

# Effects of Timing of Endoscopy on Clinical Outcomes of Cirrhotic Patients with Acute Variceal Bleeding in a Tertiary Hospital

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## ABSTRACT

**Background and Objective.** Evidence regarding the impact of performing endoscopy within 12 hours of variceal bleeding (VB) on outcomes is inconclusive, and there is a lack of local data on this topic. This study aimed to determine if the timing of endoscopy is associated with clinical outcomes.

**Methods.** This was a single-center retrospective cohort study which included adult cirrhotic patients admitted for VB from January 2016 to September 2022. The primary outcomes were in-hospital and 6-week mortality. Secondary outcomes included 5-day rebleeding, length of hospital stay (LOS), and blood transfusion requirements (BTR). The relationships between timing of endoscopy and outcomes were evaluated using regression analysis.

**Results.** In 140 patients, 5.7% underwent urgent endoscopy ( $\leq 12$  hours). The overall median door-to-endoscopy time (DET) was 39.4 hours (IQR 20.0-73.4). The overall in-hospital mortality, 6-week mortality, and 5-day rebleeding rates were 12.9%, 11.4%, and 8.6%, respectively, without significant variability at different DET ( $p > 0.05$ ). Prolonged LOS was evident when endoscopy was delayed to  $> 12$  hours from admission (3.5 [IQR 2.25-5.75] vs 6 days [IQR 4-9.75],  $p = 0.021$ ), while BTR was greater starting at endoscopies performed at  $> 24$  hours from admission (1 [0-2] vs 2 units [1-3],  $p = 0.000$ ). Delayed endoscopy was significantly correlated with LOS (Beta 0.316, SE 0.011,  $p = 0.000$ ) and BTR (Beta 0.214, SE 0.469,  $p = 0.003$ ), but not with mortality and early rebleeding.

**Conclusion.** Timing of endoscopy may be independent of mortality and early rebleeding. Timely endoscopy may shorten hospitalization and decrease need for blood transfusion. Other factors affecting clinical outcomes may be at play.

**Keywords:** cirrhosis, variceal bleeding, endoscopy



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## INTRODUCTION

Variceal bleeding (VB) is a medical emergency which constitutes the second most common decompensating event after ascites in patients with cirrhosis.<sup>1</sup> It is associated with high 5-year mortality rate of 20% when presenting as an isolated complication, increasing to 80% when presenting in association with other complications.<sup>2</sup> The developments in endoscopic therapy and its widespread use contributed to the decline in bleeding-related mortality in the past decades.<sup>3</sup>

Guidelines recommend performing endoscopy for VB within 12 hours of presentation.<sup>4-6</sup> It appears logical that urgent endoscopy is beneficial to achieve rapid hemostasis, prevent complications, and shorten hospital stay, but this recommendation is only based on experts' opinion. There is also conflicting evidence to prove its favorable effects on clinical outcomes.<sup>7-11</sup> Locally, outcomes of patients with

cirrhosis admitted for VB and how timing of endoscopy affects outcomes are unknown.

On March 11, 2020, the World Health Organization (WHO) declared the novel coronavirus (COVID-19) outbreak a global pandemic.<sup>12</sup> The Philippine General Hospital (PGH) was designated as one of the country's COVID-19 referral centers, diverting services primarily for COVID-19 cases. Endoscopic procedures were restricted to emergency cases such as gastrointestinal bleeding, foreign body ingestion, and acute cholangitis. Procedures were grouped according to COVID-19 status and manpower was also reduced to a skeletal scheduling system, further restricting the number of cases the endoscopy unit could perform at a given time.<sup>13</sup> These changes in workflow led to a 68% decline in the volume of procedures performed in the hospital's endoscopy unit in 2020. With the improvement in COVID-19 cases and relaxation of community quarantine restrictions, regular endoscopy services resumed which caused a gradual rise in the volume of endoscopic procedures. Compared to 2020, endoscopic procedures increased to 65% and 325% in 2021 and 2022, respectively. This was also parallel with the congestion of the emergency department (ED), with reported 200% overcapacity affecting the delivery of services in the ED.<sup>14</sup> Overcrowding of the ED is a perennial problem of the institution even before the COVID-19 pandemic.<sup>15</sup>

The study primarily aimed to determine the relationship between timing of endoscopy and clinical outcomes. The secondary objectives were as follows: (1) to describe and compare the clinical profile of patients who received urgent and non-urgent endoscopy; (2) to compare the average door-to-endoscopy time (DET) between urgent and non-urgent endoscopy groups, and during and outside the COVID-19 pandemic, (3) to compare the outcomes based on different time intervals to endoscopy; and (4) to analyze other clinical factors predictive of clinical outcomes.

## MATERIALS AND METHODS

### Setting, Design and Patients

This was a single-center, retrospective cohort study which included cirrhotic patients, age 19 years or over, admitted for VB from January 1, 2016 to September 30, 2022 at the ED of PGH, a high-volume, tertiary academic referral center. Only those who underwent endoscopy were eligible for inclusion in the study. Cirrhotic patients who developed in-hospital VB, with non-variceal cause of upper gastrointestinal bleeding (UGIB), and were discharged against advice, transferred to other hospitals or went home per request were excluded from the study. Cases where documentation of time of endoscopy was lacking and admissions were not under Internal Medicine (IM) or its subspecialties also excluded from the analysis. If a patient was admitted more than once during the study period, the earliest admission was selected for inclusion in the analysis. The minimum sample size, computed by modified Cochran formula, was 139 patients.

### Data Collection

Medical records were identified using codes from International Classification of Diseases tenth revision (ICD-10) for the following diagnoses: UGIB, esophageal varices and gastric varices. All records found eligible were included in the study (Figure 1). Three independent reviewers examined the medical records, including demographic, laboratory, clinical and endoscopic data. The Child-Pugh (CP) and model for end-stage liver disease-sodium (MELD-Na) scores were calculated from the data from the first 24 hours of admission. All subsequent in- and outpatient medical records following index admissions of included patients were subsequently reviewed to determine survival status and interval rebleeding events.

### Outcome Assessment

The primary outcomes were in-hospital mortality and, in accordance with Baveno VII recommendations, 6-week mortality.<sup>4</sup> Secondary outcomes included 5-day rebleeding, length of hospital stay (LOS) in days, and blood transfusion requirements (BTR) (number of red cell units transfused).

### Definition

DET was defined as the time interval (in hours) from ED admission to initial endoscopic examination. Endoscopy performed within 12 hours from admission was classified as urgent; endoscopy conducted beyond 12 hours from admission was defined as non-urgent. Five-day rebleeding was defined as either by absence of control of bleeding or by rebleeding within the first 5 days from index endoscopy.<sup>4</sup> The COVID-19 pandemic period would span from March 11, 2020, when COVID-19 was declared by the WHO as a global pandemic, to March 1, 2022, when Metro Manila and its neighboring regions were placed under the lowest level of community quarantine.<sup>12,16</sup>

### Statistical Analysis

SPSS was used for data analysis. Categorical data were summarized using frequencies and percentages. All normally distributed discrete or continuous data were presented as means and standard deviations (SD), while non-normally distributed data were summarized using medians and interquartile ranges (IQR). Statistical differences between groups were investigated using student's t-test for normally distributed numerical data, Mann-Whitney test for non-normally distributed numerical data, and chi-square test for categorical variables. To determine the association of timing of endoscopy and clinical factors with outcomes, regression analyses were performed. Cases with missing values on any variables were omitted from regression analyses. All p values <0.05 were considered significant.

### Ethical Considerations

The study was reviewed and approved by the University of the Philippines Manila Research Ethics Board.

## RESULTS

### Patient Characteristics

There were 2,203 records identified using the index terms above, 997 of which were duplicates and removed. Two records were missing and not reviewed. Of the 1,204 charts screened, 1,040 were excluded: 686 without cirrhosis, 86 without endoscopy, 58 non-VB cases, 162 not admitted at the ED, 14 without UGIB, nine went home against medical advice, 22 discharged per request, one transferred to another hospital and two pediatric cases. After an in-depth review of 164 charts, 24 cases were further excluded: one without time of index endoscopy and 23 re-admissions. A total 140 cases were included in the final analysis (Figure 1). Data on outcomes of interest were complete, except for 6-week mortality where only 50% ( $n = 70$ ) of cases have known survival status at 6 weeks from index admission.

The baseline characteristics of these patients are shown in Table 1. Non-urgent endoscopy was performed in 94.3% of patients ( $n = 132$ ), while only 5.7% ( $n = 8$ ) of endoscopies were conducted within the recommended 12-hour period. No urgent endoscopies were performed during the COVID-19 pandemic.

Majority of the patients were male ( $n = 89$  [63.6%]), and the mean age of the patients was 51.2 years ( $\pm 15.7$ ). Alcoholic liver disease (ALD) ( $n = 57$  [40.7%]) was the leading cause of cirrhosis, followed by miscellaneous etiologies ( $n = 33$  [23.6%]) and chronic hepatitis B infection ( $n = 32$  [22.9%]). Majority of patients admitted for VB had severe underlying liver disease. Most patients were classified as CP B ( $n = 55$  [48.2%]), and the overall MELD-Na score was elevated to an average of 19.4 ( $\pm 7.8$ ). The groups were similar in these aforementioned characteristics. Among those who underwent urgent endoscopy, a higher percentage (87.5%) had experienced previous variceal bleeding events and were already prescribed beta blockers (75%). On admission, ascites ( $n = 73$  [52.1%]) was the most common concurrent decompensating event identified, followed by hepatic encephalopathy (HE) ( $n = 32$  [22.9%]). Laboratory parameters, including baseline hemoglobin levels, creatinine, platelet counts, and INR values, showed no significant differences between the two groups. Detailed baseline clinical and demographic characteristics can be found in Table 1.

Vasoactive therapy and antibiotic prophylaxis, cornerstones in the management of VB in cirrhosis, were not universally provided. Only 86.4% ( $n = 121$ ) and 85.7% ( $n = 120$ )

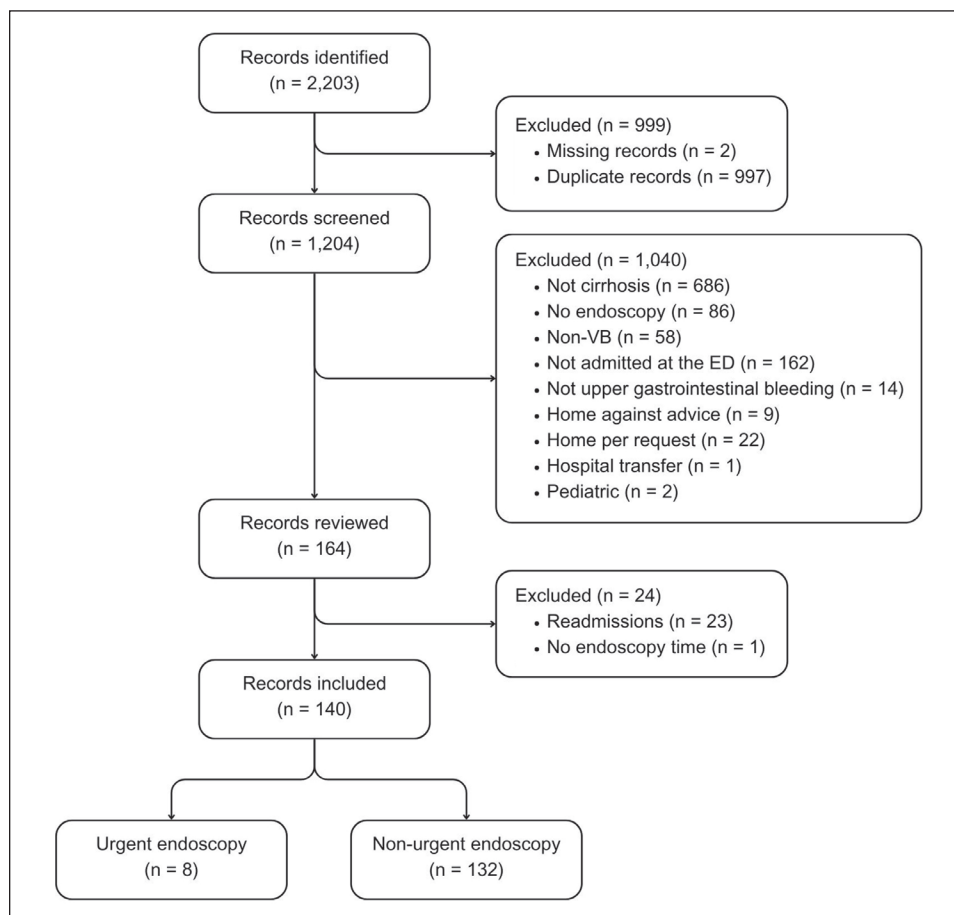


Figure 1. Flowchart of cases included in the study.

of patients received these interventions, respectively. There were 32 patients (22.9%) who needed inotropic support and 16 patients (11.4%) were admitted in the ICU. All of these patients underwent non-urgent endoscopy. Nevertheless, the groups were still comparable in these aspects.

Propensity probabilities derived from logistic regression, utilizing clinical and demographic characteristics, were employed for the purpose of performing inverse probability weighting. However, owing to the limited number of cases in the group that underwent urgent endoscopy, there was insufficient variability to establish a statistically significant predictive model.

### Time to Endoscopy

The overall median DET was 39.4 hours (IQR 20.0-73.4) after admission. Urgent endoscopic procedures were carried out within a median time of 10.1 hours (IQR 8.6-10.9), whereas non-urgent endoscopies had a significantly delayed median of 40.8 hours (IQR 22.1-75.8) ( $p = 0.000$ ). The median DETs exhibited similar values during and outside the COVID-19 pandemic period (29.8 hours [IQR 19.5-67.2] vs 39.7 hours [IQR 21.5-77.9],  $p = 0.249$ ).

**Table 1.** Baseline Characteristics of Patients

| Characteristics                                                                  | Unweighted              |                                 |                                        | <i>p</i> |
|----------------------------------------------------------------------------------|-------------------------|---------------------------------|----------------------------------------|----------|
|                                                                                  | All patients<br>N = 140 | Urgent endoscopy<br>N = 8 (5.7) | Non-urgent endoscopy<br>N = 132 (94.3) |          |
| <b>Sex</b>                                                                       |                         |                                 |                                        | 0.148    |
| Male                                                                             | 89 (63.6)               | 7 (87.5)                        | 82 (62.1)                              |          |
| Female                                                                           | 51 (36.4)               | 1 (12.5)                        | 50 (37.9)                              |          |
| <b>Age, years (mean <math>\pm</math> SD)</b>                                     | 51.2 (15.7)             | 51.8 (15.9)                     | 51.1 (15.7)                            | 0.968    |
| <b>Cause of cirrhosis</b>                                                        |                         |                                 |                                        | 0.768*** |
| Hepatitis B                                                                      | 32 (22.9)               | 2 (25.0)                        | 30 (22.7)                              |          |
| Hepatitis C                                                                      | 2 (1.4)                 | 0 (0.0)                         | 2 (1.5)                                |          |
| Alcoholic liver disease                                                          | 57 (40.7)               | 4 (50.0)                        | 53 (40.2)                              |          |
| Non-alcoholic fatty liver disease                                                | 16 (11.4)               | 1 (12.5)                        | 15 (11.4)                              |          |
| Others                                                                           | 33 (23.6)               | 1 (12.5)                        | 32 (24.2)                              |          |
| <b>Child-Pugh</b>                                                                |                         |                                 |                                        | 0.934    |
| A                                                                                | 30 (26.3)               | 2 (25.0)                        | 28 (26.4)                              |          |
| B                                                                                | 55 (48.2)               | 5 (62.5)                        | 50 (47.2)                              |          |
| C                                                                                | 29 (25.4)               | 1 (12.5)                        | 28 (26.4)                              |          |
| <b>Model for end-stage liver disease-sodium score (mean <math>\pm</math> SD)</b> | 19.4 (7.8)              | 19.7 (7.9)                      | 17.0 (5.3)                             | 0.342    |
| <b>History of variceal bleeding</b>                                              | 68 (48.6)               | 7 (87.5)                        | 61 (46.2)                              | 0.023    |
| <b>Use of beta blockers</b>                                                      | 48 (34.3)               | 6 (75.0)                        | 42 (31.8)                              | 0.012    |
| <b>Other decompensating events</b>                                               |                         |                                 |                                        |          |
| Hepatocellular carcinoma                                                         | 24 (17.1)               | 0 (0.0)                         | 24 (18.2)                              | 0.185*** |
| Ascites                                                                          | 73 (52.1)               | 2 (25.0)                        | 71 (53.8)                              | 0.113*** |
| Hepatic encephalopathy                                                           | 32 (22.9)               | 1 (12.5)                        | 31 (23.5)                              | 0.472*** |
| <b>Use of inotropes</b>                                                          | 32 (22.9)               | 0 (0.0)                         | 32 (24.2)                              | 0.113*** |
| <b>Use of vasoactive drug</b>                                                    | 121 (86.4)              | 7 (87.5)                        | 114 (86.4)                             | 0.927    |
| <b>Use of antibiotic/s</b>                                                       | 120 (85.7)              | 7 (87.5)                        | 113 (85.6)                             | 0.882    |
| <b>Intensive care unit admission</b>                                             | 16 (11.4)               | 0 (0.0)                         | 16 (12.1)                              | 0.295    |
| <b>Period of admission</b>                                                       |                         |                                 |                                        | 0.038*** |
| Pandemic                                                                         | 17 (33.6)               | 0 (0.0)                         | 47 (35.6)                              |          |
| Non-pandemic                                                                     | 93 (66.4)               | 8 (100.0)                       | 85 (64.4)                              |          |
| <b>Hemoglobin, g/L (mean <math>\pm</math> SD)</b>                                | 76.6 (28.0)             | 86.8 (21.8)                     | 76.0 (28.3)                            | 0.402    |
| <b>Platelet count, <math>10^9</math>/L (median, IQR)</b>                         | 156 (107-249)           | 128 (69-249)                    | 158 (108-249)                          | 0.418    |
| <b>Creatinine, <math>\mu</math>mol/L (median, IQR)</b>                           | 78 (60-119)             | 91 (64.8-112.0)                 | 77 (59-119)                            | 0.600    |
| <b>Albumin, g/L (mean <math>\pm</math> SD)</b>                                   | 29.9 (6.6)              | 33.4 (3.7)                      | 29.7 (6.6)                             | 0.051    |
| <b>Total bilirubin, <math>\mu</math>mol/L (median, IQR)</b>                      | 33.8 (17.0-110.8)       | 35.4 (20.6-55.1)                | 33.8 (16.8-116.9)                      | 0.971    |
| <b>International normalized ratio (median, IQR)</b>                              | 1.5 (1.3-1.8)           | 1.5 (1.3-1.7)                   | 1.5 (1.3-1.8)                          | 0.507    |

Data are expressed as frequency (percentage) unless otherwise specified.

\*\*\* Chi square was performed with minimum expected count of less than 5 in more than 20%. The decision to reject the null was based on cell chi square and that significance was due to cell size rather than true statistical significance.

**Table 2.** Clinical Outcomes of Patients according to Different Time Intervals to Endoscopy

| Clinical Outcomes                                                   | All patients | Urgent endoscopy (≤12 hours), n=8 | Non-urgent endoscopy (>12 hours), n=132 | p        | ≤24 hours n=44 | >24 hours n=96 | p     | ≤48 hours n=88 | >48 hours N=52 | p     |
|---------------------------------------------------------------------|--------------|-----------------------------------|-----------------------------------------|----------|----------------|----------------|-------|----------------|----------------|-------|
| <b>In-hospital mortality</b><br>N = 140                             | 18 (12.9%)   | 0 (0.0%)                          | 18 (13.6%)                              | 0.263*** | 9 (20.5%)      | 9 (9.4%)       | 0.069 | 12 (13.6%)     | 6 (11.5%)      | 0.720 |
| <b>6-week mortality</b><br>N = 70                                   | 8 (11.4%)    | 0 (0.0%)                          | 8 (11.8%)                               | 0.606*** | 4 (22.2%)      | 4 (7.7%)       | 0.095 | 6 (13.0%)      | 2 (8.3%)       | 0.557 |
| <b>5-day rebleeding</b><br>N = 140                                  | 12 (8.6%)    | 1 (12.5%)                         | 11 (8.3%)                               | 0.683*** | 6 (13.6%)      | 6 (6.3%)       | 0.147 | 9 (10.2%)      | 3 (5.8%)       | 0.363 |
| <b>Length of stay, days</b><br>(median [IQR])                       | 6 (4-6)      | 3.5 (2.25-5.75)                   | 6 (4-9.75)                              | 0.021    | 4 (3-6)        | 7 (5-10)       | 0.000 | 5 (3-7)        | 9 (5-12.75)    | 0.000 |
| <b>Blood transfusion requirement, red cell units (median [IQR])</b> | 2 (0-3)      | 0.0 (0.0-1.38)                    | 2 (1-3)                                 | 0.042    | 1 (0-2)        | 2 (1-3)        | 0.000 | 1 (0-2)        | 2 (1-3)        | 0.001 |

\*\*\* Chi square was performed with minimum expected count of less than 5 in more than 20%. The decision to reject the null was based on cell chi square and that significance was due to cell size rather than true statistical significance.

### Clinical Outcomes

The overall in-hospital mortality and 6-week mortality rates were 12.9% (n = 18) and 11.4% (n = 8), respectively. All mortalities were from the non-urgent endoscopy group. The overall 5-day rebleeding rate was 8.6% (n = 12), where 91.7% (n = 11) of cases were from the non-urgent endoscopy group. These outcomes did not exhibit significant variations based on the timing of endoscopy. However, the data displayed a notable bias against urgent endoscopic procedures (Table 2).

A detailed binary logistic regression analysis concerning in-hospital mortality and potential influencing factors can be found in Table 3. The regression model that was developed proved to be statistically significant with  $p < 0.0005$  and could account for 70.4% of the variability in in-hospital mortality. It is important to emphasize that the urgency of endoscopy did not contribute to this model due to a lack of variability. Instead, it was the presence of HE (OR 537.50, 95% CI 4.97-58,164.46,  $p = 0.009$ ) and CP C class (OR 27,523.98, 95% CI 5.34-1.4x10<sup>8</sup>,  $p = 0.019$ ) which were significantly associated with increased risk of in-hospital mortality.

The analysis of factors influencing 6-week mortality and 5-day rebleeding, on the other hand, did not yield statistically significant models.

Patients who underwent non-urgent endoscopy had significantly longer median LOS (3.5 days [IQR 2.25-5.75] vs 6 days [4-9.75],  $p = 0.021$ ). Prolonged hospitalization was likewise evident in endoscopies delayed to >24 and >48 hours from admission. BTR was comparable between urgent and non-urgent endoscopy groups (0 red cell units [IQR 0-1.38] vs 2 red cell units [IQR 1-3],  $p = 0.042$ ), but significant variability in BTR was seen in endoscopies performed at >24 and >48 hours from admission (Table 2).

Multiple regression analysis was performed to anticipate the duration of hospitalization, taking into account DET, initial hemoglobin levels, ICU stay, and the presence of HE as predictors. None of the other variables under consideration significantly contributed to the predictive model. Predictive

performance was evaluated by examining R<sup>2</sup> change and F change in a stepwise manner and collinearity statistics was done to identify any multicollinearity. Additionally, standardized prediction plots were employed to screen for linear associations and Q-Q plots for normality. The 4 variables included in the analysis exhibited significant predictability for LOS, as indicated by  $F(4, 134) = 13.581$ ,  $R^2 0.288$ , and  $p < 0.0005$ . All 4 variables made substantial contributions to the predictive model, with  $p < 0.05$  (Table 4).

A similar analysis was executed to forecast the quantity of transfused packed red blood cells. We assessed the impact of factors using a stepwise evaluation based on significant R<sup>2</sup> and F changes. The resulting model, comprising door-to-endoscopy time, initial hemoglobin levels, and ICU stay, was found to be predictive of BTR (Table 4).

### DISCUSSION

This is the first study to provide insights on the outcomes of cirrhotic patients with VB, practice of endoscopy, and association of timing of endoscopy on outcomes in the local setting.

This study notably found that almost 95% of endoscopies were performed outside the recommended 12-hour period. ICU utilization was low and, interestingly, all patients transferred to the ICU and requiring inotropic support underwent non-urgent endoscopy. Delayed endoscopy was also common in the United Kingdom (UK) in a multicenter audit in 2007.<sup>17</sup> A decade later, majority of centers in the UK still failed to meet the national standards for time to endoscopy.<sup>18</sup> In contrast, there was a high level of adherence to urgent endoscopy in two North American centers.<sup>19</sup> Several centers in Asia also reported averages of time to endoscopy compliant with the recommendation.<sup>8,10,11</sup>

Timing of endoscopy could be influenced by variability in preferences of gastroenterologists, akin to real-practices of gastroenterologists in other countries.<sup>20,21</sup> In a prospective

**Table 3.** Clinical Factors Predictive of Clinical Outcomes by Binary Logistic Regression

| Characteristics                                       | In-hospital Mortality OR (95% CI)     | p     |
|-------------------------------------------------------|---------------------------------------|-------|
| <b>Cause of cirrhosis</b>                             |                                       |       |
| Hepatitis B                                           | 1.11 (0.03-37.76)                     | 0.952 |
| Hepatitis C                                           | -                                     | -     |
| Alcoholic liver disease                               | 26.87 (0.62-1168.81)                  | 0.087 |
| Non-alcoholic fatty liver disease                     | -                                     | -     |
| Others                                                | Reference                             |       |
| <b>Child-Pugh</b>                                     |                                       |       |
| A                                                     | Reference                             |       |
| B                                                     | 57.78 (0.36-9291.18)                  | 0.118 |
| C                                                     | 27,523.98 (5.34-1.4x10 <sup>8</sup> ) | 0.019 |
| <b>Model for end-stage liver disease-sodium score</b> | 0.91 (0.71-1.18)                      | 0.486 |
| <b>History of variceal bleeding</b>                   | 0.81 (0.07-9.28)                      | 0.867 |
| <b>Other decompensating events</b>                    |                                       |       |
| Hepatocellular carcinoma                              | 0.61 (0.04-10.15)                     | 0.730 |
| Ascites                                               | 3.04 (0.11-84.58)                     | 0.512 |
| Hepatic encephalopathy                                | 537.50 (4.97-58164.46)                | 0.009 |
| <b>Use of inotropes</b>                               | 12.81 (0.75-219.50)                   | 0.078 |
| <b>Failure to use vasoactive drug</b>                 | 0.03 (0.00-1.21)                      | 0.062 |
| <b>Failure to use antibiotic/s</b>                    | 1.000                                 | 1.000 |
| <b>Intensive care unit admission</b>                  | 0.09 (0.00-6.24)                      | 0.268 |
| <b>Creatinine</b>                                     | 1.01 (0.99-1.02)                      | 0.285 |
| <b>Albumin</b>                                        | 1.33 (0.99-1.81)                      | 0.070 |
| <b>Total bilirubin</b>                                | 0.99 (0.98-1.00)                      | 0.097 |
| <b>International normalized ratio</b>                 | 0.16 (0.00-17.90)                     | 0.160 |
| <b>Timing of endoscopy</b>                            |                                       |       |
| ≤12 hours                                             | Reference                             | -     |
| >12 hours                                             | 1.0                                   | 1.000 |
| >24 hours                                             | 0.92 (0.04-23.91)                     | 0.958 |
| >48 hours                                             | 0.01 (0.00-1.34)                      | 0.066 |
| <b>Period of admission</b>                            |                                       |       |
| Non-pandemic                                          | Reference                             |       |
| Pandemic                                              | 0.09 (0.00-1.99)                      | 0.127 |

Omnibus F (23) = Chi<sup>2</sup> 54.417; p < 0.00; R<sup>2</sup> = 0.704

Percentage of Correct Predictions 95.6%

multicenter audit by Siau et al., referrals from the ED and late referrals for endoscopy (≥16 hours) were associated with delayed endoscopy (>24 hours) in UGIB, while patients admitted directly through acute medicine were less likely to have delayed endoscopy.<sup>18</sup> In PGH, patients admitted at the ED for UGIB are first managed by the ED team before they are referred and admitted to IM. Referrals for endoscopy are decided upon and made by the latter. This workflow could incur delays as time to referral for endoscopy is dependent on the efficiency of the frontline services. The lack of on-call gastroenterologists and endoscopy unit personnel, shortage of anesthesiologists, and frequent overcapacity of the ED could have also affected the momentum of care and timeliness

**Table 4.** Clinical Factors Predictive of LOS and BTR by Multiple Regression Analysis

| Outcome                              | Factors                                                 | Beta (SE)      | p     |
|--------------------------------------|---------------------------------------------------------|----------------|-------|
| <b>Length of stay</b>                | Door to endoscopy time                                  | 0.316 (0.011)  | 0.000 |
|                                      | Hemoglobin                                              | -0.187 (0.021) | 0.016 |
|                                      | Intensive care unit admission                           | 0.292 (1.778)  | 0.000 |
|                                      | Hepatic encephalopathy                                  | 0.218 (1.393)  | 0.006 |
|                                      | F (4,134) = 13.581, R <sup>2</sup> = 0.288, p < 0.0005  |                |       |
| <b>Blood transfusion requirement</b> | Door to endoscopy time                                  | 0.214 (0.469)  | 0.003 |
|                                      | Hemoglobin                                              | -0.463 (0.003) | 0.000 |
|                                      | Intensive care unit admission                           | 0.196 (0.461)  | 0.007 |
|                                      | F (3, 135) = 21.154, R <sup>2</sup> = 0.320, p = 0.0005 |                |       |

at which endoscopies were conducted. Timeliness and appropriateness of resuscitation prior to endoscopy could also potentially impel delays in endoscopy.

Time to endoscopy was faster by almost 10 hours during the COVID-19 pandemic, although not significantly different to that outside the pandemic period. While emergency cases were still accommodated during the COVID-19 pandemic, there was reduced availability and strict prioritization of endoscopic procedures in the institution. Before procedures were scheduled, results of COVID-19 tests and/or the availability of highly trained endoscopists (e.g., consultants and senior endoscopists) were typically awaited.<sup>13</sup>

Overall outcomes of cirrhotic patients with VB were found to be poor, as in other studies. Although overall in-hospital mortality rate was higher in this study, 6-week mortality and early rebleeding rates were lower than in other centers in Asia.<sup>7-11</sup>

Time to endoscopy was not found to be significantly associated with mortality (i.e., in-hospital and at 6 weeks) and early rebleeding. There have been several studies evaluating the impact of endoscopy timing on clinical outcomes, but these have conflicting results. Hsu et al. demonstrated that non-urgent endoscopy increased the risk of in-hospital mortality by almost 4-fold. However, non-urgent endoscopy was defined as endoscopy performed >15 hours after admission.<sup>7</sup> In another study by Chen et al., urgent endoscopy was associated with improved 6-week mortality and rebleeding only in patients with a chief complaint of hematemesis. Outcomes were not different between urgent and non-urgent endoscopy groups in patients without hematemesis.<sup>9</sup> On the other hand, Huh et al. found that urgent endoscopy was significantly associated with poorer 6-week composite outcomes (mortality and rebleeding) in patients with MELD score <17.<sup>11</sup> Lastly, Cheung et al. and Yoo et al. also did not show differences in outcomes with different urgency times, although the former limited their analysis to hemodynamically stable VB.<sup>8,10</sup> When these studies were examined in a meta-analysis, significant heterogeneity was observed even after doing sensitivity analyses, suggesting that

there were unaccounted factors which could have affected the outcomes.<sup>22</sup> Instead, this study showed that HE and severity of liver dysfunction (i.e., CP C) were the important predictors of in-hospital mortality. HE and CP C have been demonstrated to substantially increase the risk of mortality in patients with cirrhosis in previous studies.<sup>23-27</sup>

On the other hand, delays in endoscopy were significantly correlated with prolonged hospitalization and increased need for blood transfusion. Whether delayed endoscopy resulted in an increase in BTR or vice versa is unknown. These findings, nonetheless, highlight that timely endoscopy may potentially improve hospital efficiency (e.g., increase room turnover rate and optimize resource utilization).

Other cornerstones of management of VB include the use of vasoactive therapy and antibiotic as prophylaxis for spontaneous bacterial peritonitis (SBP).<sup>4-6</sup> This study found that vasoactive therapy and SBP prophylaxis were inconsistently given pre-endoscopically, but the proportions of patients failing to receive such interventions were lower compared to those seen in a previous report.<sup>17</sup> Lack of clinical suspicion of VB and recurrent shortages of resources could be factors resulting in such deficiencies.

Clinical profile of cirrhotic patients admitted for VB in PGH did not vary through the years. Similar to the findings of Limquiaco et al., most patients were classified as CP B on admission, and ascites was also prevalent in as much as half of the population.<sup>28</sup> ALD and chronic hepatitis B infection remained as some of the leading etiologies of cirrhosis, although a rising number of non-ALD and non-viral hepatitis causes of cirrhosis was observed in the present study. The common causes of cirrhosis and severity of liver dysfunction were comparable to studies in other parts of Asia.<sup>7-11</sup>

The authors acknowledge several limitations of the study. First, owing to the limited cases in the group which underwent urgent endoscopy, there was insufficient variability to establish a statistically significant predictive model to account for the imbalance of confounding factors across groups. Second, the authors could not account for the time elapsed from actual time of arrival of patients at the ED to the time patients were triaged, admitted, and referred to appropriate services. Third, factors and criteria considered for timing of endoscopy, quality of care, and adherence to practice recommendations were not evaluated.

## CONCLUSION

Timing of endoscopy appears to be independent of mortality and early rebleeding. However, timely endoscopy may shorten hospitalization and decrease BTR. Appropriately timed endoscopy remains relevant in the care for cirrhotic patients with VB. Improving outcomes is more complicated than mere timely endoscopy. There are other important factors at play which need further evaluation so these aspects could be addressed and optimized.

## Recommendations

To address knowledge gaps and limitations of the present study, the authors recommend to identify and investigate factors leading to delays in endoscopy, quality of care, and adherence to practice recommendations which can help streamline inpatient and endoscopy services. The authors also highly recommend a prospective study design to eliminate the biases and limitations inherent of a retrospective analysis. In view of the recent developments in the hospital's services (e.g., increased capacity of the endoscopy unit, additional gastroenterology fellows in training, and ED renovation), a prospective analysis will also capture updated data which will more accurately reflect the current status of VB cases and the endoscopy unit's key performance indices.

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## Statement of Authorship

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