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UPPER GASTROINTESTINAL BLEEDING: ASSOCIATED RISK FACTORS AND OUTCOMES IN BRUNEI DARUSSALAM.

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ABSTRACT

Background: Upper gastrointestinal bleeding (UGIB) is a common cause for hospitalizations and remains an important cause of morbidity and mortality. This study reports on our experience with UGIB in a tertiary center. **Material and Methods:** All patients with UGIB (hematemesis, coffee ground vomitus, melena, with significant drop of hemoglobin >2gm/dL or needing blood transfusion) admitted between July 2017 and November 2018 were included. **Results:** There were 151 patients (male 62.3%) with mean age 62.1 ± 15.2 years included in the study. Majority had comorbid conditions and one in five were using medications associated with UGIB. Over 88.1% required transfusions and 88.7% had early endoscopy (<24 hours) from time of admissions/referrals. Most common etiology was ulcers and 45% required endoscopic interventions. The median Rockall score was 4.6 ± 2.1. Rebleeding occurred in 9.9% and mortality in 20.9% (inpatient [12.6%] and post-discharge [7.3%]). Female patients had less *H. pylori* infection (p=0.001), but higher post-discharge mortality (p=0.030) and older group (>60 years) had lower *H. pylori* infection (p=0.002) and higher Rockall score (p=0.016). Higher Rockall score (>2) was associated with higher rates of rebleeding (p=0.027) and mortality (p=0.035). The Rockall score positively correlated with length of hospitalization. There was no correlation between treatment modality and rebleeding rate, and there was no correlation between time of endoscopy and treatment modality with morality. **Conclusion:** Among our patients with UGIB, rebleeding rate and mortality rates remains high. High post-discharge mortality rates are due to significant comorbid conditions. Higher Rockall score was associated with higher rates of rebleeding and mortality and correlated with length of hospitalization.

Keywords: Brunei Darussalam, Endoscopy, Gastrointestinal haemorrhage, Upper, Helicobacter pylori, Mortality.

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ABSTRACT

Background: Upper gastrointestinal bleeding (UGIB) is a common cause for hospitalizations and remains an important cause of morbidity and mortality. This study reports on our experience with UGIB in a tertiary center. **Material and Methods:** All patients with UGIB (hematemesis, coffee ground vomitus, melena, with significant drop of hemoglobin >2gm/dL or needing blood transfusion) admitted between July 2017 and November 2018 were included. **Results:** There were 151 patients (male 62.3%) with mean age 62.1 ± 15.2 years included in the study. Majority had comorbid conditions and one in five were using medications associated with UGIB. Over 88.1% required transfusions and 88.7% had early endoscopy (<24 hours) from time of admissions/ referrals. Most common etiology was ulcers and 45% required endoscopic interventions. The median Rockall score was 4.6 ± 2.1. Rebleeding occurred in 9.9% and mortality in 20.9% (inpatient [12.6%] and post-discharge [7.3%]). Female patients had less *H. pylori* infection (p=0.001), but higher post-discharge mortality (p=0.030) and older group (>60 years) had lower *H. pylori* infection (p=0.002) and higher Rockall score (p=0.016). Higher Rockall score (>2) was associated with higher rates of rebleeding (p=0.027) and mortality (p=0.035). The Rockall score positively correlated with length of hospitalization. There was no correlation between treatment modality and rebleeding rate, and there was no correlation between time of endoscopy and treatment modality with morality. **Conclusion:** Among our patients with UGIB, rebleeding rate and mortality rates remains high. High post-discharge mortality rates are due to significant comorbid conditions. Higher Rockall score was associated with higher rates of rebleeding and mortality and correlated with length of hospitalization.

Keywords: Brunei Darussalam, Endoscopy, Gastrointestinal haemorrhage, Upper, Helicobacter pylori, Mortality.

INTRODUCTION

Upper gastrointestinal bleeding (UGIB) is the most common GI emergency requiring hospitalizations and is associated with mortality rates of between 10% and 33%.[1-4] Mortality rate remains high despite declining prevalence of *Helicobacter pylori* (*H. pylori*) infections, wide spread use of proton pump inhibitors (PPIs) and strategies to reduce adverse effects of non-steroidal anti-inflammatory drugs

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(NSAIDs) or use of analgesia with less gastrointestinal adverse effects.[1,2,5] The most common cause of UGIB is ulcer disease. Recent trends have reported overall decreasing incidence, but UGIB remains more common among men and older age groups.[6] Factors contributing to the high mortality rates include changes in patients' demographics such as ageing population and multiple comorbidities, increasing use of dual anti-platelets, anticoagulation and NSAIDs.[7,8]

The management of acute UGIB remains challenging despite use of predictive scores (i.e., Rockall score, Glasgow-Blatchford score and AIMS65) to guide management and available endoscopic treatment modalities.[9-13] Available treatment apart from fluid resuscitation include injection therapies (adrenaline or sclerosants), heater probe coagulation, hemoclips, rubber band ligation, argon plasma, and laser therapy. Failing endoscopic management, patients proceed with radiological embolization or surgery. The Rockall score that predict rebleeding and mortality uses a combination of clinical, laboratory, and endoscopic variables.[10] Based on the rebleeding risks without interventions, decisions to proceed with endoscopic treatment are made based on the stigmata encountered on endoscopy. The score also predicts the risk of mortality, recurrent hemorrhage, need for clinical intervention, or suitability for early discharge. [11-13] A newer score that had been developed is the Blatchford score which uses baseline clinic and laboratory parameters to help to decide on need for admissions and provide guidance for safe discharge to outpatient management. It is also used to predict the need for endoscopic interventions. However, these scores are not perfect and have limitations.[9]

In Brunei Darussalam, the last published study for UGIB was in 2004, which reported a mortality rate of 18%.[14] In this study we report our experience with UGIB over an 18-month period and assessed the differences between the genders and the age groups (<60 and ≥ 60 years) in relation to outcomes.

MATERIALS AND METHODS

Study Population

All patients aged 16 years and above who had UGIB between July 2017 and November 2018 treated in the Raja Isteri Pengiran Saleha (RIPAS) Hospital, Brunei Darussalam, were included in the study. These included patients who were hospitalized with acute UGIB and those who developed UGIB during hospitalizations for other reasons. UGIB was defined as symptoms/signs consistent with UGIB (hematemesis, coffee ground vomitus and melena) with significant drop of hemoglobin >2gm/dL or needing blood transfusion. Patients who presented with low hemoglobin with iron deficiency anemia but no overt UGIB were excluded.

Data Collection

All patients fulfilling the inclusion criteria, demographic data, co-morbidity, drug history, laboratory results, clinical outcome (including inpatient and outpatient deaths), time-to-endoscopy, endoscopy reports and details of management including endoscopic interventions, rebleeding and mortality were retrospectively collected. Patients name and national identity numbers were omitted and only Bru-HIMs numbers were used as identifier. A complete Rockall score (post endoscopy) was calculated (Appendix I). Patients were considered as high-risk group (Rockall score >2), low-risk group if Rockall score ≤2).[10] The Rockall score is available in Appendix 1.

The Forrest classification was used to categorized endoscopic stigmata; Forrest 1a (spurting hemorrhage with rebleeding rate of 70%), Forrest 1b (oozing hemorrhage), Forrest 2a (non-bleeding visible vessel), Forrest 2b (adherent clot), Forrest 2c (pigmented

spot at ulcer base) and Forrest 3 (Clean base ulcer). [15]

Statistical Analysis

All statistical analyses were performed using SPSS software version 20.0 (SPSS Inc. Chicago, IL) for Windows. Descriptive statistics were computed for all factors. These were presented in means (M) ± standard error of means (SEM) for normally distributed data, median (Me) with interquartile range (IQR) or range for non-normally distributed data, and percentiles and frequencies for categorical factors. Comparison between the gender and age groups (<60 years and ≥60 year) was carried out to assess for significance. Categorical data analysis was performed using Pearson's Chi-Square. A *p* value of < 0.05 was considered significant.

Ethical consideration

This was a retrospective cross-sectional study and data was anonymized (Hospital number removed) for analysis. The study was conducted following the guideline set out in the Declaration of Helsinki.

RESULTS

Demographic

There was a total of 151 patients with UGIB with a mean age of mean age 62.1 ± 15.2 years, more men (n=94, 62%) with more elderly (≥60 years old) patients (Table I). The most common comorbid conditions were hypertension, dyslipidemia, diabetes mellitus and chronic kidney disease. A proportion (17.2%) of patients had history of previous ulcers. Between 3.3% and 14.6% of patient were using medications that were associated with increased risk for bleeding either mono or in combinations.

There were significant differences in the age, comorbidities and medications used among genders and age groups with UGIB. There were significantly more older patients (≥60 years) and hypertension among female patients. The older age groups (≥60 years) had significantly more comorbid conditions (hypertension, dyslipidemia and chronic kidney disease), and were on anticoagulant compared to those <60 years of age.

Table I: Characteristics of study population and comparisons of co-morbidities, previous history of ulcers and medications between genders and age groups.

Variables	Total (N=151)	Male n=94(%)	Female n=57(%)	*P* value	<60 yrs n=90(%)	≥60 yrs n=61(%)	*P* value
Age in years (Median/range)	62.1 ± 15.2	60.7 ± 16.4	64.4 ± 12.9	0.15			
< 60 years	61 (40.4)	46 (48.9)	15 (26.3)	***0.005****			
≥ 60 years	90 (59.6)	48 (51.1)	42 (73.7)				
Co-morbidities							
Hypertension	118 (78.1)	68 (72.3)	50 (87.7)	***0.020****	40 (65.5)	78 (86.7)	***0.002****
Dyslipidemia	88 (58.3)	52 (55.3)	36 (63.2)	0.219	27 (55.3)	61 (63.2)	***0.003****
Diabetes mellitus	59 (39.1)	33 (35.1)	26 (45.6)	0.133	20 (32.8)	39 (43.3)	0.128
CKD	51 (33.8)	29 (30.9)	22 (38.6)	0.212	13 (21.3)	38 (42.2)	***0.006****
Cardiovascular	39 (25.9)	24 (25.2)	15 (26.3)	0.531	11 (25.2)	28 (26.3)	0.052
Malignancy	16 (10.6)	7 (7.4)	9 (15.8)	0.091	6 (9.8)	10 (11.1)	0.052
Previous Ulcer	26 (17.2)	17 (18.1)	9 (15.8)	0.449	14 (15.5)	12 (19.6)	0.095
Medications							
Aspirin	21 (13.9)	14 (14.9)	7 (12.3)	0.424	5 (8.2)	16 (17.8)	0.074
Clopidogrel	22 (14.6)	14 (14.9)	8 (14)	0.542	5 (8.2)	17 (18.9)	0.053
DAPT	5 (3.3)	3 (3.2)	2 (3.5)	0.626	2 (3.2)	3 (3.3)	0.678
Anticoagulant	20 (13.2)	9 (9.6)	11 (19.3)	0.074	3 (4.9)	17 (18.9)	***0.01****
NSAIDs	17 (11.3)	11 (11.7)	6 (10.5)	0.524	7 (11.5)	10 (11.1)	0.571

CKD: chronic kidney disease; DAPT: dual antiplatelet; NSAIDs: non-steroidal anti-inflammatory drugs.

Table II: UGIB Outcomes - Overall and comparisons between the genders and age groups.

Variables	Toral (N=151)	Male n=94(%)	Female n=57(%)	*P* value	<60 yrs n=90(%)	≥60 yrs n=61(%)	*P* value
Transfusion							
Yes	133 (88.1)	84 (89.4)	49 (86)	0.353	52 (85.2)	81 (90)	0.263
No	18 (11.9)	10 (10.6)	8 (14)		9 (14.8)	9 (10)	
Time to Endoscopy							
≤ 12 hours	63 (41.7)	37 (39.4)	50 (87.7)		25 (40.1)	38(42.2)	
12 to 24 hours	71 (47.0)	43 (45.7)	36 (63.2)	0.188	28 (45.9)	43(47.8)	0.838
> 24 hours	17 (11.3)	14 (14.9)	26 (45.6)		8 (13.1)	9 (10)	
Endoscopy Intervention							
Yes	70 (46.3)	46 (51.1)	24 (57.9)	0.259	30 (49.2)	40 (44.4)	0.342
No	81 (53.7)	48 (48.9)	33 (42.1)		31 (50.8)	50 (55.6)	
Rockall score (M±SEM)	4.6 ± 2.1	4.5 ± 2.1	4.9 ± 2.1	0.303	4.1 ± 0.3	5.1 ± 0.2	***0.016****
***H. pylori* infection**	19 (12.6)	18 (19.1)	1 (1.8)	0.001	14 (22.6)	5 (5.6)	***0.002****
Rebleed	15 (9.0)	8 (8.5)	7 (12.3)	0.315	8 (13.1)	7 (7.8)	0.211
Outcome							
In-hospital mortality	19 (12.6)	13 (13.8)	6 (10.5)	0.373	8 (13.3)	11 (12.2)	0.530
Mortality after discharge	11 (7.3)	3 (3.2)	8 (14.0)	0.030	9 (14.8)	21 (23.3)	0.138

Outcomes

The outcomes are shown in Table II. Most patients required transfusion (88.1%) and had endoscopy within 24 hours (88.7%). The spectrum of endoscopic findings is shown in Figure 1.

Endoscopic interventions were carried out in 71 (47%) patients (monotherapy/ injection 19.2%, n=29, combination 17.9%, n=27, or others 9.9%, n=15) and the mean Rockall score was 4.6 ± 2.1. Rebleeding occurred in 9% and the overall mortality was

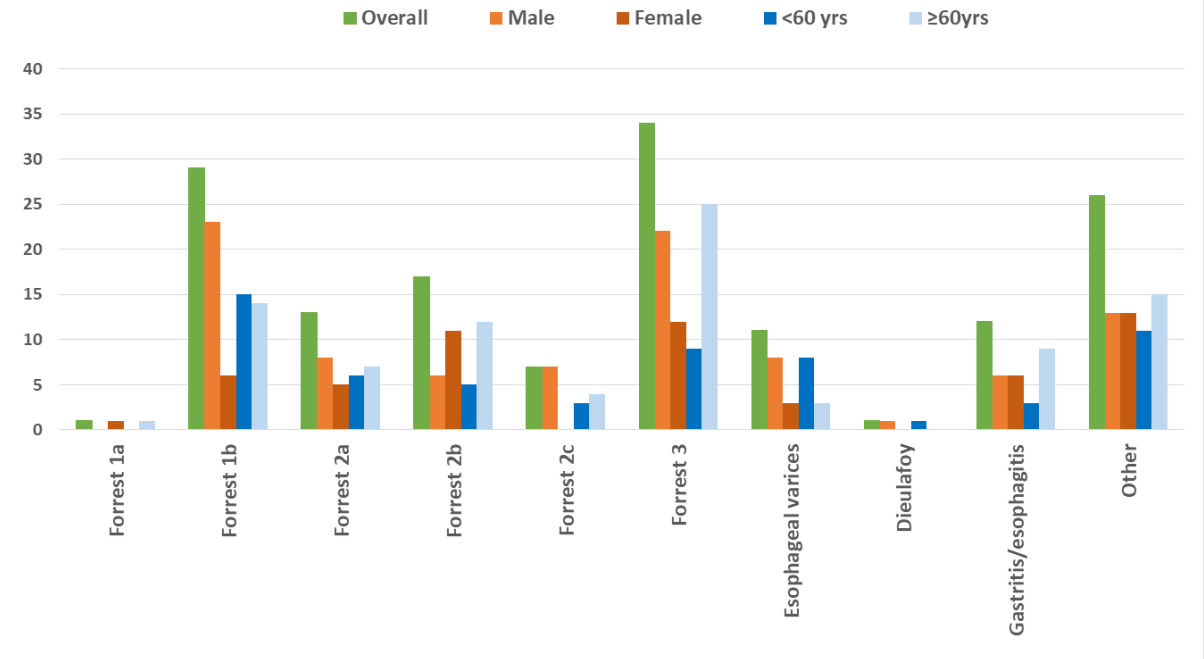

Figure 1: The breakdown of endoscopic findings. (Click on image to enlarge)

19.9%; inpatient mortality in 12.6% and post discharge mortality in 7.3%. In-hospital mortality occurred mostly in patients who developed UGIB during hospitalization (n=14), compared to patients who were admitted due to acute UGIB (n=5).

Between the genders, there was significantly less *H. pylori* infection and higher post discharge mortality among female patients. Between the age groups, there was significantly lower *H. pylori* infection and higher Rockall score among the older group (≥60 years).

The Rockall scores were significantly higher in rebleeding group compared to the non-rebleeding group (5.80 ± 2.04 vs 4.54 ± 2.07, p=0.027). There was significant difference in mortality (p=0.035) and endoscopic intervention (p=0.008) rate between low-risk (Rockall score <2) vs high risk (Rockall score >2) groups. No in-hospital mortality was recorded for the low-risk group. There was significant difference in the length of hospitalization between patients categorized as low-risk and high-risk (2.74 ± 1.25 vs. 10.40 ± 11.64, p=0.002). Among patients who were admitted with UGIB, the Rockall score showed a good correlation with length of hospitalization with r=0.607 (Figure 2).

There was no correlation between endoscopic treatment modalities and rebleeding (Table III). There was also no correlation between time of endoscopy and treatment modality and death (Table IV).

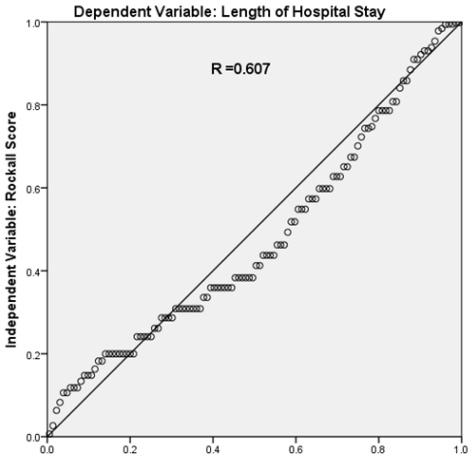

Figure 2: Linear Regression plot – Length of Hospital stay & Rockall score, showed linear moderate correlation of R=6.07. (Click to enlarge)

Table III: Correlation between endoscopic treatment and rebleeding.

	Rebleeding		*P* value
	Yes n(%)	No n(%)	
Endoscopic intervention			
Monotherapy	5 (17.2)	24 (82.8)	
Combination	5 (22.7)	22 (77.3)	0.097
Others	1 (6.6)	14 (93.4)	

Table IV: Correlations between time of endoscopy and types of intervention and mortality.

	Outcome		*P* value
	Discharge n(%)	Death n(%)	
Time to Endoscopy			
≤ 12 hours	53 (40.2)	10 (52.6)	
12 to 24 hours	64 (48.5)	7 (36.8)	0.415
> 24 hours	15 (11.4)	2 (10.5)	
Endoscopic intervention			
Monotherapy	27 (93.1)	2 (6.9)	
Combination	22 (81.5)	5 (18.5)	0.250
Others	12 (80)	3 (20)	

DISCUSSION

Our study is to date the largest study on acute UGIB in the Brunei Darussalam and many of the findings were not unexpected. Our patients were generally older with a median age of 64 years, comparable to studies done in other countries. [16, 17] More than half of our patients had significant multiple comorbidities, with more than a third having CKD, cardiovascular disease, and more than 10% having underlying malignancy. This includes almost one in five (17%) having had history of ulcer disease. Furthermore, use of ulcerogenic or medications associated with UGIB were not uncommon and this is due demographic of our patient populations, older

to demographic of our patient populations, older with multiple comorbid conditions.

In our setting, all patients with suspected UGIB are offered endoscopy and typically undergo endoscopy within 24 hours of admissions or referrals. In our study, 88% had endoscopy within 24 hours, in line with what have been recommended in all major guidelines. In contrast, a study from the United Kingdom (UK) reported that only 74% of those admitted with acute UGIB proceeded with endoscopy.[16] The difference is most likely due to demands on endoscopy service. In countries like UK, the demand on endoscopy services is large and hence waiting time is long even for hospitalized patients. Early endoscopies have been shown to be associated with better outcomes. [18-20] However, in our study there was no significant difference in the mortality rate between early and late endoscopy. Most of our patients in the late endoscopy group had only gastritis/esophagitis with no significant high-risk stigmata. This may reflect effective risk assessment which categorized patients as low risk and hence delayed endoscopy. Downgrading of bleeding stigmata during the waiting intervals whilst being treated with potent acid suppression therapy is also a factor.

Among patients with UGIB, ulcer disease was the most common endoscopic diagnosis in our study, comparable to what have been shown in the literatures. However, there are differences in proportion differed compared to studies from UK and Egypt.[4,16] The Egyptian and UK studies reported rates of UGIB secondary to varices to be 31% and 12% respectively.[4, 16] This could be explained by more than half (58%) of our study population being on either on antiplatelet, anticoagulant or NSAIDs, which are all ulcerogenic agents or associated with increased risk for bleeding whereas in the Egyptian study[4], many of the patients had chronic hepatitis C and schistosomiasis, and in the UK study[16], alcoholic liver disease was common. This increase in medications related UGIB is now observed in not just developed but also developing nations with changing patient demographic, especially with aging populations and multiple comorbid conditions as reflected by our patients. This is considering that prevalence of H. pylori infection, an important cause of peptic ulcer disease has and continue to decline globally.

In our study, only 44% of patients needed endoscopic interventions. This slightly low number can be accounted for by early use of potent acid inhibitions that may have downgraded stigmata and our aggressive approach to suspected UGIB. For endoscopic interventions, current recommendation is the use of dual therapy to reduce risk of rebleeding.[21] However, in our experience, 40.8% had monotherapy or single modalities of treatment. This could be explained by several reasons: preference of the endoscopists, milder endoscopic stigmata, patient intolerance during procedure or difficult ulcer locations. Despite this, we did not show any correlation between modalities of treatment and rebleeding or mortality.

The in-patient mortality rate was 12.6%, comparable to other population-based study around the world.[3,4,16,17,22] Despite this, the current rate is much lower to the previously reported rate of 18% in an earlier study conducted in the same institution in 2004.[11] This is likely a reflection in improvement in the management of UGIB. This is likely due to the changing patients' demographic, declining prevalence of *H. pylori* and the availability of treatment modalities. We also showed that mortality due to acute UGIB is uncommon in the absence of comorbidity.[16] Of concern is the mortality (7.3%) after discharge. We were not able to ascertain the exact causes of deaths but were likely related to poor underlying health status of patients rather than related to the UGIB.

Post discharge deaths were more common among female patients which had a large proportion of patients in the older age group. Further studies are required to assess this as such deaths are considered preventable.

Our study showed that post-endoscopy Rockall score is a good risk assessment tool in predicting re-bleeding and in-hospital mortality rate. These are all consistent with all studies previously done in other parts of the world including in elderly population with acute UGIB.[11,22-26] We also showed a moderate linear correlation (r=0.607) of Rockall score in predicting length of hospitalization among patients who were admitted with UGIB. This result also had been reported in another study, although at a lower correlation (r=0.313).[27]

We showed that there were some differences between the genders and age groups. Female patients were more likely to be in the older age groups and had less *H. pylori* infections but more post discharge mortality. Male patients tended to have more significant stigmata of recent bleeding (Forrest 1b ulcers). There were otherwise no differences in the other parameters assessed. Between the age groups, as expected older patients tended to have more comorbidities, used more medications associated with UGIB and had higher Rockall score. The younger age had more *H. pylori* infection and this show UGIB in older patients tended to be medications related.

There are several limitations that need to be considered when interpreting our results. First, our study is a retrospective study which is inherently associated with retrospective design such as missing or incomplete data. Second, it is a single centre data and hence our result may not be generalized to other settings. However, our centre is a tertiary referral centre with a large population catchment and a referral centre for two other hospitals. Rockall score to predict length of hospital stay need to be determined further in larger study population.

CONCLUSION

Our findings of UGIB are comparable to what have been reported in the literature. There were some differences between the genders and the age groups. Our inpatient mortality remains high but lower than findings reported almost two decades ago. Interestingly, slightly more than a third of the total death were post discharge mortality. This requires further study as we were not able to ascertain the causes of deaths. The time of endoscopy and modality of interventions were correlated with outcomes, rebleeding or mortality.

CONFLICTS OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

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