution of patients according to the timing between admission or presentation of symptoms and endoscopy;
4. To determine the association of the timing between admission to endoscopy procedure and its clinical outcomes such as:
    a. Primary outcome
        i. 30-day all-cause in-hospital mortality
    b. Secondary outcomes
        i. Further bleeding rate within 30 days;
        ii. Therapeutic endoscopy within 30 days;
        iii. The average units of blood transfused within 30 days;
        iv. Admission to the intensive care unit (ICU) within 30 days;
        v. Length of stay in-hospital.

Selection of cases

All eligible patients admitted in a tertiary hospital in Davao City from January 1, 2019 to December 31, 2022 with a diagnosis of UGIB who underwent upper endoscopy.

Inclusion Criteria

1. Adult patients aged ≥19 years old;
2. Admitted in a tertiary hospital in Davao City within the specified study period;
3. Initial diagnosis of UGIB based on clinical criteria; and
4. Underwent upper gastrointestinal endoscopy.

Exclusion Criteria

1. Patients aged <19 years old;
2. Incomplete data and;
3. Normal findings on UGIE and were diagnosed with LGIB by subsequent colonoscopy within the same admission.

Sample Size Determination

Based on the Taro Yamane Sample size formula, with a study population of 215 patients who underwent upper endoscopy, at least 139 patients are needed to detect a significant difference at an alpha error of 5%.

Operational Definition of Terms

Upper gastrointestinal bleeding (UGIB) – It is defined as bleeding proximal to the ligament of Treitz with at least one of the following presentations: melena, hematochezia, hematemesis, and anemia. Information on the presence of UGIB will be obtained from final diagnosis on the front sheet of the clinical chart.

Glasgow Blatchford score (GBS) - It identifies patients who are at low-risk and candidates for outpatient management. For this study, clinical and laboratory data are taken on the day of admission and when upper gastrointestinal bleeding was diagnosed. A score of 0 is stratified as low risk while scores of ≥ 6 are associated with high risk for needing intervention.

Rockall score – It stratifies patients with a high mortality or risk of rebleeding using the following variables: age, shock, comorbidity and stigmata of recent hemorrhage. For this study, the pre-endoscopic and post-endoscopic Rockall score is calculated from the clinical, laboratory and endoscopic data in the clinical chart.

Hypotension – It is defined as admission systolic blood pressure of less than 90 mmHg.

Bleeding during hospitalization – It refers to occurrence of UGIB in patients who were admitted for reasons other than UGIB (i.e cerebrovascular accident, acute coronary syndrome, pneumonia, etc.). For this study, the interval is calculated from the onset of UGIB symptoms during admission to the time of endoscopy.

30-day all-cause in-hospital mortality – It refers to the percentage of patients who died from any cause within 30 days of being admitted to the hospital from any cause.

Data Collection Process

Approval from the Ethics Committee before data collection was obtained and a Data Privacy Letter for access to the charts addressed to the DMSFH Data Protection Officer (Appendix A) was furnished. A Data Privacy Agreement (Appendix B) and an Agreement of Confidentiality (Appendix C) were signed by the researchers, the Data Protection Officer, and the Data Information Controller and presented to the Medical Records Section for the retrieval of charts.

The hospital's database of daily admissions from January 2019 to December 2022 was reviewed to identify potential cases. Using the inclusion and exclusion criteria, all eligible patient charts were included in the review and were assigned a unique code. Charts with missing data were excluded. Data from the charts were recorded using a Data Collection Form (Appendix D) which consisted of the demographic information, including age and gender; the clinical data on admission, including systolic blood pressure, heart rate, coexisting comorbid diseases, history of bleeding peptic ulcers, risk factors for PUD such as medications that contribute to different clinical outcomes. Patients who were readmitted within 30 days were classified as rebleeding if the same stigmata of hemorrhage was confirmed on endoscopy, while patients readmitted beyond 30 days were classified as new cases. All the collected data were collated in a spreadsheet program of a password-protected laptop and were analyzed accordingly.

Description of Outcome Measures

The primary outcome was the 30-day all-cause in-hospital mortality rate. Secondary outcomes were (1) further bleeding (defined as persistent and recurrent bleeding) within 30 days, (2) endoscopic therapy within 30 days, (3) the average units of blood transfused within 30 days, (4) the admission to the intensive care unit (ICU) within 30 days, and (5) the length of stay in-hospital.

Statistical Analysis

Descriptive statistics in the form of mean, standard deviation for the interval variables, and frequency with percentages for categorical variables were used. One-way ANOVA was used to see significant mean differences among inpatient groups, and Chi-square tests were performed to see a significant association between inpatient groups and other categorical variables, including the primary outcome and secondary outcomes. All data analyses were performed using the JASP

software. A p value 0.05 with a two-tailed test were considered statistically significant.

Ethical Considerations

The principal authors are committed to upholding rigorous standards of data privacy and participant confidentiality. The patients were deidentified using a unique code to eliminate bias and maintain anonymity. Data access was restricted solely to the research team and biostatistician, with no participant contact during the study. Detailed chart review findings and data from the data collection forms were meticulously tallied in a secure, password-protected Excel file and laptop. The data collected will be kept for five years and will be disposed afterwards.

Results

A total of 147 charts of patients who were ≥ 19 years old, with signs and symptoms of acute UGIB, and underwent UGIE from January 1, 2019 to December 31, 2022 were initially screened (*Figure 2*). However, five patients who had unremarkable upper endoscopy findings but with bleeding localized in the lower gastrointestinal region during subsequent colonoscopy were excluded. In total, 142 patients were included and distributed into four groups based on the timing of their endoscopy: Urgent Endoscopy (4, 2.8%), Early Endoscopy (38, 26.8%), Late Endoscopy (54, 38.0%), and Very Late Endoscopy (46, 32.4%) groups.

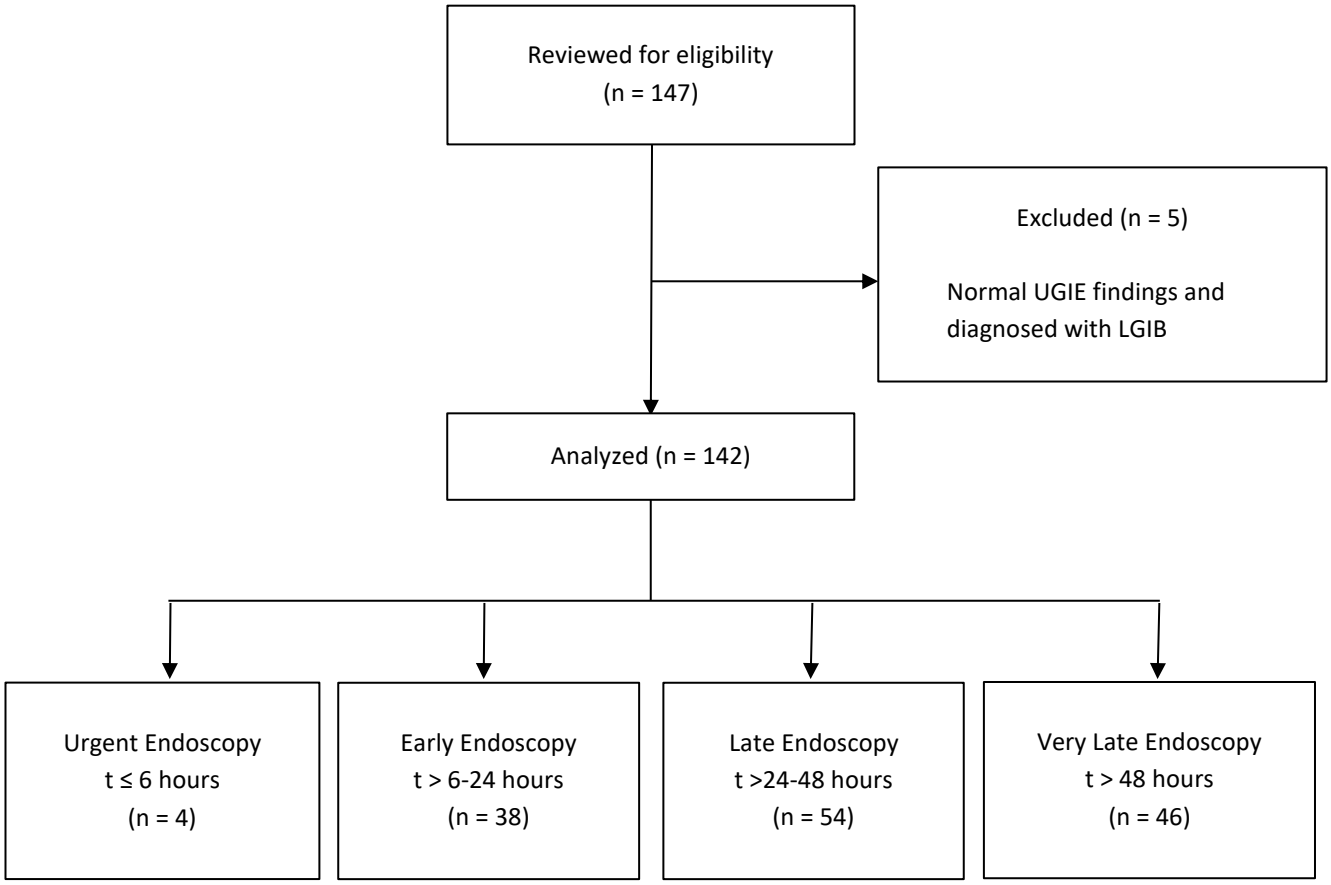


Figure 2. Flow diagram of patient sample collection.

Patient Characteristics

The baseline demographic and clinical characteristics of the study population are summarized in *Table I*. The mean age of the study population was 62 ± 14.4 years, with a slight predominance of patients within the age group of 60-79 years old (72, 50.7%). Among the 142 patients, there were a total of 94 (66.2%) males and 48 (33.8%) females (Figure 3).

Table I. Baseline Characteristics of the Patients

Characteristics and Clinical Data	Urgent Endoscopy Group (n = 4)	Early Endoscopy Group (n = 38)	Late Endoscopy Group (n = 54)	Very Late Endoscopy Group (n = 46)
Age (years)				
< 60	1, 25%	13, 34.2%	23, 42.6%	16, 34.8%
60-79	2, 50%	21, 55.3%	27, 50%	26, 56.5%
≥ 80	1, 25%	4, 10.5%	4, 7.4%	4, 8.7%
Mean	62.75 ± 22.7	63.2 ± 15.5	61.2 ± 13.2	62.0 ± 14.6
Sex				
Male	4, 100%	28, 73.7%	32, 59.3%	30, 62.5%
Female	0	10, 26.3%	22, 40.7%	16, 37.5%
Coexisting diseases				
Hypertension	2, 50%	16, 42.1%	29, 53.7%	23, 47.9%
Diabetes	3,	10, 26.3%	20, 37.0%	20, 41.7%
CKD	75% 0	3, 7.9%	13, 24.1%	13, 27.1%
Cardiac diseases	1, 25%	6, 15.3%	12, 22.2%	7, 14.6%
Cancer	1, 25%	6, 15.3%	7, 13.0%	10, 20.8%
Liver cirrhosis	0	2, 5.3%	9, 16.7% 5,	5, 10.4%
Gouty arthritis	0	3, 7.9%	9.3%	4, 8.3%
CVA	1, 25%	2, 5.3%	7, 13.0%	6, 12.5%
History of BPUD	2, 50%	17, 44.7%	23, 42.6%	15, 31.3%
Risk factors for PUD				
Alcoholism	2, 50%	14, 36.8%	17, 31.5%	20, 41.7%
Antiplatelets	1, 25%	3, 7.9%	7, 13.0%	13, 27.1%
H. pylori	0	5, 13.2%	11, 20.4%	4, 8.3%
NSAIDs	0	4, 10.5	7, 13.0%	7, 14.6%
Previous GIB	0	3, 7.8%	3, 5.6%	6, 12.5%
Anticoagulants	0	1, 2.6%	4, 7.4%	5, 10.4%
Liver disease	0	1, 2.6%	5, 9.3%	4, 8.3%
Presenting Symptom				
Melena	2, 4.25%	12, 25.5%	16, 34.05%	17, 36.2%
Epigastric pain	2, 6.1%	14, 42.4%	10, 30.3%	7, 21.2%
Hematemesis	0	7, 26.0%	10, 37%	10, 37%
Hematochezia	0	3, 16.7%	8, 44.4%	7, 38.9%
Body malaise	0	1, 12.5%	3, 37.5%	4, 50%
Dizziness	0	0	1, 12.5%	7, 87.5%
Syncope	0	0	0	1, 100%

Hemoglobin level on admission (mg/dL)				
< 70	0	4, 10.5%	15, 27.8%	11, 23.9%
≥ 70	4, 100%	24, 89.5%	39, 72.2%	35, 76.1%
Mean	114 ± 28.3	113.54 ± 31	120 ± 22.4	93.0 ± 30.9
Systolic blood pressure (mmHg)				
< 90	1, 25%	3, 7.9%	7, 13.0%	7, 15.2%
≥ 90	3, 75%	35, 92%	47, 87.0%	39, 84.8%
Mean	117.5 ± 33.0	121 ± 21.9	120 ± 22.4	117.2 ± 25.1
Heart rate (bpm)				
≤ 100	1, 25%	4, 10.5%	45, 83.3%	31, 67.4%
> 100	3, 75%	34, 89.5%	9, 16.7%	15, 32.6%
Mean	103.3 ± 13.2	83.3 ± 14.5	88.4 ± 15.1	90.3 ± 19.6
Glasgow-Blatchford Score				
0 - 5	2, 50%	22, 57.9%	19, 35.2%	13, 28.2%
≥ 6	2, 50%	16, 42.1%	35, 64.8%	33, 71.7%
Mean *	7.8 ± 9.0	5.4 ± 5.3	7.5 ± 5.0	8.5 ± 5.2
Rockall Score (Pre-endoscopy) - Mean †	3.25 ± 2.2	3.0 ± 1.2	3.1 ± 1.1	3.3 ± 1.4
Rockall Score (Post-endoscopy) - Mean‡	5.8 ± 2.2	4.5 ± 2.0	4.7 ± 1.3	4.8 ± 1.8
Bleeding during hospitalization	1, 25%	3, 7.9%	6, 11.1%	9, 19.6%

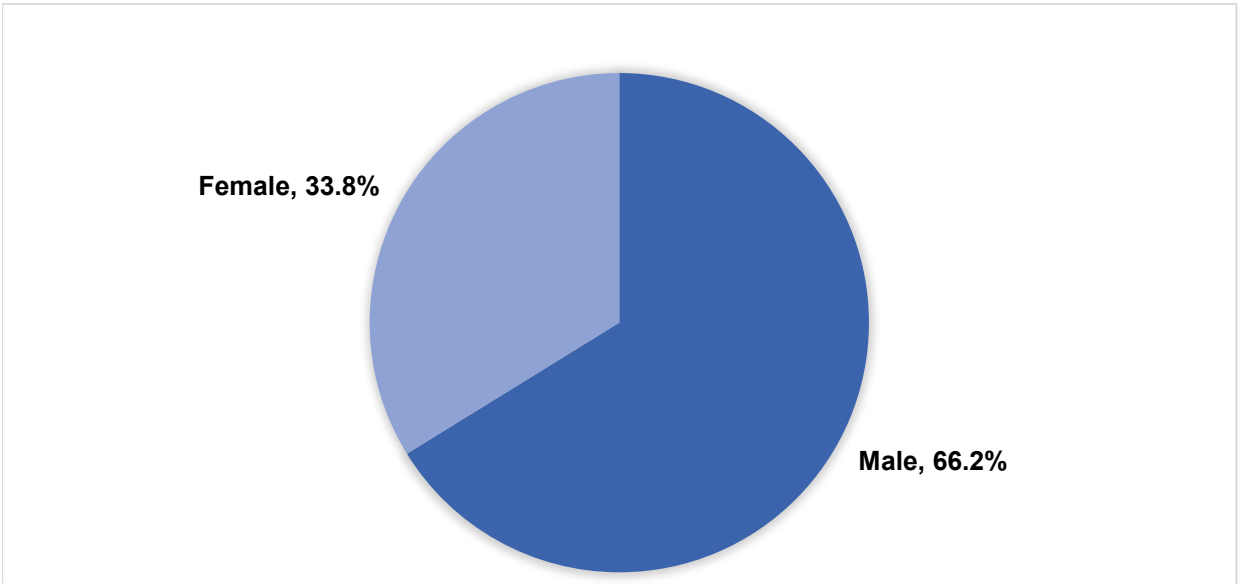
Values are presented as mean ± standard deviation or number, %.

* The Glasgow-Blatchford score ranges from 0 to 23, with higher scores indicating a higher risk of further bleeding or death.

†The Rockall score (Pre-endoscopy) ranges from 0-7, with 7 representing the highest mortality risk

‡The Rockall score (Post-endoscopy) ranges from 0 to 11, with 11 representing the highest rebleeding and mortality risks

Abbreviations: BPUD, Bleeding peptic ulcer disease; CAD, Coronary artery disease; CKD, Chronic kidney disease; CVA, Cerebrovascular accident; GIB, Gastrointestinal bleeding; NSAID, non-steroidal anti-inflammatory drug.



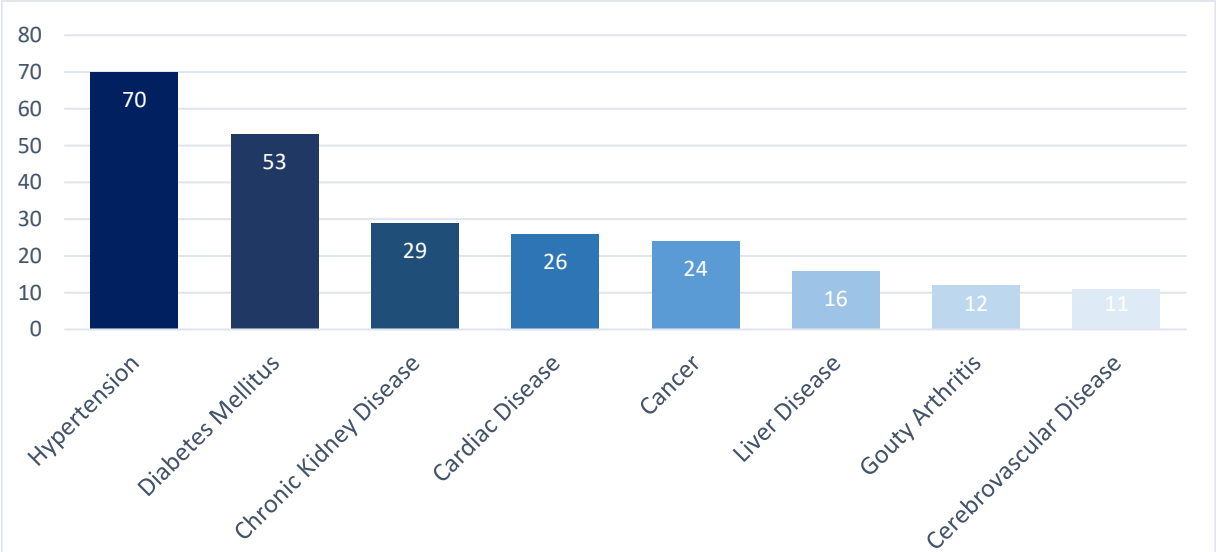


Figure 4. Frequency of comorbidities present among the patients

Among the eight comorbidities listed in *Table I* and *Figure 4*, Hypertension had the highest frequency of 70 (49.3%). This was followed by Type 2 Diabetes Mellitus (T2DM) with 53 (37.3%); and subsequently by chronic kidney disease (29, 20.4%), cardiac diseases such as coronary artery disease, heart failure, cardiac arrhythmias, or structural cardiac diseases (26, 18.3%); cancer (24, 16.9%); liver cirrhosis (16, 11.3%); gouty arthritis (12, 8.5%); and cerebrovascular diseases (11, 7.7%).

Moreover, fifty-seven patients (40.1%) had a history of bleeding PUD. The major risk factor identified was alcoholism which was present in 53 patients (37.3%), followed by antiplatelet use (24, 16.9%), H. pylori infection (20, 14.1%), NSAID use (18, 12.7%), a history of

previous GIB (12, 8.5%), anticoagulant use (10, 7.0%), and liver disease (10, 7.0%).

The most common presenting symptom was melena (47, 33.1%), followed by epigastric pain (33, 23.2%), hematemesis (27, 19.0%), hematochezia (18, 12.7%), body malaise/easy fatigability (8, 5.6%), dizziness (8, 5.6%), and syncope (1, 0.7%). At the time of presentation, the mean Hemoglobin (Hb) level was 101.4 ± 33.5 mg/dL. There were 30 (21.1%) patients who had Hb levels below 70 mg/dL. The average systolic blood pressure was 120 ± 23.71 mmHg. There were 18 patients (12.7%) who presented at the emergency room with hypotension (SBP <90 mmHg). The mean heart rate was 88 ± 16.7 bpm with nearly half of all patients (61, 43.0%) were tachycardic (HR > 100 bpm) on presentation.

All 142 patients with UGIB were scored for both GBS and Rockall scores (pre- and post-endoscopy). The mean GBS was 7.2. Majority of the patients (86, 60.5%) had a GBS of ≥ 6 conferring a high risk for the need for interventions such as transfusion, endoscopy, or surgery. In comparing the endoscopy groups, the proportion of patients with GBS ≥ 6 was 2 (50%) in the urgent group, 16 (42.1%) in the early group, 35 (64.8%) in the late group, and 33 (71.7%) in the very late group. Meanwhile, 46 (32.4%) patients had a pre-endoscopy Rockall scoring of 3 (46, 32.4%) and a mean score of 3.2 ± 1.2 which corresponded to an 11% mortality rate. Of those scored, 35 (24.6%) of the patients had a Rockall score of 5, thus conferring a 24.1% rebleeding rate and 10.8% mortality rate.

The mean post-endoscopy Rockall score was 4.7 ± 1.7. As for bleeding during hospitalization, there are 19 patients (13.4%) previously admitted due to non-GIB cases who presented with signs and symptoms of UGIB during the course of admission.

Timing and endoscopy findings

Table II describes the endoscopy findings grouped according to the timing of endoscopy. The mean time from admission or presentation of symptoms to endoscopy was 3.5 ± 1.7 hours in the urgent endoscopy group, 18.6 ± 4.4 hours in the early endoscopy group, 37.9 ± 6.4 hours in the late endoscopy group, and 80.4 ± 32.1 hours in the very late group. Majority of the patients (54, 38%) were classified under the late endoscopy group. Non-variceal causes were the major sources of upper gastrointestinal bleeding. Moreover, the most frequently encountered non-variceal cause was shared between erosive and non-erosive gastropathy, reported by a total of 76 patients or 38 patients (26.85%) each [urgent = one (25%), early = 12 (31.6%), late = 15 (27.8%), very late = 10 (20.8%) and 38 (26.85%) [urgent = 0, early = 12 (31.6%), late = 13 (24.1%), very late = 13 (27.2%)], respectively. These were followed by gastric and duodenal ulcers, each having 29 patients (10.4%), and esophageal ulcers with 3 patients (2.1%). Malignancy and portal hypertension (esophageal and gastric varices) were identified in 12 patients (8.45%) and 11 patients (7.75%), respectively. Sixty-four patients (45%) were positive for *Helicobacter pylori* infection using Rapid Urease Test at time of endoscopy.

Table II. Timing of Endoscopy and Endoscopy Findings

Parameter	Urgent Endoscopy Group (n = 4)	Early Endoscopy Group (n = 38)	Late Endoscopy Group (n = 54)	Very Late Endoscopy Group (n = 46)
Interval from UGIB to endoscopy (mean)	3.5 ± 1.7	18.6 ± 4.4	37.9 ± 6.4	80.4 ± 32.1
Endoscopy findings				
Non-variceal causes				
Erosive Gastropathy	1, 25%	12, 31.6%	15, 27.8%	10, 20.8%
Non-erosive Gastropathy	0	12, 31.6%	13, 24.1%	13, 27.2%
Esophageal ulcer	0	0	1, 1.9%	2, 4.2%
Duodenal ulcer	2, 50%	7, 18.4%	14, 26.0%	6, 12.5%
Variceal causes	**0**	**2, 5.3%**	**6, 11.1%**	**3, 6.5%**

Esophageal varices	0	2	4	3
Gastric varices	0	0	2	0
Malignancy	**0**	**4, 10.5%**	**1, 1.9%**	**7, 15.2%**
Other findings on endoscopy	**2, 50%**	**7, 18.4%**	**5, 9.2%**	**12, 26.1%**
Esophagitis	0	6	2	9
Duodenitis	1	1	2	3
Dieulafoy's Lesion	0	0	1	0
Post-sphincterotomy bleeding	1	0	0	0
H. pylori Infection	**1, 0.70%**	**19, 50%**	**30, 55.5%**	**14, 30.4%**

Values are presented as mean ± standard deviation or number, %.

In the urgent endoscopy group, emergency endoscopy within 3 hours was performed in 1 patient (25%) due to new-onset melena after Endoscopic Retrograde Cholangiopancreatography (ERCP) for choledocholithiasis. Meanwhile, in the late endoscopy group, one patient (1.85%) had Dieulafoy's lesion on endoscopy. Most malignant lesions were recorded in 7 patients (15.2%) from the very late endoscopy group.

Primary and Secondary Outcomes

Table III shows the primary and secondary outcomes of UGIB patients in the study. The all-cause mortality rate within 30 days was 9.1% in total (13/142), 25% (1/4) in the urgent endoscopy group, 2.6% (1/38) in the early endoscopy group, 9.3% (5/54) in the late endoscopy group and 13.0% (6/46) in the elective endoscopy group, respectively However, the results were not statistically significant ($p = 0.791$). In-hospital deaths occurred in these patients. The most common cause of death was hypovolemic shock associated with uncontrolled bleeding in 3 (60%) patients in the late endoscopy group and 3 (50%) patients in the very late endoscopy group. This was followed by septic shock from infectious causes which had a total of 5 (36.4%) deaths [urgent = one (100%), early = one (100%), late = 1 (20%), very late = 2 (33.3%)]. The causes of deaths are listed in *Table S1* (Appendix F).

Table III. Primary and Secondary Endpoints*

Outcome	**Urgent Endoscopy group (n = 4)**	**Early Endoscopy group (n = 38)**	**Late Endoscopy Group (n = 54)**	**Very Late Endoscopy Group (n = 46)**	***p*-value**
Primary endpoint					
Death from any causes within 30 days (number, %)	1, 25%	1, 2.6%	5, 9.3%	6, 13.0%	0.26
Secondary endpoints					
Further bleeding within 30 days (number, %)†	1, 25%	4, 10.5%	8, 14.8%	5, 10.9%	
Sources of further bleeding (number)					
Bleeding non-variceal cause	1	2	6	4	
Bleeding varices	0	2	1	1	

Other	0	0	1	0	
Treatment for bleeding					
Endoscopic treatment administered during initial endoscopy (number, %)	2, 50%	8, 21.1%	10, 18.5%	6, 13.0%	
Endoscopic treatment for bleeding non-variceal (no. of patients/ total no. with non-variceal causes)	2/4	3/32	3/47	4/41	
Endoscopic treatment for varices (no. of patients/ total no. with varices)	0	1/2	5/6	2/3	
Endoscopic treatment for other causes of bleeding (no. of patients/ total no. with other causes)	0	4/7	3/5	0	
Surgical treatment (number, %)	1, 25%	0	1, 1.9%	0	
Angiographic embolization (number, %)	0	0	0	0	
Median duration of hospitalization (range) in days§	5 (3-29)	4 (2-28)	6 (2-37)	9 (3-115)	0.032
ICU admission	1, 25%	5, 13.2%	11, 20.4%	10, 21.7%	0.747
Number of patients requiring red cell transfusion	2, 50%	15, 39.5%	35, 64.8%	32, 69.6%	
Units of red cells received by transfusion within 30 days	4 ± 1.4	2.2 ± 4.3	3.6 ± 3.9	3.8 ± 4.0	0.246

* Plus-minus values are mean ± SD

† Further bleeding was defined as a composite of persistent bleeding or recurrent bleeding. Other source of further bleeding includes mass, polyps, post-sphincterotomy bleed and Dieulafoy's lesion

§ For patients in whom bleeding developed during hospitalization, the duration of the hospital stay was calculated from the day of presentation.

A total of 18 patients (12.7%) had a recurrence of bleeding during hospitalization within 30 days [urgent = one (25%), early = 4 (10.5%), late = 8 (14.8%), very late = 5 (10.9%)]. Persistent bleeding despite endoscopy occurred in 1 patient in the late endoscopy group (the patient had multiple ulcerations ranging from Forrest class I-A, 1-B and III, who underwent 3 repeat endoscopy procedures but was counted only once in the data analysis for further bleeding) and in 2 patients in the very late endoscopy group (one had Gastric ulcer Forrest Grade 1B while the other patient had an initial finding of non-erosive gastropathy which progressed to erosive gastropathy).

Endoscopic treatment was administered during the first endoscopy in 2 (50%) patients in the urgent endoscopy group, 8 (21.1%) patients in the early endoscopy group, 10 patients (18.5%) in the late group, and 6 patients (13.0%) in the very late endoscopy group. The four groups did not differ substantially in the number of patients who underwent surgery. Surgical treatments in the form of distal antrectomy were only done in 1 (25%) patient in the urgent group and 1 (1.9%) patient in the

late endoscopy group with further bleeding. None of the patients underwent angiographic treatment.

The median hospital stay was 5 days in the urgent group, 4 days in the early group, 6 days in the late group, and 9 days in the very late group. There is a significant association on the duration of hospitalization with the early and late endoscopy groups (p = 0.032). Patients who underwent endoscopy at > 6 – 24 or > 24 – 48 hours from presentation were most likely to stay in the hospital for only one week.

For the number of patients who were admitted to the intensive care unit, the late and very-late endoscopy groups had the highest frequency of 11 and 10, respectively, however this was not statistically significant when compared among the four groups. The percentage of patients who requiring blood transfusion [urgent = 2 (50%), early = 15 (39.5%), late = 35 (64.8%), very late = 32 (69.6%)], and the mean number of units of packed red cells received by transfusion (urgent = 4, early = 2.2, late = 3.6, very late = 3.8) were compared and this was likewise noted to be non-statistically significant.

Discussion

The study compared the clinical outcomes of 142 patients with acute upper gastrointestinal bleeding by the timing of endoscopy. The findings demonstrate that the mortality rate, further bleeding rate, average units of blood transfusion, and admission to the intensive care unit within 30 days did not differ statistically between patients who underwent urgent, early, late and very late endoscopy. On the contrary, significant association was noted on the duration of hospitalization between the early and late endoscopy group.

In terms of demographic characterization, the mean age of patients was 62 ± 14.4 years old, more commonly males (66.2%). The study population is close to the mean age and percentage of male patients described in a study by Alexandrino et al, at 67 ±14.17 years old and 75.5%, respectively.[18] Likewise, the percentage of male patients was also higher at 64% in another study by Kim et al.[19]

Moreover, the most frequent comorbidities were hypertension (49.3%), T2DM (37.3%), and chronic kidney disease (20.4%). Indeed, hypertension, T2DM, and chronic kidney disease are among the most common co-existing diseases in patients with UGIB in other studies.[19,20] Other co-existing diseases listed were cerebrovascular accident, liver cirrhosis, heart failure and malignancy.

The majority of the patients (33.1%) complained of melena. Hematemesis and melena are the most common presenting symptoms in the emergency department in both non-elderly and elderly groups.[21] In a similar study by Sourabh et al, hematemesis and melena had a prevalence of 41.7% and 59.64%, respectively.[22]

Severe anemia with Hb level below 70 mg/dl was only observed in 21.1% of the patients in this study, while in a study conducted by Rajan et al, over half (>50%) of their patients had severe anemia with Hb level below 80 mg/dL.[23]

The most prevalent risk factor identified in the study was alcoholism (53, 37.3%), followed by antiplatelet use (24, 16.9%), H. pylori infection (20, 14.1%), NSAID use (18, 12.7%), a history of previous GIB (12, 8.5%), anticoagulant use (10, 7.0%), and liver disease (10, 7.0%). NSAIDs and aspirin are commonly prescribed in elderly, with a prevalence of 24.7%.[24,25] Up to 70% of patients with long-term NSAID use present with endoscopic abnormalities such as mucosal erosions, ulcerations, and subepithelial hemorrhage.[7] All doses of aspirin are associated with a dose-related increase in the risk of GIB.[26,27] Anticoagulants can also potentiate bleeding from a preexisting gastrointestinal injury or induce bleeding by compromising GI mucosal integrity.[28,29,30,31] In addition, both NSAID use and H. pylori infection are independent risk factors for UGIB but, when present, have synergistic and additive effects for developing PUD.[25]

The Glasgow-Blatchford scoring (GBS) system and Rockall score (Appendix E) are validated scoring systems that predict the need for clinical intervention and mortality.[32] A GBS score of 0 identifies low-risk patients who can be monitored on an outpatient basis, while scores of ≥ 6 are associated with a >50% risk of needing after any intervention.[12,33] Meanwhile, the full Rockall score yields a subject's risk score on a scale of 0 to 11, with 11 representing the highest risk.[12] A pre-endoscopy Rockall score, which ranges from 0-7, may be useful for initial patient assessment.[34] In this study, the majority of the patients had a GBS of ≥ 6 (86, 60.5%) which translates to >50% of patients with the risk of needing any intervention and death. However, previous literatures achieved variable cutoff points for GBS. The study by Rajan used a lower threshold for low and high-risk patients and 71 (86.6%) had GBS of ≥3, thus characterizing these patients as high risk for any adverse events.[23] Similarly, the Rockall score among patients in this study was comparable to the study by Rajan where most (51.2%) had moderate risk clinical Rockall score of 3-4 and >4.[23]

The majority of the endoscopic diagnoses in the study were non-variceal lesions, particularly gastropathy, and peptic ulcers (gastric and duodenal ulcers). This was followed by malignancy. Meanwhile, the study of Bhattarai showed that PUD was also the most common cause of UGIB, accounting for 236 (36.7%) patients.[36] On the contrary, previous international studies reported esophageal varices as the most common cause of UGIB.[35] While multiple studies variably report peptic ulcers or esophageal varices as the most common cause of UGIB, the characteristics of their enrolled patients, or prevalence of both diseases and lifestyle practices may differ between localities. One way to address this is to lengthen the study period to include more subjects and increase statistical power of the study.

The mortality rate, further bleeding rate, and need for endoscopic intervention observed in the urgent

endoscopy group were higher compared to the early, late and very late endoscopy groups. Similarly, a retrospective study described that patients who underwent urgent endoscopy (less than 6 hours) had the worst outcomes and were associated with higher 30-day all-cause in-hospital mortality, increased ICU admission, and repeat therapeutic endoscopy rates.[16,23] Factors that may contribute to the high observed mortality rate include: higher disease severity, disposition status and gaps in management of these patients.[23] However one must take into account that there were only four patients included in this group. A substantially larger sample would have been required to rule out smaller benefits or harm.

Endoscopic interventions, like epinephrine, clips and rubber band ligation for varices, were commonly used to stop the bleeding in the study. A study showed that fewer endoscopic interventions were performed in patients having upper endoscopy >24 hours.[14] This is contrary to our study which revealed that patients who underwent upper endoscopy in >48 hours received fewer numbers of interventions. Surgery was performed in only two patients, and when performed, the intervention was not significantly related to the timing of upper endoscopy.

As for the duration of hospitalization, there is significant association (*p* value = 0.032) with the early and late endoscopy group. Patients who had endoscopy at a later time (> 6 – 24 or > 24 – 48 hours from presentation) were more likely to stay in the hospital for a week. The researchers also observed more deaths and longer duration of hospitalization in the very late endoscopy group. This suggests the possibility that patients received treatment for coexisting medical illnesses and stabilization of hemodynamic status prior to endoscopy. Patients in the very late endoscopy group were first resuscitated with fluids, started on intravenous PPI infusion and given blood transfusion which is expected when treating high risk cases. Acid suppression also helped control active bleeding, eventually stabilizing the patient until endoscopy was scheduled.[16,17] On the contrary, the delayed time before endoscopy may also contribute to difficulty achieving hemostasis without endoscopic therapy.[17] The patient will continue to have ongoing bleeding and subsequent deterioration which reflected a numerically higher mortality rate in the very late endoscopy group.

More than half of the patients from the late (35, 64.8%) and very late group (32, 69.6%) received blood transfusion but was likewise noted to be non-statistically significant. It conforms with the study of Saleem et al, that neither the number of units for blood transfusion, including the need for surgery and mortality, were not influenced by the timing of endoscopy.[14] In contrast to the study of Kim et al, age and RBC transfusion were associated with mortality and poor clinical outcomes in patients with UGIB.[19] Age remains an important and independent risk factor for mortality which is attributable to a tendency to having multiple comorbidities and susceptibility to physiological changes.[19]

Therefore, the results of this study are in accordance with previous data that did not reveal differences in mortality rates and outcomes with different timings of endoscopy.[14,19] Early endoscopy within 24 hours continues to have the lowest mortality rate, better outcomes, and shorter duration of hospital stay among patients with acute upper gastrointestinal bleeding.[10,14,16,19]

There are limitations in this study. First, some patients were excluded due to lack of required data given its retrospective nature. Patient randomization and a prospective research design address these unmeasured biases however it would be difficult to apply in hemodynamically unstable patients. Second, there were only two endoscopy timeframes identified. Another timeframe involving the time from the onset of symptoms prior to admission to endoscopy (symptoms-to-endoscopy) may be included in future studies. Lastly, although there were no statistical differences between the different endoscopy timings, the proportion of patients in this cohort study were small. The authors therefore recommend extending the study period and including patients from multiple centers to increase the study population and further strengthen statistical data. Meta-analysis studies could also be done to achieve this. Likewise, the number of cases for other causes of upper gastrointestinal bleeding like varices, were limited. The findings may not be applicable in localities with a high prevalence of esophageal or gastric varices. Nonetheless, despite the limited sample size, the data and results measured can provide useful information to apply in clinical practice. The findings in this study are congruent with other studies that emphasize hemodynamic stabilization with optimal medical treatment before performing endoscopy in an acute setting.

Conclusion

In conclusion, patients with acute upper gastrointestinal bleeding who underwent urgent (<6 hours) endoscopy had no difference in 30-day all-cause in-hospital mortality, further bleeding, admission to ICU, or the number of units of blood transfused when compared to the early (>6 to 24 hours), late (>24 to 48 hours) and very late (>48 hours) timing. The duration of hospitalization was the only parameter significantly correlated with the timing of endoscopy, with patients in both the early and late endoscopy groups typically having hospital stays of only one week. Hence, performing elective endoscopy within 24 hours or until the patient is stabilized remains safe in most acute UGIB patients.

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