CAUSES, MANAGEMENT AND SHORT TERM OUTCOMES OF UPPER GASTROINTESTINAL BLEEDING AT KENYATTA NATIONAL HOSPITAL

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A dissertation submitted in partial fulfillment of the degree of Master of Medicine, Internal Medicine.

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DECLARATION

This research proposal is my original work and has been presented as a prerequisite for a Master's degree to the Department of Clinical Medicine and Therapeutics, University of Nairobi, Kenya. It has not been presented for a degree to any other university.

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DEDICATION

'It is by standing on the shoulders of great men that I have been able to see far'.

To my supervisors who painstakingly sit with me and help refine my work,

To my mother and sisters who continually support me,

To my colleagues who help to nourish my ideas,

To God for wisdom, strength and health,

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LIST OF ACRONYMS AND ABBREVIATIONS

AASLD	American Association for the study of Liver Diseases
APASL	Asia Pacific Association for Study of Liver Diseases
APTT	Activated Partial Thomboplastin Time
ASA	Aspirin
ASGE	American Society of Gastrointestinal Endoscopy
GIT	Gastrointestinal Tract
Hb	Hemoglobin
HVPG	Hepatic Venous Pressure Gradients
INR	International Normalized Ratio
IV	Intravenous
KNH	Kenyatta National Hospital
LFTs	Liver Function Tests
NG	Nasogastric
NICE	National Institute for Health and Care Excellence
NSAIDs	Non -Steroidal Anti-inflammatory Drugs
NVB	Non -Variceal Bleeding
PPIs	Proton Pump Inhibitors
PUB	Peptic Ulcer Bleeding
PUD	Peptic Ulcer Disease
SIGN	Scottish Intercollegiate Guidelines Network
SRH	Stigmata of recent hemorrhage
SSA	Sub- Saharan Africa
SSRIs	Selective Serotonin Reuptake Inhibitors
UGIB	Upper Gastrointestinal Bleeding

UGIT Upper Gastrointestinal Tract

UON University of Nairobi

ABSTRACT

BACKGROUND Upper gastrointestinal bleeding is considered as the most common gastroenterological emergency and is a significant cause of morbidity and mortality worldwide. This study aimed at evaluating the causes, management and short-term outcomes of UGIB at Kenyatta National Hospital as these had not been evaluated in the past two decades

OBJECTIVE To document the causes at endoscopy, management and determine short term outcomes of patients with upper gastrointestinal bleeding at Kenyatta National Hospital.

METHODOLOGY This was a prospective cohort study carried out at in patient medical wards and endoscopy unit of the Kenyatta National Hospital. 150 adult patients who presented with upper gastrointestinal bleeding at the Kenyatta National Hospital were consecutively recruited. Demographic information and clinical history was obtained from subjects. Subjects were also examined and their physical examination findings, laboratory and endoscopy results were recorded. Data was extracted from patient files. The study population was described using demographic and clinical characteristics.

RESULTS The male to female ratio was 2.8:1. The mean age was 45.07 ± 16.57 years. 20 patients did not have endoscopy done. Time to endoscopy ranged from 1 to 29 days with a median time of 5 days. The source of bleeding was identified in 80.8% of patients. Varices were the most common cause (39.2%) followed by peptic ulcer disease (25.3%) and erosive mucosal diseases. Forty-eight patients had therapy at endoscopy, the most common method used was band ligation. Sixty five (43.3 %) patients had blood transfusion during their hospital stay. The mean blood transfused was 1.98 ± 0.94 unit. Following transfusion, 81.6 % of those transfused had check Hb and the mean post transfusion Hb level was 7.59 ± 2.06. The most common pharmacological treatment was PPI administered to 76.3% of all patients. The length of hospital stay ranged from 1 to 35 days with a median length of hospital stay of 9 days. Patients were followed up to 14 days following discharge. There was control of bleeding in 145,(96.7 %) of patients, Re-bleeding occurred in 14 (9.3%) of patients and 11 (7.3%) patients died within the two week follow up.

CONCLUSION Gastro-esophageal varices were found to be the most common cause of UGIB following endoscopy. It is likely that there were challenges in access to endoscopy and in

obtaining blood products and this was reflected in long duration of hospital stay and time to endoscopy. In comparison to other regions in SSA there was a lower re-bleeding and mortality rate. This could have been due to a smaller sample size and shorter duration of follow up.

1.0 INTRODUCTION

Upper gastrointestinal bleeding is the most common gastroenterological emergency and is associated with significant morbidity and mortality. It is approximately 4 times as common as lower gastrointestinal tract bleeding. [1] UGIB is defined as bleeding occurring in the gastrointestinal tract proximal to the ligament of treitz. It commonly presents with hematemesis (40-50%) and/ or melena (70-80%). [2]If bleeding is brisk, patients may present with hematochezia (10-15%) and often associated with hemodynamic compromise. [3]Other presentations include symptoms of anemia or blood loss and in patients with underlying chronic liver disease, signs of de-compensation including encephalopathy.

Endoscopy is the primary diagnostic tool, in up to 20% of cases however, the source of bleeding is not identified. At presentation, by use of clinical parameters, the UGIB etiology score is useful in predicting source of bleeding prior to endoscopy therefore guiding initial management. [4,5] Nasogastric lavage can be used at presentation if there is doubt as to whether source of bleeding is from the UGIT. A serum urea nitrogen creatinine ratio can be used to differentiate upper from lower GIT bleeding. A ratio greater than 36, in the absence of underlying renal insufficiency, suggests a source of bleeding in the upper GIT whereas a ratio less than 36 does not help to locate source of bleeding. [6,7,8]

Clinical history and physical examination is crucial in patient management. In addition, various clinical scoring systems have been developed to ensure appropriate patient management, enable cost effective use of available resources and provide prognosis of patients upon initial evaluation.

Endoscopy should be undertaken immediately following resuscitation in those with hemodynamic compromise and within 24 hours for all other patients with UGIB. Recent guidelines recommend risk stratification of patients with UGIB so as to identify patients at high risk of adverse outcomes. [9,10]

2.0 LITERATURE REVIEW

2.1 Epidemiology and causes of UGIB

Over the past decade, the overall incidence of UGIB has been reported to have decreased. This reduction has been noted especially in the developed world. The incidence is generally higher among males and patients of low socioeconomic status. [11,12,15]

Causes of UGIB are generally categorized as either variceal or non-variceal as shown in table 1 below. In Sub- Saharan Africa, varices account for majority of causes of UGIB due to high prevalence of Schistosomiasis. In addition, Hepatitis B is endemic in Africa and to a lesser extent Hepatitis C in certain regions of Africa leading to chronic liver disease and portal hypertension with eventual formation of varices. In the rest of the world, non-variceal bleeding is the major cause. Recent studies however indicate that this pattern of UGIB is changing in some regions.

Table 1: Causes of non-variceal upper gastrointestinal bleeding

Esophagus: Mallory Weiss tear, esophagitis, esophageal ulcer, Barret's ulcer, Cameron ulcer within hiatus hernia*, esophageal leiomyoma, malignancy
Stomach: gastric ulcer, gastric erosions, hemorrhagic gastritis, gastric carcinoma, gastric lymphoma, gastric leiomyoma, gastric polyp. Hereditary hemorrhagic telangiectasia, dieulafoy lesion *, gastric antral vascular ectasia (GAVE) *, angiodysplasia*, gastrointestinal stromal tumor (GIST)
Duodenum: duodenal ulcer, duodenal erosions, vascular malformations, aorto- duodenal fistula, polyps, carcinoma of ampulla, carcinoma of pancreas, hemobilia*
***important causes of obscure UGIB**

Improvement in pharmacological treatment of peptic ulcers, use of prophylactic proton pump inhibitors as well as better Helicobacter pylori eradication rates have led to a reduction in the incidence of peptic ulcer bleeding that has contributed to reduction in overall incidence of UGIB observed in the west. However, bleeding secondary to peptic ulcers remains as the most common

cause of UGIB in resource rich settings and this has been attributed to an aging population with increased use of non- steroidal inflammatory agents, oral anticoagulant and anti-platelet therapy. [11,12,15,16]

In Africa studies in the past on UGIB conducted in various regions have revealed varices to be the most common cause. Recent studies however indicate that the prevalence of bleeding from peptic related causes seems to be increasing.

In Egypt, a recent hospital based study reported an almost equal prevalence of bleeding secondary to peptic ulcers and varices at 31% and 28% respectively. [22] This was in contrast to an earlier study also carried out in Egypt 5 years prior that reported varices as the predominant cause accounting for 60% of cases. [23]Similarly, In Nigeria, a study on patients presenting with UGIB carried out over a 6-year period from 2007 to 2013 found duodenal ulcers as the main cause (30.6%) followed by varices (18.1%) and gastritis (17.1%). [24]However a previous study carried out between 2003-2008 reported varices as the most common cause accounting for 45.3%. [25]

Over the past years, there have been advances in management of UGIB, with establishment of management guidelines, availability of endoscopy and PPIs which has led to better outcomes with reduced rates of re-bleeding, need for surgery and transfusion. However, mortality has remained somewhat unchanged. [11,12,13,14,15,16] In Africa, the outcomes remain poor compared to the west.

A retrospective study in Ghana on patients presenting with UGIB between 2007 and 2013 was carried out by Nkrumah et al. The most common causes on endoscopy were identified as gastro-esophageal varices (21.9%) and gastritis 21.7%. Variceal bleeding was associated with increased mortality compared to peptic ulcer disease 10:1 and mortality related to variceal bleeding was observed to be increasing with time ranging from 45.9% in 2010 to 76.9% in 2013. It was noted that limitation of resources was a significant contributor to the high mortality observed. [21]

A summary of studies showing trends in causes and outcome of UGIB is shown in tables 2 and 3 below.

Table 2: Studies in other populations showing trends in causes and outcome of upper gastrointestinal tract bleeding

Study	Year	Sample size	Etiology	Outcome
Rockall et al[13] UK UGIB audit Prospective	1993	4185 pts 74 hospitals	Ulcer (35%) Erosion (11%) Oesophagitis (10%) Varices (4%) No finding (25%)	Mortality-14% (OP-13, 33-IP) Incidence- 103/100000 adults/yr
Hearnshaw et al[14] Uk Bleeding Registry Prospective	2007	5004 pts 208 hospitals	Ulcer (36%) Oesophagitis (24%) Erosion (22%) Varices (11%) No finding (17%)	Mortality -10% ; 7%-new admissions, 26%- In-patients
Theocaris et al Greece Retrospective[15]	1995-2005	353, 489	33% ↓ incidence UGIB 30%↓ PUD incidence	Re-bleeding ↓12% (1995) 5.9% (2005) Mortality 3.9% (1995), 6.5% (2005)
J. Henrion et al France Prospective[16]	1984-2004	200, 200	PUD 58% (1984) vs 48% (2004) Varices 15%	Re-bleeding- 30% (1984) vs 15% (2004) Mortality-10% Surgery – 11.5% (1984) vs 6% (2004)
Leerdam et al Netherlands Prospective[11]	1993,2000	951,769	23%↓incidence UGIB PUD 40% vs 46% Varices 9% vs 7%	Re-bleeding 16% vs 15% Mortality 14% vs 13%
Loperfido et al Italy Prospective[12]	1983,2002	587 35%↓ incidence UGIB PUD 32.7% vs 19.5%		Re- bleeding 32.5 vs 7.4% 60%↓ mortality

Table 3: Studies in Africa showing trends in causes and outcome of Upper Gastrointestinal Bleeding

Study	Year	Sample size	Etiology	Outcome
Hansen et al KNH, Kenya Prospective Am J Trop. Med 1978 [17]	1978	66	Duodenal ulcer 53% Esophageal varices 20%	N/A
Lule G.N, Teteiyan et al KNH, Kenya Prospective EAMJ 1994[18]	1991	97	Esophageal varices 35% Duodenal ulcer- 17.5%	Re-bleeding- 11% Mortality- 5%
Mohamed Abdel-Hay Aubaid et al Cairo, Egypt[22]	2002-2005	1089	Esophageal varices (60.1%) Ulcers (16.5%) Erosions (7.6%)	N/A
Ahmed Gado et al Egypt Retrospective[21]	2004-2011	1000	Esophageal varices 31% PUD 28%	Mortality 15%
S. Mustapha et al N. East Nigeria[24] Retrospective	2003-2008	106	Esophageal varices (45.3%) Erosive mucosal disease (23.7%) PUD-16.9% Gastric cancer &Mallory-Weiss syndrome-1.9% 10.4%-Unidentified	Mortality- 17.9%. (Variceal)
Kavamba V et al Zambia Retrospective[19]	1977-2014	1532	PUD 30%, 22% ↑per decade in GU Varices 24%, 14%↑ per decade in varices	N/A
Nkrumah et al Ghana Retrospective[20]	2007-2013	695	PUD 30% Varices 21%	Mortality- Variceal: PUD 10:1 Variceal 46% (2010) 76% (2013)

2.3 Management of Upper Gastrointestinal Bleeding

Following presentation with symptoms of UGIB, source of bleeding can be suspected through thorough clinical history and examination. Relevant history includes, demographic information, history of alcohol intake, known chronic liver disease or peptic ulcer disease, known co-morbidities, history of intake of drugs associated with UGIB, prior history of UGIB and interventions done.

Physical examination should be focused on assessment of hemodynamic status and stigmata of chronic liver disease. Various guidelines have been developed for management of UGIB in general as well as for variceal and non- variceal bleeding specifically.

Management strategies in UGIB include primary prophylaxis to prevent index bleed, management of UGIB and secondary prophylaxis to prevent recurrent bleeding.

2.3.1 Initial assessment and triage

This involves a quick assessment of general status of patient with specific attention to airway, breathing and circulation.

There's no benefit in prophylactic endotracheal intubation as it has not been shown to have any morbidity or mortality benefit. The Asia Pacific Association for Study of Liver Diseases (APASL) recommends intubation in those patients with severe bleeding or in patients unable to protect their airway due to mental status changes. [26]

The severity of blood loss can be estimated through measurement of hemodynamic parameters and other clinical signs as shown in table 4 below.

Table 4: Classification of hemorrhagic shock

	Compensated	Mild	Moderate	Severe
Blood Loss (mL)	≤1000	1000–1500	1500–2000	>2000
Heart rate (bpm)	<100	>100	>120	>140
Blood pressure	Normal	Orthostatic change	Marked fall	Profound fall
Respiration	Normal	Mild increase	Moderate	Marked tachypnea
Urinary output (mL/h)	>30	20–30	5–20	Anuria
Mental status	Normal/ agitated	Agitated	Confused	Lethargic, obtunded

Peripheral venous access should be established and blood volume restored by use of fluids or blood products initiated to obtain a systolic blood pressure that is greater than 100mmhg and heart rate below 100b/min. [26] The Scottish Intercollegiate Guidelines Network (SIGN) guidelines recommend transfusion of red blood cells after loss of 30% or more of blood volume.[27] A Cochrane review comparing colloid and crystalloids fluid administration for resuscitation in critically ill patients found no statistical difference in outcomes therefore either may be used in UGIB prior to transfusion of blood products [28,29]

Excessive fluid administration should be avoided as it has been found to be associated with increased portal pressure above baseline with failure to control bleeding, re-bleeding and mortality. [30]

A randomized clinical trial in patients with severe UGIB was carried out to evaluate outcomes following restrictive blood transfusion (<7mg/gl) versus liberal transfusion (<9mg/dl). Survival was higher in the restrictive group and increase in portal pressure was observed in the liberal group. [29] Following this observation, blood transfusion should be done to a target of 7-8mg/dl (hematocrit 21-24) [25,26,30]The Baverno VI consensus guidelines recommend blood transfusion with higher levels of hemoglobin in those with severe or ongoing blood loss, in elderly and in those with co-morbidities such as cardiac ischemia. [30]

American Association for the Study of Liver Diseases (AASLD) guidelines recommend transfusion of platelets and fresh frozen plasma should only be given to those who have active bleeding with a platelet count less than 50x 10^9/l and severe coagulopathy: International

normalized ratio (INR) or Activated Partial Thromboplastin Time (APTT) more than 1.5 times normal. [31]

A multicenter placebo controlled trial of recombinant factor VIIa in patients with advanced cirrhosis and bleeding, found a reduction in mortality at 6 weeks, [32] however most guidelines do not recommend its use. [27,30,33]

2.3.2 Clinical scoring

Various clinical scoring systems have been developed to ensure appropriate patient management, enable cost effective use of available resources and provide prognosis of patients upon initial evaluation.

The Glasgow-Blatchford and Rockall scores are the most widely used and have been validated in various clinical settings.

The Glasgow-Blatchford score is used as a screening tool to identify patients at first presentation who need intervention such as blood transfusion or endoscopy. Those with a score of zero can be treated as an outpatient. [34]

The Rockall score is based on criteria such as age of patient, presence of shock or co-morbidities and findings on endoscopy can be used in both variceal and non-variceal bleeds. [35]. The SIGN guidelines recommend that scoring should be performed pre-and post-endoscopy. [27] Patients with a pre-endoscopic score of zero have a low risk of mortality and re-bleeding and should be treated as an outpatient or discharged early following admission. Endoscopy is recommended in those with a pre-endoscopic score> 0. Post endoscopic score is predictive of mortality but less satisfactory in prediction of re-bleeding. A post endoscopic score of less than 3 indicates low risk of re-bleeding and mortality and patients can be managed either as an outpatient or discharged home early. A score of 8 and above indicates patient at high risk of mortality. [35,36,37] The Rockall score is presented in table 5 below.

Table 5: Rockall score

Item indicators	Categories	Criteria	Score
Age (years)	<60		0
	60-79		1
	>80		2
Shock	No Shock	SBP > 100 mm Hg Pulse < 100/min	0
	Tachycardia	SBP > 100 mm Hg Pulse > 100/min	1
	Hypotension	SBP < 100 mm Hg	2
Comorbidity	No major comorbidity		0
	Cardiac failure		2
	Ischemic heart disease		3
	Any major comorbidity		
	Renal or liver failure		
	Disseminated malignancy		
Diagnosis	Mallory Weiss tear, no lesion identified and no SRH/blood		0
	All other diagnoses		1
	Malignancy of upper GIT		2
Major SRH	None or dark spot only		0
	Blood in upper GIT, adherent clot, visible or spurting vessel		2

2.3.3 Endoscopy :

Timing of endoscopy

A systematic review evaluating the impact of early(<6h) vs late (24h) endoscopy on outcomes found that early endoscopy was associated with a reduction in length of hospital stay and need for transfusion but had no impact on mortality. [38,39]

Guidelines recommend endoscopy to be performed within 12 hours for hemo-dynamically unstable patients after resuscitation or with co morbidities and within 24 hours for all other patients. [25,31,33]

2.3.4 Endoscopic management of upper gastrointestinal bleeding

Endoscopy remains the gold standard for diagnosis and treatment of UGIB. [47] The American Society of Gastrointestinal Endoscopy (ASGE) recommends use of prokinetic agents in cases of suspected severe bleeding to promote upper GIT motility and facilitate gastric emptying of retained blood prior to endoscopy improving visibility and diagnostic yield that has been associated with better outcomes. Erythromycin 250mg IV is given 30 -120 min before endoscopy, metoclopramide may also be used. [33]

Size and location of lesions should be noted on endoscopy. Diagnosis of variceal bleeding is made using the following criteria: active bleeding from a varix, clot overlying a varix, presence of varices without any other potential source of bleeding and presence of fresh blood in stomach. [41]

At endoscopy, the Forrest classification of ulcers shown in table 6 below is used to stratify patients into high and low risk for re- bleeding and mortality. In addition, this classification is also used to guide endoscopic management. High risk lesions include grade IA, IB, IIA, IIB while low risk lesions include grade IIC and IIIA. [42]

Table 6: Forrest classification of ulcers

Grade		Signs observed on endoscopy
I	Ia	Spurting hemorrhage
	Ib	Oozing hemorrhage
II	IIa	Visible vessel
	IIb	Adherent clot
	IIc	Flat pigmented hematin or ulcer base
III	IIIa	Lesions without sign of recent hemorrhage or fibrin-covered clean ulcer base

Endoscopic therapy is indicated for Forrest I and 2A. Ulcers with adherent clot should be irrigated and endoscopic therapy performed if this fails. Endoscopic modes of treatment of bleeding peptic ulcers injection therapy, thermal therapy and mechanical therapy. Injection mediums include Normal saline. vasoconstrictors, sclerosing agents, tissue adhesives or a combination that are injected into area surrounding ulcer. Thermal therapy may be either contact (multipolar electrocoagulation or heater probe) or non-contact by use of argon plasma coagulation. Mechanical therapy involves use of clips to achieve hemostasis. [42] The recommended mode of treatment is use of combination therapy, use of epinephrine injection followed by contact thermal therapy. [25]

Endoscopic band ligation is the preferred means of treatment over sclerotherapy in esophageal varices as it has less complications and re-bleeding and mortality rates. [43]

Sclerotherapy involves injection of a sclerosant (ethanol, polidocanol or sodium tetradecyl sulfate) either into or around the varix through an injection needle placed at the end of endoscope. The amount of sclerosant used depends on type of sclerosant used, number and size of varices. Following injection of sclerosant, there is necrosis, fibrosis and eventually obliteration of varix. Band ligation involves strangulation of varix by placing elastic bands around varices. In confirmed gastric variceal bleeding, band ligation should be used for

esophageal varices extending to lesser curvature of stomach (GOV1) and injection therapy with cyanoacrylate is the treatment of choice for other types. [26,33]

In approximately 10-20% of patients with acute variceal bleeding, there is failure to control bleeding with endoscopic measures and pharmacotherapy. These cases of refractory bleeding are then managed with salvage therapies such as balloon tamponade, surgery (azygoportal vein disconnection), insertion of trans-jugular intrahepatic portosystemic shunt and more recently the fuse of self- expandable metallic stents that achieve hemostasis by direct compression of varices. [44]

2.3.5 Pharmacotherapy

A meta-analysis of 5 randomized clinical trials evaluating use of Proton Pump Inhibitors (PPIs) prior to endoscopy following UGIB showed no benefit in terms of mortality, re-bleeding or need for surgery. [45] Guidelines however recommend that patients with UGIB to be initiated on intravenous PPI therapy until cause is identified on endoscopy. [25]

Short term antibiotic therapy administered for 7 days should be given to patients suspected to have cirrhosis and variceal bleeding as it has been shown to reduce length of hospital stay, mortality and risk of re-bleeding. Recommended choice of antibiotic is norfloxacin 400mg bd or IV ciprofloxacin 200mg bd in those unable to take orally. Patients with advanced cirrhosis, Child Pugh class B or C should be treated with ceftriaxone. [30,33]

Vasoactive agents used in variceal bleeding include somatostatin, octreotide, vapreotide, vasopressin or terlipressin. A meta-analysis of these agents in variceal bleeding found no difference in mortality or re-bleeding rate and found similar efficacy in achieving hemostasis though vasopressin use was associated with more adverse effects. [46] The AASLD guidelines recommend initiation of these vasoactive agents as soon as variceal bleeding is suspected and continued for 5 days after endoscopy. [31]

2.3.6 Post endoscopic management of UGIB

Following successful endoscopy for bleeding peptic ulcers, the use of high dose PPIs (omeprazole or pantoprazole may be used, as 80mg bolus followed by 8mg/hr infusion for 72

hours) is recommended by various guidelines as it has been shown to reduce re-bleeding and mortality. [25,47]

Proton pump inhibitors are recommended for 6-8 weeks following UGIB and/or endoscopic treatment of PUD to allow for full mucosal healing. Patients with bleeding peptic ulcers should be tested and treated for H. Pylori. [48,49]

Combined pharmacological and endoscopic therapy is associated with better outcome than either alone as measures of secondary prophylaxis following variceal bleed.

Endoscopic ligation is preferred over sclerotherapy with ligation sessions performed at 7-14-day intervals until obliteration of varices. AASLD guidelines and the Baverno consensus recommend use of non- selective beta blockers (propranolol, nadolol) in combination with endoscopic ligation for secondary prophylaxis. Non- selective beta blockers should be initiated after 5 days following variceal bleeding and dose titrated to up to 25% reduction in heart rate or heart rate of 55 beats/minute. [30,31] The use of isosorbide mononitrate in combination with non-selective beta blockers is associated with a greater reduction in portal pressures but with increased risk of adverse effects. In addition, a meta-analysis found no difference in re-bleeding and mortality with use of this combination therapy in comparison to the use of non-selective beta blockers alone. [50]

The utility of carvedilol in the setting of secondary prophylaxis of variceal bleeding is still under study and as such not recommended in current guidelines as a form of secondary prophylaxis. [51,26,31] However, the AASLD guidelines recommend use of carvedilol, non-selective beta blockers or endoscopic ligation for primary prophylaxis. [31]

2.4 Outcomes in upper gastrointestinal tract bleeding

Control of bleeding is defined as cessation of bleeding with hemodynamic stability for 24 h after therapy. Variceal bleeding is associated with higher rates of re- bleeding and mortality in comparison to non- variceal bleeding. Spontaneous cessation of bleeding occurs in 40% of patients with variceal bleeding as compared to 80% in non-variceal bleeding. [52]

Failure to control bleeding is defined as any of the following events within 48h of initiation of combination therapy: fresh hematemesis after 2h of combination therapy, >2g drop in Hb if no transfusion is given, development of hypovolemic shock or death. [31]

Re-bleeding is classified as early (< 6wks) or late (>6wks) and defined as: >2g drop in Hb if no transfusion, new onset of hematemesis/melena following a period of 24h of hemodynamic stability. The highest risk of re-bleeding is in the first 48-72hours and over 50% of all re-bleeds occur within the first 10days. The risk returns to baseline after 6 weeks. [52,53]

Guidelines provide that prophylactic second-look endoscopy is however not indicated, and repeat endoscopy should only be done following a confirmed re-bleed. [33]

Early mortality defined as death occurring within 6 weeks of bleeding episode. [52]

3.0 Study justification

The epidemiological and clinical characteristics of UGIB as well as its management and prognosis have changed over the past 20 years. However, despite advances in management of UGIB, outcomes have not improved in Sub- Saharan Africa.

There are few follow up studies on UGIB in Africa thus difficult to determine trends in incidence, etiological factors at endoscopy and mortality. There is no current local data on etiology of UGIB in our set up and as evidenced by previous studies done, there may be changes in the etiology and outcome of UGIB in our setting.

This study therefore aimed to define the epidemiology, describe the clinical characteristics, management practices and prognosis of patients presenting with UGIB at a large referral hospital in East Africa.

This study also described the management of UGIB at KNH in accordance to established guidelines and was aimed at highlighting areas in the management of patients with UGIB that can be targeted for improvement to reduce morbidity and mortality rates and as a result provide evidence for the need to establish an UGIB management protocol.

3.1 Research questions

1. What are the causes at endoscopy of UGIB in patients presenting at Kenyatta National Hospital?
1. What are the management practices of UGIB at Kenyatta National Hospital?
2. What are the short-term outcomes of patients presenting with UGIB at Kenyatta National Hospital?

3.2 Objectives

Broad objective

The broad objective of this study was to determine the etiology and short-term outcomes of patients presenting with acute upper gastrointestinal tract bleeding at Kenyatta National Hospital and to document the management of upper gastrointestinal tract bleeding at Kenyatta National Hospital.

Specific Objectives

1. To describe the diagnosis at endoscopy of patients presenting with upper gastrointestinal tract bleeding at Kenyatta National Hospital.
2. To document the management (therapeutic interventions including transfusion practices, use of PPIS, antibiotics, vasopressors, timing of endoscopy and secondary prophylactic measures) of patients presenting with upper gastrointestinal tract bleeding at Kenyatta National Hospital.
3. To determine the short-term outcomes (rates of re-bleeding, need for surgery, length of hospital stay and deaths) of patients presenting with UGIB at KNH up to two weeks follow up period after discharge.

4.0 METHODOLOGY

4.1 Study design

This was a prospective cohort study in patients who were managed at Kenyatta National hospital for upper gastrointestinal tract bleeding. Patients were followed from time of admission up to a period of 2 weeks following discharge from the wards.

4.2 Study site

Kenyatta National Hospital is the national referral hospital, located in the capital city of Kenya with 1800 in- patient bed capacity and receives patients with upper gastrointestinal bleeding including those who are referred from other facilities in the country for further investigation and management.

Patients presenting with UGIB are first seen at the KNH emergency department and after stabilization are admitted to the medical wards by residents in the Internal Medicine program. Endoscopies are done daily in the endoscopy department of the hospital by consultant gastroenterologists and surgeons.

This study was therefore carried out in the in-patient medical wards and endoscopy department of Kenyatta National Hospital.

4.3 Study Population

The study population included patients aged over 13 years seen in KNH who had UGIB and met study eligibility criteria. They were identified based on symptoms of UGIB which include, hematemesis, melena and/or hematochezia.

4.4 Inclusion Criteria

All patients who were older than 13 years of age diagnosed to have UGIB were included in the study. Informed consent was obtained from all patients and assent was given by all patients who were under 18 years of age. Consent was obtained from the caregiver or guardian incase the patient was unable to give consent.

4.5 Exclusion criteria

Patients were excluded from the study if they had any contraindications to undergo endoscopy, did not give consent or were unwilling to be followed up.

4.6 Sample size estimation

The study used Fisher et.al. 1998 formula to calculate sample size as follows;

$$n_0 = \frac{Z^2 \times p \times (1-p)}{d^2} = \frac{1.96^2 \times 0.2 \times (1-0.2)}{0.025^2} = 983$$

Where n_0 is the initial sample size, Z is the abbisca of the normal distribution under 5% error estimate (1.96), p is the estimated mortality from UGIB (20 %) and d is the standard error allowed (2.5%).

Several studies from the African setting report mortality rates ranging from 5% to 17% across different settings. The mortality estimates used in this study were derived from a study by Mustapha et al conducted in Nigeria where the mortality rate following UGIB was found to be 17% [25]This study was used as the mortality estimates are closer to that observed from KNH central records. In this study, we used a conservative estimate for mortality rate of 20% which also gave us the largest possible sample size allowing sufficient power to elicit associations between clinical, endoscopic profile and outcome.

Given that the entire population is 135 patients for the 6 months study period (based on a monthly average of 22.5 patients) is <10,000, finite population correction factor was applied to determine the final samples size given by:

$$n = \frac{n_0}{1 + \frac{n_0 - 1}{N}} = \frac{983}{1 + \frac{983 - 1}{135}} = 118.9 \approx 119$$

Allowing for 10% loss to follow, a minimum of 130 patients were required for the study.

4.7 Participant Recruitment

Recruitment of study participants was done by principal investigator or research assistant trained in study procedures and data collection. Consecutive sampling method was used to attain the minimum sample size.

Participants who met the inclusion criteria were recruited into the study on presentation to the KNH emergency department with UGIB. The principal investigator obtained files for in-patients suspected to have UGIB, following which patients were approached and requested to participate.

Patients who met the inclusion criteria and were willing to participate in the study were required to provide a written informed consent (see Appendix 1) For patients aged less than 18 years, assent was obtained from a parent or legal guardian.

Demographic data and contacts of the patient were taken in order to follow up on the patients for study purposes. Patients who had consent were followed up while in the wards and up to a period of 2 weeks after discharge from the wards. For patients who were discharged, their mobile phone contacts were used to facilitate follow up.

4.8 Data Collection

Data was collected by principal investigator with research assistants through patient interview and abstraction of medical records. Patient interviews were conducted at recruitment using a structured questionnaire. The form was designed to obtain the following information from the patient. At the first interview, demographic data, history and examination findings of the patient. The demographic data included the name, age, sex, in-patient number, contact and home residence. The history included past medical history such as previous upper gastrointestinal bleeding episodes and treatment given, secondary prophylaxis if any, chronic medical conditions, detailed drug history and alcohol intake.

Records of clinical evaluation especially initial vital signs, blood pressure and pulse were abstracted from the file by the research assistant guided by the principal investigator and were used as measures of severity of UGIB. Details of the physical examination including grading of hepatic encephalopathy and ascites if present, size of liver and spleen were also abstracted from the patient files and recorded in study proforma. Lab measurements at presentation- hemoglobin,

platelet count and prothrombin time/ International Normalized Ratio and liver function tests were recorded.

All fluid resuscitation measures undertaken from presentation and all treatment given were recorded in the study proforma. The time to endoscopic evaluation following presentation was recorded. Patients were starved for 8 hours prior to endoscopy which was performed by consultant gastroenterologists. A consent form to undergo endoscopy was signed by the patient after an explanation of the endoscopic procedure as well as benefits and risks. At time of endoscopy, patients were gowned, laid on their left side and topical anesthesia of oropharynx with lidocaine spray given. A mouth guard was put in patient's mouth and endoscope advanced through mouth, esophagus, stomach, first and second parts of duodenum making note of any pathology. Light sedation when necessary was given with dose titrated as required. Images were taken during endoscopy and reviewed by a second gastroenterologist. Biopsies were taken when necessary.

The report of endoscopy was recorded and included type and number of lesions and stigmata of recent hemorrhage. The size and location of varices was recorded. The Forrest classification was used in patients found to have ulcers. An ulcer was defined as breach in mucosa of alimentary tract extending through the muscularis mucosa into submuscosa or deeper. An erosion was defined as breach in integrity of alimentary tract limited to the epithelium of mucosa. A dieulafoy lesion was defined as dilated tortuous arteriole within the gut wall. The choice of therapy was dependent on the cause of the bleed, expertise and preference of the endoscopist (gastroenterologist) as well as the capacity for therapeutic endoscopy. Any endoscopic intervention, if done was recorded.

Patients were followed up while in the ward while being managed by primary physician and up to 14 days after discharge in order to determine outcome. During this period, patients were interviewed to determine if symptoms of UGIB were still present and patients' files and treatment sheets were reviewed so as to record treatment given.

Outcomes of interest were control of bleeding, failure to control bleeding, re-bleeding, length of hospital stay and deaths. Control of bleeding was defined as cessation of bleeding with hemodynamic stability for 24 h after therapy. Failure to control bleeding was defined as any of

the following events within 48h of initiation of combination therapy: fresh hematemesis after 2h of combination therapy, development of hypovolemic shock or death.

Re-bleeding was defined using any of the following criteria following a period of 24h of hemodynamic stability: new onset of hematemesis/melena, red nasogastric aspirate, or development of hypovolemic shock. The length of hospital stay was calculated as days from admission to discharge by primary physician.

Those who were still hospitalized at 14 days after discharge were reviewed by the principal investigator and outcome ascertained.

Those who had been discharged were contacted on phone, consent having been obtained prior to study enrollment.

4.9 Study Variables

These included clinical and laboratory parameters recorded at presentation, findings on endoscopy and follow up while in the wards.

Dependent variables were control of or failure to control bleeding, re- bleeding, mortality, need for surgery and length of hospital stay.

Independent variables were age and gender of patient, systolic blood pressure, initial hemoglobin level, platelet count, INR, LFTs (AST, ALT, serum albumin levels), number of blood units transfused and endoscopic diagnosis.

Systolic blood pressure below 100mmHg was classified as hypotension, normal SBP as 100-140mmHg, and SBP above 140mmHg as hypertension. Size of liver was described as (<8cm span as reduced size), (8-13cm as normal) and (>13cm as enlarged). Size of spleen was classified as normal (if not palpable) and enlarged (if palpable). Degree of anemia was classified according to initial Hb level as: severe (< 5g/dl), moderate (5-8g/dl) and mild (>8g/dl). Platelet count was classified as normal (150,000-450,000/ml), reduced (<150,000/ml) and increased (>450,000/ml). INR was classified into normal (≤1.1) or deranged (>1.1). Liver function tests of interest were transaminase levels (AST/ALT) and serum albumin levels. Transaminase levels were classified according to degree of elevation from upper normal level (0-40). Serum albumin level was

classified as normal (≥35g/dl) or reduced (<35g/dl). At endoscopy, varices were classified according to size (see Appendix 5,6) and ulcers according to Forrest classification (see Appendix 4). Rockall scores/ strata were used following endoscopy where patients were stratified according to risk of adverse outcomes as: low risk (>3) and high risk (<8) (see Appendix 8)

4.9 Data analysis

The study population was described using demographic and clinical characteristics.

Continuous data was analyzed into means and medians while categorical data was analyzed using percentages.

Causes of UGIB at endoscopy were presented as proportions.

Outcomes at 2 weeks following discharge were determined and presented as percentage of patients with control of bleeding, failure to control bleeding, re-bleeding and deaths.

Length of stay in the hospital was analyzed and presented as median with inter-quartile range.

Data was analyzed using STATA analytical package version 14, while presentation was in form of tables, charts and graphs.

All statistical tests were performed at 5% level of significance (p value<0.05) and corresponding 95% confidence intervals were reported**.**

4.10 Data Management

Data was collected using an interviewer administered questionnaire. Medical records provided additional information which was entered in the standardized questionnaire as required. Checks were performed for data completion and inconsistencies were manually resolved with a review of medical records. De-identifiable data was entered into Microsoft Access database with in-built consistency and validation checks, data was cleaned and stored in a password protected external storage device (USB/disc) with data being accessible to the principle investigator, statistician and the supervisors.

4.11 Data presentation

The results of data analyses were presented using tables and bar graphs.

4.12 Ethical Considerations

Ethical approval was sought from the Department of Clinical Medicine and Therapeutics in the University of Nairobi and the Ethics and Research Committee (ERC) KNH/ UON. Prior authorization from the administration offices at the Kenyatta National Hospital was sought before commencement of this study. Data was collected within seven months of approval. Results and final book were presented to the ERC within one year of approval.

Consent obtained was informed and written. This study was explained to every participant in a language they understood and they were allowed to ask questions and seek clarification. There was no financial re-imbursement given to study participants and this was made clear during informed consent.

Study numbers were assigned to the patients. The information obtained was strict and confidential. Participants were allowed to opt-out from the study without any form of discrimination. After completion of the study, all raw data was destroyed within the specified time.

5.0 RESULTS

The study was conducted from September 2016 to June 2017 however it was interrupted by a 4-month industrial action by doctors when there were no patients in the wards. A total of 150 adult patients managed at the Kenyatta National Hospital with upper gastrointestinal tract bleeding who met the inclusion criteria were consecutively selected and recruited after consenting to take part in the study. Endoscopy was done in 130 patients while in 20 patients endoscopy was not performed. All patients were reviewed daily while in the ward, up to a period of 2 weeks following discharge from hospital. However, 8 patients were lost to follow up.

5.1 Demographic Information

The demographic distribution of the patients is as shown by Table 7 below.

Table 7: Demographic Distribution of the Patients

	Endoscopy	No Endoscopy	p-value
Age (years)			
Mean (SD)	44.75 (16.13	47.20 (19.51)	0.539
Sex			
Male	101 (77.7)	10 (50.0)	0.009
Female	29 (22.3)	10 (50.0)	

During the study period, a total of 150 patients presented with upper gastrointestinal bleeding, of which 111 (74%) were male while 39 (26%) were female, with a male to female ratio of 2.8:1. Patient ages ranged from 18 to 88 years with a median age of 43 years with interquartile range of 31-56 years.

5.2 Observed co-morbidities

Fifty-eight (38.6%) patients were reported to have underlying illnesses that included malignancy, cardiac disease, chronic renal disease, diabetes, hypertension and HIV as shown in Fig 1 below. Overall, 11.3 % were known to have chronic liver disease.

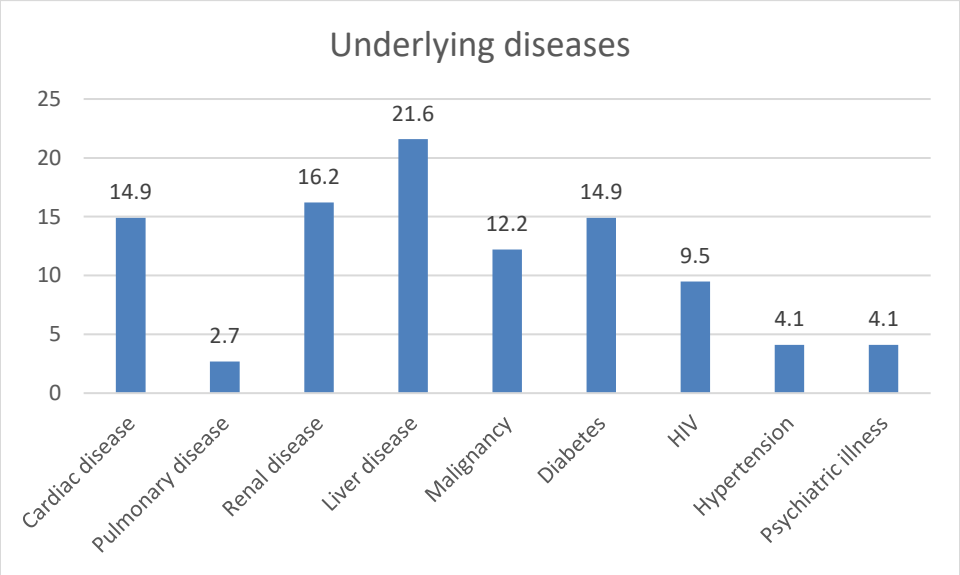

Figure 1: Bar chart showing the underlying diseases in the study population

Thirty-nine patients (26%) reported use of medication known to increase risk of UGIB within one month of presentation. Of these, 84.7% reported intake of NSAIDs as shown in Fig 2 below.

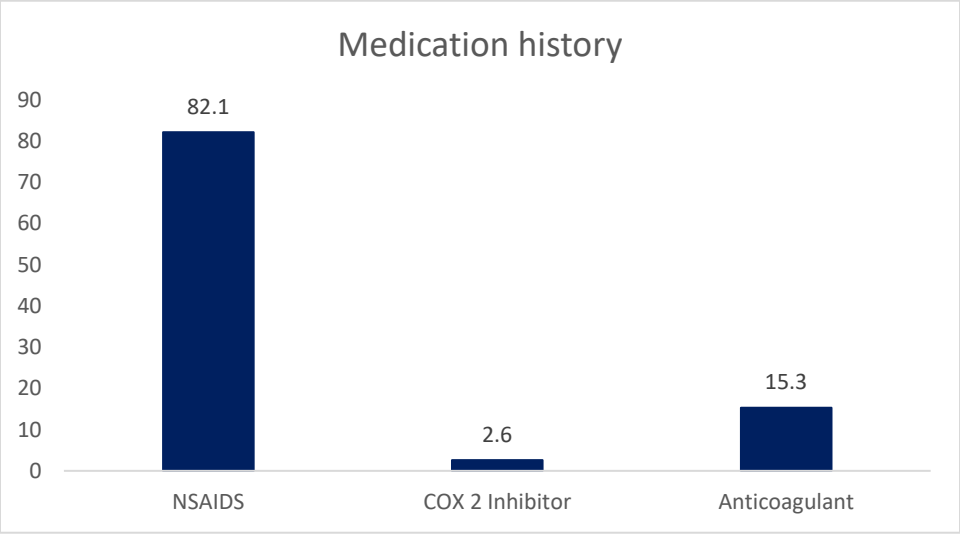

Figure 2: Medication History used prior to onset of symptoms by study population.

5.3 Physical examination findings

The distribution of patients by physical examination findings at hospitalization of the study patients is as shown in Table 8 below.

Table 8: Distribution of study Patients by Findings at Physical Examination

	Endoscopy	No endoscopy	p value
Systolic Blood Pressure			
Normal	38 (29.2)	9 (45.0)	0.365
Hypotension	74 (56.9)	9 (45.0)	
Hypertension	18 (13.8)	2 (10.0)	
Pulse			
Less than 100	58 (44.6)	12 (60.0)	0.722
100 – 119	50 (38.5)	6 (30.0)	
120 – 139	19 (14.6)	2 (10.0)	
140 +	3 (2.3)	0 (0.0)	
Ascites			
Present	7 (5.4)	1 (5.0)	0.943
Absent	123 (94.6)	19 (95.0)	
Size of liver (cm)			
Reduced	5 (3.8)	2 (10.0)	0.432
Normal	115 (88.5)	17 (85.0)	
Enlarged	10 (7.7)	1 (5.0)	
Size of spleen			
Enlarged	24 (18.5)	2 (10.0)	0.352
Normal	106 (81.5)	18 (90.0)	

Eighty-three, (55.3 %) patients presented with hypotension, 5.3% had ascites, 17.3 % had an enlarged spleen while only 4.7 % had a reduced liver span.

Results of laboratory investigations done at admission were recorded and 24.7 % of patients had severe anemia, 22.6% had reduced platelet count, 20.6 % had elevated liver transaminase levels while 78.7 % of patients had hypoalbuminemia. Table 9 shows a summary of distribution of patients by laboratory results.

Table 9: Key Laboratory Results of the study patients at Hospitalization

	Frequency n (%)
Anemia/Hb (n=150)	
Severe (<5.0g/dl)	37 (24.7)
Moderate (5-8g/dl)	69 (46.0)
Mild (8-11g/dl)	17 (11.3)
Normal >11g/dl	27 (18.0)
Platelets (n=150)	
Reduced	34 (22.6)
Normal	116 (77.3)
LFTs	
AST (n=150)	
Normal	119 (79.3)
≤3x	18 (12.0)
>3x	13(8.7)
ALT (n=150)	
Normal	130 (86.7)
≤3x	14 (9.3)
>3x	6 (4.0)
Serum Albumin (n=150)	
Normal	32 (21.3)
Reduced	118 (78.7%)
INR (n=150)	
Normal	132(88%)
Deranged	18(12%)

5.4 Diagnosis at Endoscopy

A total of 130 patients underwent endoscopy while 20 patients did not. As shown below, the source of bleeding was identified in 80.8% of patients. Gastro-esophageal varices (39.2%) was the commonest cause of bleeding followed by peptic ulcer (25.4%) Among 14 patients (10.7%) more than one diagnosis was found at endoscopy. Among patients with variceal bleeding, 42 (82.3%) had esophageal varices with commonest being grade 3, (71.4%) followed by grade 2 in 23.8% of patients. Nine patients (17.6 %) had esophageal varices with gastric extension. The most common grade was esophageal varices with extension to fundus of stomach (GOV 2) in six of these patients.

Table 10: Endoscopic Diagnosis of the study patients.

	Frequency (n)	Percentage of cases (n=130)
Gastro- Esophageal varices	**51**	**39.2**
Upper GI Malignancy	**15**	**11.5**
Normal OGD mucosa	**25**	**19.2**
Duodenal ulcer	**21**	**16.2**
Gastric ulcer	**12**	**9.2**
Erosive disease	**27**	**20.7**
Dieulafoy's lesion	**1**	**0.7**
Mallory Weiss tear	**1**	**0.7**
Total	**130**	**117.7**

	Varices Present		p-value
Albumin	**Non variceal**	**Variceal**	
≤ 35	82 (74.5)	36 (90.0)	0.041
> 35	28 (25.5)	4 (10.0)	
Size of spleen			
Palpable	14 (12.7)	12 (30.0)	0.013
Non palpable	96 (87.3)	28 (70.0)	

	Diagnosis of PUD		p-value
Medical history of PUD	**Yes**	**No**	
Yes	16 (34.0)	16 (15.5)	0.010
No	31 (66.0)	87 (84.5)	

5.4 Time to Endoscopy

Time to endoscopy ranged from 1 to 29 days with a median time of 5 days with interquartile range of 1-7 days.

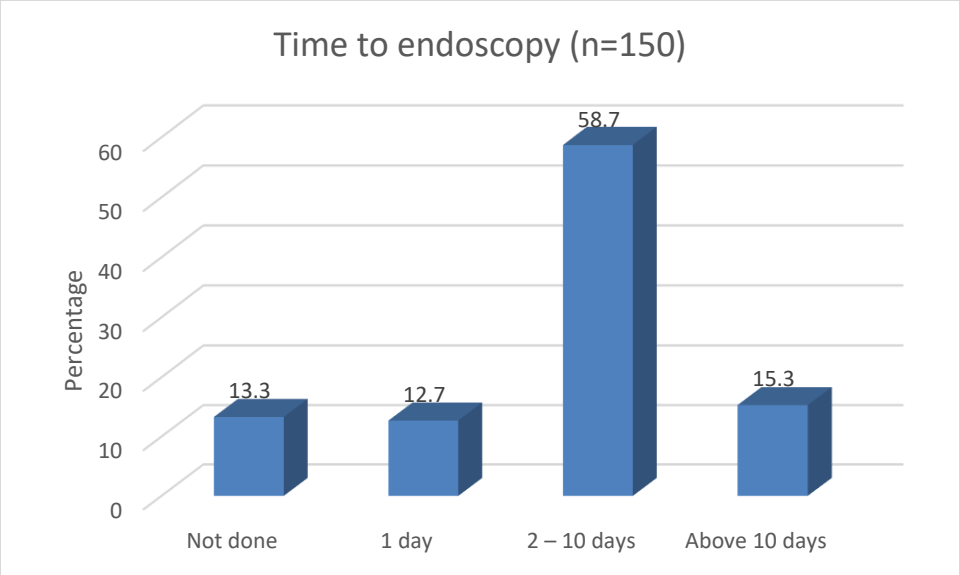

Figure 3: Bar chart depicting time-to-endoscopy of the study patients

5.5 Rockall score for Risk of Re-bleeding and Mortality

Post-endoscopic Rockall score was calculated for all patients who underwent endoscopy. The mean Rockall score for the 130 patients was 2.96 ± 1.95. As shown in figure 4 below, the scores obtained ranged from 0 - 8 with the median score at 3.0 while the modal score was 1. Of these 47.0 % were in the low risk group (<3) and 0.8% were in the high-risk group (<8).

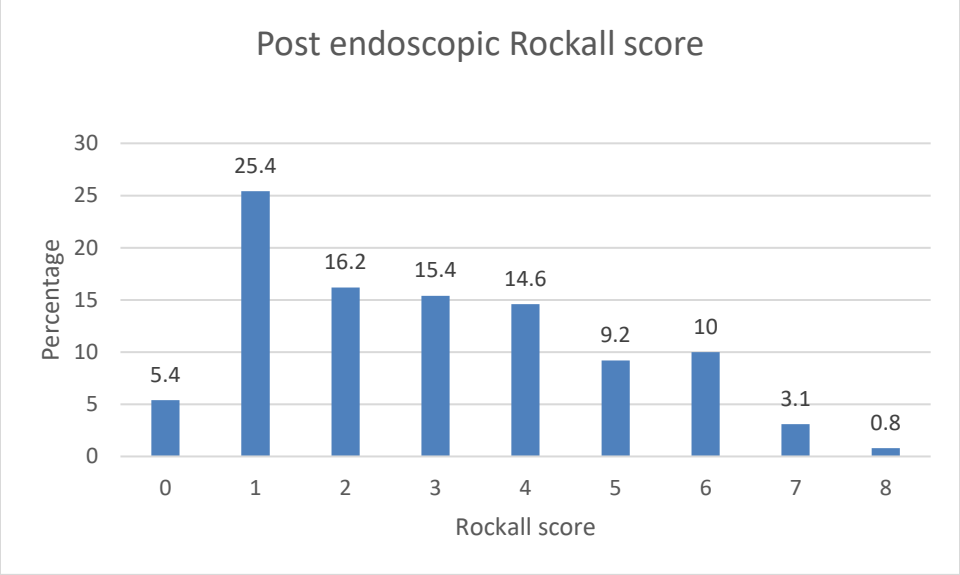

Figure 4: Distribution of study patients by post endoscopic Rockall score

5.6 Management

All patients had medical management consisting of blood transfusion, fluid resuscitation, PPIs, antibiotics, vasoactive medication or endoscopic interventions. Two patients (1.3%) underwent surgery to control bleeding.

5.6.1 Blood transfusion requirement

Sixty-five (43.3%) patients had blood transfusion during their hospital stay. The mean number of units of blood transfused was 1.98 ± 0.94. As shown in table 14 below, the median number of units transfused was 2.0 with an interquartile range of 1-3 units.

Following transfusion, 81.6 % of those transfused had check Hb and the median post transfusion Hb level was 7.44 g/dl (interquartile range of 6.5-8.4g/dl.)

Table 11: Pre-transfusion and Post Transfusion Hemoglobin levels and number of units of blood transfused in the study patients

	Endoscopy	No Endoscopy	p-value
Blood transfusion			
Yes	61 (46.9)	4 (20.0)	0.024
No	69 (53.1)	16 (80.0)	
Hb before transfusion			
2.0 – 3.9	16 (25.0)	2 (50.0)	0.666
4.0 – 5.9	28 (43.8)	2 (50.0)	
6.0 – 7.9	16 (25.0)	0 (0.0)	
8.0 +	4 (6.3)	0 (0.0)	
Number of units given			
1	22 (36.1)	2 (50.0)	1.000
2	22 (36.1)	1 (25.0)	
3	12 (19.7)	1 (25.0)	
4	5 (8.2)	0 (0.0)	
Repeat Hb transfusion			
3.0 – 4.9	5 (10.0)	1 (33.3)	0.620
5.0 – 6.9	10 (20.0)	0 (0.0)	
7.0 – 8.9	25 (50.0)	2 (66.7)	
9.0 – 10.9	7 (14.0)	0 (0.0)	
11 +	3 (6.0)	0 (0.0)	

5.6.2 Management at Endoscopy

At endoscopy, 48 (36.9%) patients had endoscopic therapy. Band ligation was the commonest form of treatment in variceal bleeding while injection therapy with use of diluted adrenaline in combination with use mechanical clips / thermal therapy was used in cases of non -variceal bleeding. The distribution of patients by endoscopic therapy is as shown in table 12 below.

Table 12: Distribution of patients by Treatment at Endoscopy

	Frequency (n)	
	Variceal	**Non- variceal**
Injection	2	13
Banding	33	0
Injection and banding	3	0

5.6.3 Distribution of Patients by Pharmacological therapy given

Overall, the commonest form of pharmacological therapy given following presentation was proton pump inhibitors. However, following endoscopy it was revealed that only 22 (51.1%) of those who were found to have peptic ulcer disease were on proton pump inhibitor therapy prior to endoscopy. Among patients with variceal bleeding, 14 (27.5%) received antibiotics and 2, (3.9%) received a vasopressin analogue.

The distribution of patients by pharmacological treatment given following admission is as shown in Table 13 below

Table 13: Distribution of patients by Pharmacological treatment

	Frequency n (% of cases)	
	Variceal	**Non-variceal**
Antibiotics	14(27.5)	28(39.4)
PPIs	34(66.7)	65(82.2)

H2RA	2(3.9)	8(10.1)
Somatostatin	2(3.9)	2(2.5
Terlipressin	2(3.9)	0
Propranolol	27(52.9)	0
Others	24(47.1)	41

5.7 Outcome

The length of hospital stay ranged from 1 to 35 days with a median length of hospital stay of 9 days with interquartile range of 12 days.

Table 14: Distribution of patients by length of hospital stay

	Endoscopy	No endoscopy	p- value
Length of hospital stay			
1 day	5 (4.1)	0 (0.0)	0.782
2 – 10 days	66 (53.7)	4 (66.7)	
11 – 19 days	32 (26.0)	2 (33.3)	
Above 19 days	20 (16.3)	0 (0.0)	

Patients were followed up to 14 days following discharge. Overall, there was control of bleeding in 145, (96.7 %) of patients. Re-bleeding occurred in 14 (9.3%) of patients and 11 (7.3%) patients died within the period of two weeks after discharge from hospital. Eight patients were lost to follow up. Table 18 below shows distribution of patients by outcomes at 14 day follow up.

Table 15: Outcome: 14 days follow up

	Frequency n (%)		
	Variceal n=51	**Non- variceal n=79**	**Endoscopy not done n=20**
Patient status: Alive	49(96.1)	75(94.9)	15(95)
Control of bleeding	49(96.1)	77(97.5)	19(100)
Failure to control bleeding	1(1.96)	2(2.53)	1(5)
Re-bleeding	7(13.7)	5(6.3)	2(10)
Surgery performed to control bleeding	0	2(2.53)	0

Table 16: Distribution of patients' outcome at 14 days follow up by time to endoscopy

	Time to endoscopy	
Outcome	**Within 24 hours (n=19)**	**Beyond 24 hours (n=111)**
Patient status: Alive	18 (94.7)	106 (95.5)
Control of bleeding	19(100)	108(97.3)
Failure to control bleeding	0	3 (2.7)
Re-bleeding	0	12 (10.8)
Surgery performed to control bleeding	0	2(1.8)

A chi-square test for association was conducted between the time to endoscopy and the outcome of the patient. There was no statistically significant association between the time to endoscopy and outcome of the patient, $\chi 2$ (2) = 1.032, p = .597.

Table 17: Distribution of patients' outcome at 14 days follow up by dosage of PPI given

PPI	**Frequency (n)**			**Total**
	Alive	**Dead**	**Unknown**	
80mg	34	2	1	37
40mg	53	3	2	58
Total	**87**	**5**	**3**	**95**

A chi-square test for association was conducted between the dosage of Omeprazole given and the outcome of the patient. There was no statistically significant association between the dosage and outcome of the patient, $\chi 2$ (2) = 0.043, p = .979

Table 18: Factors associated with Re-bleeding outcome

	Re-bleeding	No Re-bleeding	OR (95% CI)	p-value
Age				
≤60 years	9 (64.3)	96 (83.5)	Ref	
>60 years	5 (35.7)	19 (16.5)	2.807 (0.846 – 9.309)	0.081
Varices				
Non variceal	6 (42.9)	84 (73.0)	Ref	
Variceal	8 (57.1)	31 (27.0)	3.613 (1.160 – 11.250)	0.030
Blood transfusion				
Yes	10 (71.4)	50 (43.5)	3.250 (0.963 – 10.972)	0.086
No	4 (28.6)	65 (56.5)	Ref	
Ascites				

Yes	4 (28.6)	3 (2.6)	14.933 (2.924 – 76.274)	0.003
No	10 (71.4)	112 (97.4)	Ref	
INR				
≤1.5	11 (78.6)	102 (88.7)	Ref	
>1.5	3 (21.4)	13 (11.3)	2.140 (0.527 – 8.686)	0.381
Albumin				
≤35	14 (100.0)	87 (75.7)	Ref	
>35	0 (0.0)	28 (24.3)	-	0.039
Co-morbidity				
Yes	11 (78.6)	44 (38.3)	5.917 (1.564 – 22.390)	0.004
No	3 (21.4)	71 (61.7)	Ref	

Table 20: Factors associated with mortality outcome

	Alive	Dead	OR (95% CI)	p-value
Age				
≤60 years	103 (82.4)	3 (60.0)	Ref	
>60 years	22 (17.6)	2 (40.0)	0.320 (0.051 – 2.032)	0.229
Varices				
Non variceal	86 (68.8)	5 (100.0)	Ref	
Variceal	39 (31.2)	0 (0.0)	-	0.321
Endoscopy done				
Yes	122 (97.6)	4 (80.0)	10.167 (0.858 – 120.509)	0.147
No	3 (2.4)	1 (20.0)	Ref	
Re-bleeding				
Yes	12 (9.6)	2 (50.0)	0.106 (0.014 – 0.824)	0.058
No	113 (90.4)	2 (50.0)	Ref	
Blood transfusion				
Yes	58 (46.4)	2 (40.0)	1.299 (0.210 – 8.041)	1.000
No	67 (53.6)	3 (60.0)	Ref	
Albumin				
≤35	97 (77.6)	5 (100.0)	Ref	
>35	28 (22.4)	0 (0.0)	-	0.584
SBP				
≤100	27 (21.6)	2 (40.0)	Ref	
>100	98 (78.4)	3 (60.0)	2.420 (0.385 – 15.224)	0.310
Co-morbidity				
Yes	51 (40.8)	5 (100.0)	-	0.013
No	74 (59.2)	0 (0.0)	Ref	
Rockall score				
≤4	100 (80.0)	1 (20.0)	Ref	
>4	25 (20.0)	4 (80.0)	0.063 (0.007 – 0.584)	0.009

6.0 DISCUSSION

This study found that the commonest endoscopic diagnosis in patients with UGIB was variceal bleeding (39%), followed by peptic ulcers (25.4%) and erosive diseases (20.7%). These findings are similar to previous studies conducted in Kenya as well as other regions of SSA have also demonstrated that variceal bleed is the commonest cause of UGIB [18,21,22,24]. The presumptive causes of gastro- esophageal varices in our set up are pipe-stem fibrosis secondary to Schistosoma mansoni infection which is common in surrounding areas of Nairobi (Eastern region of Kenya), liver cirrhosis secondary to chronic Hepatitis B infection and probable cryptogenic cirrhosis. Although, this study did not evaluate the cause of varices, it was found that the most common underlying disease was chronic liver disease that was reported in 11.3 % of study patients. However, the cause of liver disease was not evaluated. There was a statistically significant association between low albumin, presence of splenomegaly and endoscopic diagnosis of varices (p=0.041, 0.013 respectively)

The M: F ratio was 2.8:1. This higher male preponderance has been found in studies [11,12,18,20] done in other parts of Africa as well as in developed countries and can be explained by higher prevalence of risk factors such as occupations at high risk of Schistosomiasis infection among males, alcohol and intravenous drug abuse. Peptic ulcer disease which is the commonest cause of UGIB in the west was the second most common cause in our study accounting for 25% of all cases, where duodenal ulcer was more common than gastric ulcers, consistent with other studies elsewhere. [15,18] The increased prevalence of PUD in the west has been attributed to higher life expectancy with increased use of non-steroidal inflammatory agents, oral anticoagulant and antiplatelet therapy due to cardiovascular diseases among those at an advanced age (>65years). Intake of NSAIDS was reported in 24.6% of patients within one month of presentation with UGIB. A chi-square test revealed a significant association between use of NSAIDs and endoscopic diagnosis of PUD (p=0.010).

Though the study did not seek to identify reasons for NSAID use, possible reasons would include pain, febrile illnesses and aspirin for cardiovascular disease prevention. Erosive disease was the third most common cause of UGIB (17.6%). These erosive diseases could have been as a result of portal hypertension as well as peptic related mucosal changes. If this category of patients were considered to have peptic related mucosal changes, then PUD would have been considered as the major cause of UGIB in our set up (42.9%).

In Kenya, there are few public centers offering endoscopy services. Most patients with UGIB in the peripheral regions are transferred to referral hospitals such as KNH for Esophago-gastroduodenoscopy services. The referral might have contributed to the delay in presentation as 55.3% had hypotension and 24% had severe anemia at admission. Guidelines recommend endoscopy to be performed within 24 hours. [25,27,33] Patients in this study had a long duration to endoscopy with median period of 5 days, IQR (1-7 days). The major possible factors contributing to delay in getting upper GIT endoscopy done may have been financial constraints and large number of patients requiring endoscopy as the endoscopy unit caters to all KNH patients (surgical, medical, in patient and outpatients) requiring endoscopy. However, in this study, duration to endoscopy had no influence on outcome of patients. No source of bleeding was identified in 19.2% of patients who underwent endoscopy and this might have been as a result of a prolonged period to endoscopy as mucosal lesions such as Mallory Weiss tears heal quickly with re-epithelization.

Among those with anemia, guidelines recommend transfusion to a target Hb level of 7-9g/dl. [25,29] .In our study, 59% of patients had HB < 7g/dl at admission, while only 43% of all study patients received transfusion and the mean number of units transfused was 1.98 ± 0.94. The median post-transfusion level of hemoglobin among those transfused was 7.44 g/dl IQR (6.5-8.4g/dl). The picture portrays the difficulty experienced in obtaining blood and its products in our set-up.

Prior to endoscopy, therapy should be initiated with intravenous proton pump inhibitors for those suspected to have peptic ulcer bleeding and use of antibiotics, vasopressor medication in those suspected to have varices [35]. Prior to endoscopy, empirical therapy with drugs was initiated according to most likely diagnosis from history and physical examination findings. In general, PPIs were prescribed in majority of the study patients (76.3%). Following endoscopy, it was found that 22 (51.1%) of the patients diagnosed to have peptic ulcer disease at endoscopy had already been initiated on proton pump inhibitor therapy. In addition, the commonest PPI dosage given was 40mg twice daily (52%) in contrast to guidelines that recommend a bolus of 80mg followed by an infusion at 8mg/hr. This study showed that there were no differences in outcome among patients who received low dose of PPI compared to high dose PPI similar to findings reported elsewhere [55] . Among those with varices, it was noted that only 14 (27.5%) received

antibiotics while only 2(3.9%) of patients received vasopressors. These shortcomings in management might have been influenced by availability and affordability of medication, a low index of suspicion of probable causes among primary physicians as well as lack of management protocols in our set-up.

Spontaneous cessation of bleeding with medical therapy occurs in 40% of patients with variceal bleeding as compared to 80% in non-variceal bleeding. [49,54] Only 4 patients who had PUD at endoscopy had high risk lesions (Forrest I and 2A) and these patients received adrenaline injection therapy in combination with either mechanical clips or thermal therapy. As varices were the commonest cause of UGIB, the commonest form of endoscopic treatment was band ligation in tandem with guidelines on management of variceal bleeding. This is because studies have shown better outcomes with band ligation when compared to other forms of treatment. [50]

The mean length of hospital stay was 12.07 ±11.08 number of days. This is a longer duration of hospital stay compared to the west with a mean duration of hospital stay of 2.8 days [56]. It is likely that this was a result of challenges in management such as obtaining blood products and financial constraints as patients are required to pay prior for endoscopy services with additional charges for purchase of bands in cases of variceal bleeding.

Patients were followed up to 14 days following discharge so as to ascertain outcome. 97.3 % of patients had control of bleeding, 9.3% of patients were classified as having re-bled. and 4 patients (2.7 %) had failure to control bleeding with 2 of these patients undergoing surgery. 11 (7.3%) patients died during period of study, five of whom died prior to endoscopy. A possible explanation for our low mortality and re-bleeding rate is a smaller sample size and shorter duration of follow up. Though our sample size was small we attempted to identify factors associated with re-bleeding and mortality. Mortality was associated with post endoscopic Rockall score >4 ($p= 0.005$) and presence of a comorbidity ($p=0.032$). Re-bleeding was associated with varices ($p=0.02$), presence of a comorbidity($p=0.004$) and low albumin < 35g/dl. ($p=0.037$).

6.1 CONCLUSION

Gastro-esophageal varices were the most common cause of upper gastrointestinal bleeding at endoscopy consistent with other studies carried out in SSA. It is likely that there were challenges in access to endoscopy and in obtaining blood products and this was reflected in long duration of hospital stay and time to endoscopy. In comparison to other regions in SSA there was a lower re-bleeding and mortality rate. This could have been due to a smaller sample size and shorter duration of follow up. However, in comparison to previous study carried out in KNH over 2 decades ago, outcomes remained largely unchanged.

6.2 STUDY LIMITATIONS

This was a single center study therefore results may not be reflective of general population.

The study was carried out over a short period of time and subject to seasonality of some causes of UGIB.

Survival bias as some patients died prior to endoscopy however demographic and clinical information of these patients was recorded.

6.3 RECOMMENDATIONS

In order as to improve outcomes, it is recommended that a protocol is established on management of patients presenting with UGIB in accordance to guidelines.

Patients should be stratified according to risk of mortality and re-bleeding and that measures are put in place so as to ensure endoscopy is performed within 24 hours of presentation among this subset of patients with closer follow up.

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1: CONSENT FORM – ENGLISH

Informed consent form for Causes, management and short-term outcomes of upper gastrointestinal tract bleeding at Kenyatta National Hospital

Principal Investigator: Dr. Olivia Nduku Kyeni

Department of Clinical Medicine and Therapeutics

Resident, University of Nairobi.

Causes, management and short-term outcomes of upper gastrointestinal tract bleeding at Kenyatta National Hospital

Introduction

I am undertaking a study titled 'Causes, management and short-term outcomes of upper gastrointestinal tract bleeding at Kenyatta National Hospital'.

This form is to give you the information you need before deciding if you want to participate in this study. As you read this form you may ask any questions on what you do not understand.

Purpose of Research

We would like to investigate the causes and outcomes of acute upper gastrointestinal tract bleeding at Kenyatta National Hospital. We will be recording what has caused you to bleed, what interventions you receive and how you will be doing up to 14 days later. This is in order to improve treatment of patients with this condition. We will need to obtain a clinical history from you as well as conduct a physical examination. We will also access your clinical information from the file to find out your clinical condition and diagnosis from the file.

Procedures involved

1. Sign a consent form
2. Respond to questions on your socio-demographic details and clinical history.
3. Obtain information from your medical file including physical examination findings, and laboratory results
4. Endoscopy will be carried out so as to find out cause of bleeding and to stop bleeding. You should not have eaten at least eight hours prior to endoscopy. At endoscopy, you will be laid on your left side and a spray given to numb your throat. You will also be given medication to help you relax while staying awake during the procedure. The doctor will then insert a tube down your throat up to the upper intestines while looking for any abnormalities. The cause of bleeding and interventions done to stop bleeding will be recorded.
5. Your progress will be assessed while in the ward and up to 2 weeks following your bleeding episode.

Your rights

i) Your participation in this research is voluntary.
ii) You will not be victimized if you refuse to participate in this study.
iii) If you choose to participate and not answer certain questions, you are free to do so.
iv) You are free to terminate the interview and withdraw from the study at any time.
v) You are free to ask questions before signing the consent form.
vi) All the results will remain confidential. Your individual responses will be stored in a locked place under my control and will only be seen by my statistician and me.

Risks and costs

There are no risks or costs to be incurred by participating in this study.

Benefits

Information obtained will improve knowledge to health care givers on the causes and outcome of upper gastrointestinal tract bleeding and how to improve the management of patients with such at the Kenyatta National hospital.

If you have any questions later, do contact:

1. Dr. Olivia Nduku Kyeni

   Tel 0720281103

2. The Chairman, Kenyatta National Hospital/University of Nairobi Ethics and Research Committee

   College of Health Sciences

   P. O. Box 19676 Code 00202 Nairobi

   Tel. (254-020) 2726300-9 Ext 44355

   E-mail: uonknh_erc@uonbi.ac.ke

   Chairperson: Professor K.M. Bhatt

   Contact person: Esther Wanjiru Mbuba

Certificate of consent

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent voluntarily to participate as a participant in this research**.**

Print Name of Participant_____ Signature _____

Left thumbprint of subject_____ Date_____

INVESTIGATOR'S STATEMENT:

I, the Principal Investigator, have fully informed the research participant on the purpose and implication of this study.

Signed: ..... Date: _____

APPENDIX 2: DATA CAPTURE FORM

STUDY ID NO……. **DATE……..**

SECTION 1: DEMOGRAPHICS

a) IP No:
b) Age:
c) Sex:
d) Home residence:
e) Contact:

SECTION II CLINICAL HISTORY

a) Indicate if patient presented with any of the following prior to admission:

-hematemesis (vomiting fresh or altered blood)

-melena (black stool)

-hematochezia (fresh blood in stool)

b) Has there been previous history of hematemesis, melena or hematochezia? Y☐ N ☐

If yes, what treatment was given?

c) Does the patient suffer from any of the following? Tick alongside where applicable:

- Cardiac disease
- Pulmonary disease
- Renal disease
- Liver disease
- Malignancy
- Diabetes

d) Is there history of alcohol intake? Y ☐ N ☐

If yes, indicate frequency and duration of alcohol intake

e) Medication history: Indicate if patient has been on any of the following drugs within past month:

	Drug	Dose	Duration
NSAIDs			
COX 2 Inhibitor			
Antiplatelet medication			
Anticoagulant			
SSRIs			
Biphosphonates			
Corticosteroids			
Prophylaxis -PPIs, H2RAs, prostaglandins			
Prophylaxis- Propranolol, EVL			

SECTION III PHYSICAL EXAMINATION

Pallor

Vital signs: BP:

Pulse:

Abdominal examination

- Ascites:

- Size of liver:
- Size of spleen:

Mental status examination: Hepatic Encephalopathy grading:

Lab results at admission

Hb:

Platelets:

INR:

LFTs:

Date and time of Admission (if admitted)

Treatment given

Intravenous fluids

Blood transfusion:

- Hb before transfusion
- Number of units given
- Check Hb after transfusion

	Name of Drug used	Date started	Duration	Dosage	Route of administration
Antibiotics					
PPIs					
H2RA					
Somatostatin					
Terlipressin					
Propranolol					
Others:					

Endoscopy

Time to endoscopy:

Diagnosis:

14-day follow up: Tick where applicable

- Is the patient alive? ☐ Or Dead? ☐ If dead, indicate date of death……..
- Following endoscopy, was there: Control of bleeding? Y ☐ N ☐

  Failure to control bleeding? Y ☐ N ☐

  Re-bleeding? Y ☐ N☐ Date of re-bleed…….

- Was surgery performed to control bleeding? Y ☐ N ☐
- Length of hospital stay in days from admission to discharge or death: ……

APPENDIX 3: ENDOSCOPY RESULT FORM

Date and Time:

Findings:

For PUD:

Location:

Please tick :

APPENDIX 4 :FORREST CLASSIFICATION

Grade		Signs observed on endoscopy	
I	Ia	Spurting hemorrhage	
	Ib	Oozing hemorrhage	
II	IIa	Visible vessel	
	IIb	Adherent clot	
	IIc	Flat pigmented hematin or ulcer base	
III	IIIa	Lesions without sign of recent hemorrhage or fibrin-covered clean uler base	

Variceal Bleeding

Location:

Grading according to size: For esophageal varices: Please tick

APPENDIX 5: GRADING OF ESOPHAGEAL VARICES

Absent	
Grade 1: small straight varices not disappearing with insufflations	
Grade 2: medium varices occupying less than one third of lumen	
Grade 3: large varices occupying more than one third of lumen	

For gastric varices, please tick:

APPENDIX 6: SARIN CLASSIFICATION OF GASTRIC VARICES

• GOV 1- esophageal varices that extend below gastro esophageal junction and along lesser curvature of stomach	
• GOV 2- esophageal varices that extend beyond the gastroesophageal junction into fundus of stomach	
• IGV 1- varices located in fundus of stomach	
• IGV 2- varices located anywhere else in the stomach	

High risk stigmata: Please tick:

APPENDIX 7 : ENDOSCOPIC HRS IN VARICEAL BLEEDS

Red wale marks	Longitudinal red streaks	
Cherry red spots	Cherry red spots	
Hemocystic spots	Raised discrete red spots, “blood blisters”	
Diffuse erythema	Diffuse red color	

Treatment carried out at endoscopy, if any:

- Injection with drug (Adrenaline)- dose
- Thermal
- Mechanical clips
- Ligation of varices
- Sclerotherapy

APPENDIX 8: ROCKALL SCORE

Item indicators	Categories	Criteria	Score
Age (years)	<60		0
	60-79		1
	>80		2
Shock	No Shock	SBP > 100 mm Hg Pulse < 100/min	0
	Tachycardia	SBP > 100 mm Hg Pulse > 100/min	1
	Hypotension	SBP < 100 mm Hg	2
Comorbidity	No major comorbidity		0
	Cardiac failure		2
	Ischemic heart disease		3
	Any major comorbidity		
	Renal or liver failure		
	Disseminated malignancy		
Diagnosis	Mallory Weiss tear, no lesion identified and no SRH/blood		0
	All other diagnoses		1
	Malignancy of upper GIT		2
Major SRH	None or dark spot only		0
	Blood in upper GIT, adherent clot, visible or spurting vessel		2