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Millennium Medical College**
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Department of Internal Medicine

Graduate Study Program

Prevalence and associated factors of non-variceal upper gastrointestinal bleeding among Cirrhosis patients on follow up at Gastroenterology and hepatology follow up clinic, St. Paul's Hospital Millennium Medical College (SPHMMC), from December 2020 to December 2023: A cross-sectional study.

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Addis Ababa, Ethiopia

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Acronyms and Abbreviations

AD: Acute decompensation

AUGIB: Acute upper gastrointestinal bleeding

CBC: complete blood count

CKD: Chronic kidney disease

CLD: Chronic liver disease

CPT: Child Pugh Turcotte

DL: Dieulafoy lesions

DM: Diabetes mellites

EV: Esophageal varices

GIB: Gastrointestinal bleeding

GVE: Gastric vascular ectasia

HCC: Hepato-cellular carcinoma

HCT: Hematocrit

HF: Heart failure

Hg: Hemoglobin

INR: International normalizing ratio

LFT: Liver function tests

LGIB: Lower gastrointestinal bleeding

MELD: Model for end-stage liver disease

NSAID: Nonsteroidal anti- inflammatory drugs

NVGIB: Non-variceal gastrointestinal bleeding

NVUGIB: Non-variceal upper gastrointestinal bleeding

PHG: Portal hypertensive gastropathy

PPI: Proton pump inhibitors

PUD: Peptic ulcer disease

RFT: Renal function test

SPHMMC: St. Paul's Hospital Millennium Medical College

UGIB: Upper gastrointestinal bleeding

Abstract

Background: Liver cirrhosis is a pathologic entity defined as diffuse hepatic fibrosis with the replacement of the normal liver architecture by nodules. One complication of cirrhosis is upper gastrointestinal bleeding, which could be classified as variceal or non-variceal bleeding. Non-variceal bleeding is reported in frequency of 24% - 42% and associated with a mortality of around 15%-30% and remains a significant cause of emergency admissions. Understanding the prevalence, and the factors associated with non-variceal bleeding can help in decreasing the incidence as well as improve clinical outcome of patients.

Objective: The aim of this study is to assess the prevalence of Non-variceal upper gastrointestinal bleeding and associated factors among cirrhosis patients at gastroenterology and hepatology follow up clinic in SPHMMC, Addis Ababa, Ethiopia.

Methods: A Hospital based cross-sectional study was conducted from December, 2020 to December, 2023. A total of 234 patients were taken into study. A structured checklist prepared in English language to collect data was used. The collected data was analyzed using Statistical Package for Social Sciences (SPSS) version 26.0. Mean, standard deviations and percentages were calculated and presented with table. Bivariable and multivariable logistic regression model was used to assess association between dependent and independent variables. Adjusted odds ratio with a 95% confidence interval was used to estimate the strength of association and level of statistical significance was declared at p value <0.05 .

Results: The prevalence of Non-Variceal Upper Gastrointestinal bleeding (NVUGIB) is 31.6% (95% Confidence Interval 26% - 37.8%). Longer duration of Cirrhosis ($p = .03$ AOR = 1.01, 95% CI [1.001-1.019], and the presence of comorbid conditions such as Retroviral infection ($p < .001$, AOR = 51.72, 95% CI [5.65-471.8]) were strong predictors of Non-variceal upper gastrointestinal bleeding, whereas patients with relatively older age ($p = .007$, AOR = 0.96, 95% CI [0.93-0.99], patients with Hepatitis C virus ($p = .009$, AOR = .118, 95% CI [.05-.66], and Schistosomiasis ($p < .001$, AOR = 0.34, 95% CI [0.01-0.19]) as the cause of cirrhosis, patients with prior use of Beta blockers ($p = .005$, AOR = 0.32, 95% CI [0.14-0.70]), and with higher International Normalized ratio (INR) ($p = .014$, AOR = 0.57, 95% CI [0.36-0.89], were less

likely to develop Non-variceal upper gastrointestinal bleeding as compared to Variceal bleeding. In addition, patients with Non-variceal Upper gastrointestinal bleeding had a relatively lower Systolic Blood Pressure (SBP) measurements at presentation ($p = .010$, AOR = 0.97, 95% CI [0.95-0.99]), however they had lesser requirement of blood products ($p = .009$, AOR = 0.25, 95% CI [0.08-0.71]).

Conclusion: Non-variceal upper gastrointestinal bleeding is an important cause of morbidity and mortality in patients with cirrhosis. Factors such as a longer duration of cirrhosis, younger age, Presence of comorbidities such as Retroviral infection are highly associated with development of Non-variceal upper gastrointestinal bleeding, while use of Beta-blockers, relatively higher International Normalized ratio are negatively associated. Methods to screen and identify those at risk and taking preventive measures is recommended in order to minimize its burden.

Key words: Cirrhosis, Non-variceal Upper gastrointestinal bleeding in cirrhosis, Upper gastrointestinal bleeding, peptic ulcer

1 Introduction

1.1 Background of the study

Chronic liver diseases (CLDs) are persistent inflammatory conditions of the liver in which the biochemical and histopathological abnormalities of the liver are present over a long period of time. It consists of a wide spectrum on a continuum between chronic hepatitis, cirrhosis and hepatocellular carcinoma(1).

Liver cirrhosis is a significant cause of morbidity and mortality, being the 14th most common cause of death worldwide (2). It is characterized by fibrosis and nodule formation of the liver secondary to chronic injury, leading to alteration of the normal lobular organization of the liver. It has different etiologies including viral hepatitis (hepatitis B, hepatitis C), alcoholic liver disease, Non-alcoholic steatohepatitis, autoimmune, toxic, metabolic, genetic and other causes (2,3) Among the many symptoms that cirrhosis patients may experience, common ones are abdominal distention, jaundice, exhaustion, right upper quadrant pain, loss of appetite, weight loss, and changes in mentation. (4)

Gastrointestinal bleeding (GIB) is one complication among patients with cirrhosis, which is a significant cause of morbidity and mortality. Upper gastrointestinal bleeding (UGIB) refers to a source of bleeding proximal to the ligament of Treitz(5). It might present as hematemesis or hematochezia with unstable hemodynamic parameters, or as chronic blood loss with melena. Gastrointestinal bleeding accounts for up to 15-30 % of overall mortality in patients with cirrhosis(6).

In patients with Cirrhosis, GI bleeding can be classified as variceal or non-variceal bleeding based on the source of the blood loss. Non-variceal upper gastrointestinal bleeding (NVUGIB) is bleeding that develops in the esophagus, stomach or proximal duodenum, and it accounts for about 24%-42% , and of this majority is due to gastroduodenal ulcers. Other causes include esophagitis, portal hypertensive gastropathy (PHG), Gastric Vascular Ectasia (GVE), Mallory-

Weiss tear, gastro-duodenal erosions, dieulafoy lesions and others(7,8). In patients with NVUGIB the common risk factors identified are, consumption of Non-steroidal anti-inflammatory drugs (NSAIDS), hypoalbuminemia, presence of significant ascites, advanced liver disease and increased International normalized ratio (INR), and alcohol consumption(9–11).

The standard procedure for both the diagnosis and treatment of UGIB is an emergency upper gastrointestinal endoscopy. The recommended course of treatment for patients with cirrhosis who have UGIB consists of careful resuscitation, preferably in an intensive care unit, medical and endoscopic therapy, early consideration for placement of a transjugular intrahepatic portosystemic shunt (TIPS), and, occasionally, surgical treatment or hepatic transplant. Band ligation of varices is the preferred endoscopic therapy for esophageal variceal hemorrhage, and sclerosing agents like Cyanoacrylate is injected to alleviate bleeding from stomach varices. Both vasoactive medications and antibiotics are started prior to or concurrently with endoscopy(12).

Common endoscopic treatments for active peptic ulcer bleeding includes local injection of drugs (e.g. adrenalin sodium chloride solution) and clip closure(13). Acid suppression agents like proton pump inhibitors (PPI) should also be used concomitantly(14). The treatment options for significant PHG include nonselective β blockers, TIPS, or surgical shunts, as well as endoscopic therapy in the form of cauterization or injection sclerotherapy, whereas the mainstay of therapy in GVE is endoscopic ablation of the lesions(12).

In Ethiopia, chronic liver disease (CLD) is the 7th leading cause of death, accounting for about 24 deaths per 100000 populations, with Hepatitis B virus, alcohol, and hepatitis C virus being the three most common etiologies accounting for a pooled estimate of 40.0%, 17.0% and 15.0%, respectively (15). Despite GIB being a common complication of cirrhosis, published data on prevalence and associated factors are limited in Ethiopia, to the researcher's knowledge.

A great number of researches have been done on variceal GI bleeding world wide so far, but data on NVGIB still remains limited, and this is a field to be widely investigated.

1.2 Statement of the problem

UGIB is one of the common medical emergencies in patients with cirrhosis, and among top causes of mortality with fatality reaching 15-30 %. It also causes a significant burden on financial and health care resources(6).

Some of the complications of GIB include chronic iron deficiency anemia, aspiration pneumonia with consequences of respiratory failure, Acute kidney injury from hypovolemia, worsening of liver function, increased susceptibility to spontaneous bacterial peritonitis and increased risk of hepatic encephalopathy(11).

However, in the actual world, emergency EGD is rarely offered in most hospitals since it's challenging to set up emergency services during non-working hours, there aren't enough skilled endoscopists and medical teams, and there isn't enough equipment. This means that at the centers with facilities, the majority of patients are often treated medically for a while before being referred for EGD(16).

Different literatures have shown variable prevalence of NVUGIB, which has ranged from 24.5%-56.93%. Most of these literatures have implied peptic ulcer is the most common etiology. (8). In most of these studies, Child Pugh A and Child Pugh B cirrhosis were shown to have increased incidence of NVUGIB(8,17), whereas in some studies advanced liver disease with Child-Pugh C was found to be associated with increased risk of bleeding, especially with ulcers (18). Use of ulcerogenic medications like NSAIDS were reported in greater association with NVIUGIB as shown in most studies(16,17). Some of the studies did not further extensively study the types of NVUGIB and associated factors (19). Hence, further studies and clarification is needed on the prevalence and associated factors.

In Ethiopia, studies have been done in assessing all causes of UGIB, including patterns and outcomes with associated factors. However, data on NVUGIB among cirrhotic patients is scanty, to the researcher's knowledge, and therefore, this is an area to be widely navigated.

1.3 Significance of the study

Studying the prevalence and associated factors associated with NVUGIB in patients with cirrhosis will give us a better knowledge on the overall burden of the problem and better assessment of risk factors and complications.

It will be used to generate information that can be used to study the nature of the problem and to formulate proper measures to be taken. It will aid with further patient management, to take preventive measures, and work with policy makers to develop a strategic guideline for management of these group of patients, with the aim of decreasing the overall burden.

It is the first research to be done in this particular topic at St. Paul's Hospital Millennium Medical College and it can further be used as basis in doing more research in this area.

2 Literature review

2.1 Gastrointestinal bleeding (GIB) in cirrhosis

GIB is one of the common presentations among patients with cirrhosis and is a significant cause of morbidity and mortality. A systematic review of 118 studies done through MEDLINE showed a mortality of 57% per year for patients with decompensated cirrhosis and GIB compared to those with decompensated cirrhosis without GIB (20% annual risk)(20).

The significant burden of GIB in cirrhotic patients was further demonstrated in a Review of Non-variceal Gastrointestinal Bleeding in Patients with Liver Cirrhosis that was done in 2012 through data base searching, and it showed that GI bleeding accounted for 25% of overall mortality in cirrhotic patients, and is associated with life threatening complications like spontaneous bacterial

peritonitis especially with presence of ascites, due to translocation of gut microbes and reduced complement activity in ascitic fluid. Acute kidney injury is another complication, either related to acute tubular necrosis or hypovolemia or due to hepatorenal syndrome. Aspiration pneumonia and respiratory failure is also another significant complication identified(11). Renal failure, rebleeding, hepatocellular carcinoma, hepatic encephalopathy, and bacterial infection are independent risk factors for mortality(11).

In a multi-centered study done in France that compared cirrhotic and non-cirrhotic patients presenting with UGIB, 21.9% were cirrhotic. Emergency hospital admissions for UGIB in the cirrhotic group were significantly higher than the non-cirrhotic group (80.6% vs. 52.8%), and age was relatively younger in cirrhotic group. The most frequent source of bleeding identified in the cirrhotic patients was esophageal or gastric varices (59.1%), whereas in noncirrhotic patients, it was found to be peptic ulcer with incidence of 41.8%, which was found in 15.7% of cirrhotic patients. Mortality was also found to be higher in the cirrhotic patients (23.5% vs. 11.2%)(21).

In a study conducted in china with screening of 492 patients with cirrhosis, UGIB was reported in 34.6% of acute decompensation of liver failure and in 37.5% of patients with acute on chronic liver failure. Previous GI bleeding, and greater INR were associated with increased risk of GIB(22).

A prospective cohort study was conducted in a tertiary hospital in Tanzania in 2017, of patients presenting with UGIB. 170 patients participated in this study, and presence of chronic liver disease was the highest among the co-morbidities accounting for 52 patients (30.6%) (23). Another prospective cohort study done in Rwanda of 194 patients presenting with UGIB, prevalence of cirrhosis was found to be around 18% (24).

In one study in Ethiopia that was done retrospectively from 2009 - 2014 G.C at SPHMMC in patients from medical wards and ICU, UGIB was found to be the 3rd most common presentation accounting for 10.2%, following abdominal distention and Jaundice.

Another cross-sectional retrospective study done in Ethiopia at St. Paul's Hospital Millennium Medical College (SPHMMC) in 2018, that assessed the pattern and outcome of UGIB in all

patients, Liver disease was found to be the most common co-morbidity found in 74 patients (57.8%) (25). Further subgroup analysis was not included in this study.

2.2 NVUGIB in cirrhosis

A hospital-based study in Thailand that was conducted from June 2006 – December 2007 studied the source of bleeding in 261 patients presenting with UGIB. Among those, eighty-two patients were either previously diagnosed with cirrhosis or had signs of chronic liver disease; however, only 40 (49%) of these patients had variceal bleeding, the remaining accounting for non-variceal bleeding(16).

A study published on 2011 that was conducted in a tertiary care hospital in Mexico, among a total of 2,217 patients with UGIB, and 1,077 patients were diagnosed with NVUGB. Of those, 160 (15%) of them were patients with CLD. Further prospective analysis of these patients showed gastroduodenal ulcers were the most frequent source of bleeding (50.6%). The mean age of patients was 56.5 years old with a male predominance (77.5%). Alcohol-induced liver disease was the most frequent etiology (63.8%) and Child-Pugh A and B status were the most frequent (36 and 38%) respectively. One third of the patients had a risk factor associated with peptic ulcer disease including NSAID use and smoking. In this study, cryptogenic etiology of cirrhosis, hypoalbuminemia, and active bleeding at the ulcer base were independent predictive factors of mortality(10).

In Pakistan a hospital based cross-sectional study published in 2016 studied a total of 267 CLD patients presenting with UGIB. It was found that frequency of NVUGIB in these patients was 56.93% (26). The incidence of NVUGIB in this study was almost comparable to the findings of the study conducted in Thailand, however, further analysis of the specific causes and associated factors were not clarified.

In one study done on 108 patients at Czech to assess etiology of UGIB among cirrhotic patients, the results showed most frequent causes of acute bleeding included oesophagus varices (57.4%)

followed by peptic gastric ulcer (13.9%) and peptic ulcer of duodenum (11.1%), then portal hypertension gastropathy (5.6%), gastric varices (4.6%), reflux oesophagitis (2.8%), Mallory-Weiss syndrome (2.8%) and erosive gastropathy (0.9%)(27). This study reflected the most common etiology of NVUGIB in cirrhotic patients is ulcer disease.

Another study published in India in 2016 that was done in 550 cirrhotic patients presenting with acute UGIB, 415 (75.5 %) bled from variceal sources (esophageal and gastric) while 135 (24.5 %) had non-variceal sources. In the NVGIB group, ulcers were found to be the most common cause (40.5%), followed by PHG (37.0%). A significant difference regarding renal function and serum glutamic-oxaloacetic transaminase (SGOT) was found, with SGOT being higher in the variceal group while renal functions were impaired more in the non-variceal group. Child-Pugh A cirrhotic patients were significantly higher in the non-variceal group, while those classified as B and C were significantly higher in the variceal group. Ascites and splenomegaly were significantly higher in the variceal group than the non-variceal group (61.9% Vs. 45.2% and 59.2% Vs. 48.8% respectively)(8)

2.3 Etiologies and factors associated with NVUGIB in cirrhosis

The incidence and prevalence of peptic ulcer disease (PUD) is increased in cirrhosis. A retrospective study done of 1,748 endoscopy showed ulcer prevalence was 6.3%. However, among those, 77.5% of the ulcers were asymptomatic and complications from ulcer were present in 29% of all patients. Asymptomatic ulcers were shown to be more prevalent with advanced disease (18) Despite its high prevalence, peptic ulcer disease only causes UGI bleeding in a relatively small proportion of patients with chronic liver disease in contrast to the general population where it is the most common source of bleeding, with a prevalence ranging between 35 and 53 % (28,29).

In cirrhosis, contrary to the general population, the role of *Helicobacter pylori* (H.P.) remains unclear. In a prospective study, the prevalence and association of PUD with H.P. infection was evaluated in 288 patients with cirrhosis, with a control group of non-ulcer dyspepsia and non-cirrhotic patients with PUD. Peptic ulcer disease presented in 24.3 % of the patients with cirrhosis (22.3 % Child–Pugh A, 21 % Child–Pugh B, 31.3 % Child–Pugh C). The prevalence of H.P. infection was 35.1 % in the cirrhosis group (51.5 % Child–Pugh A, 30.5 % Child–Pugh B, 20 % Child–Pugh C), whereas it was 62.4 % in the non-ulcer dyspepsia group and 73.7 % in the peptic ulcer–non-cirrhotic group(30). H.P. eradication did not protect the patients from ulcer recurrence, with most ulcer relapses occurring in H.P.-negative patients(31).

Other suggested mechanisms for peptic ulcer disease in liver cirrhosis are portal hypertension-induced impairment of the gastric mucosal defenses(32), reduced prostaglandins, decreased gastric acid secretion, elevated serum gastrin concentration, impaired mucus secretion, a reduction in potential difference of the gastric mucosa (30).

The prevalence of acute UGI bleeding from PHG in liver cirrhosis ranges between 2 and 12 % (17,33) compared to 2.5 % in the general population(28). Two forms of endoscopic lesions are described in PHG: mosaiclike pattern lesions and red marks; both are typically located in the gastric body and fundus. Some reports suggest that endoscopic ligation or sclerotherapy of esophageal varices increase the risk of developing PHG(11).

Dieulafoy's lesion (DL) is characterized by exteriorization of a gastrointestinal submucosal arterial vessel, 1–3 mm in diameter, related to a congenital vascular malformation. In a study done in USA, on the association between DL-like bleeding and advanced liver disease in 4,469 cases presenting with UGIB, 954 (20.9 %) had advanced liver disease, and DL was cited as the cause of bleeding in six (0.13 %) of all the cases, of which five had advanced liver disease. Three cases (50%) had a history of previous upper GIB. There was a history of significant alcohol intake in four DL-like bleeding cases and NSAIDS intake in two.(34)

In a study done in University Hospital in Switzerland of 480 patients with acute UGIB, 28 (5.8 %) were endoscopically diagnosed with DL, of whom four (14.3 %) had alcoholic liver cirrhosis.

Three patients had previous history of bleeding from peptic ulcers, one had anastomosal bleeding with a history of gastric resection, one patient had a DL treated conservatively in another hospital with recurrent bleeding episodes within one year before admission(35).

A study done in china published in 2020 compared the clinical and endoscopic characteristics of variceal and peptic ulcer bleeding in liver cirrhosis. The mean age was higher in peptic ulcer group (55.58 ± 11.37 vs. 52.87 ± 11.57) and higher male: female ratio (4.51:1 vs. 2.87:1). Most common presentation in the variceal group was red blood and coffee ground emesis (67.16%), whereas in the ulcer group melena was more prevalent (62.10%). Higher number of variceal groups had prior history of UGIB (212 vs. 80). In the ulcer group, Hepatocellular carcinoma (HCC) was more prevalent, and 47.98% had treatment for tumor like surgery and other interventions, 15.73% patients had previous PUD, 39.11% had a history of specific medications within 1 month, and 19.76% had surgical stress or trauma within 3 months. Those with variceal bleeding had significantly more severe varices on endoscopy. Albumin level was higher in variceal group, whereas serum bilirubin, creatinine and INR was significantly higher in the ulcer group. Occurrence of SBP and Hepato-renal syndrome (HRS) immediately after bleeding was also higher in the ulcer group (1.74% vs 6.08% and 1.49% vs 9.27% respectively). Child-Pugh score was also higher in ulcer group (8.93 ± 2.03 Vs. 11.13 ± 2.17). Concerning the outcome, more patients with variceal bleeding required blood transfusion, but this study did not find significant difference in rebleeding rate, length of stay or mortality between the two groups(13). In this study, the clinical characteristics in the ulcer bleeding were somehow worse than the ulcer bleeding and this could be due to that those in variceal bleeding had prior bleeding episodes and targeted therapy, hence reducing the risk of variceal bleeding.

2.4 Conceptual framework

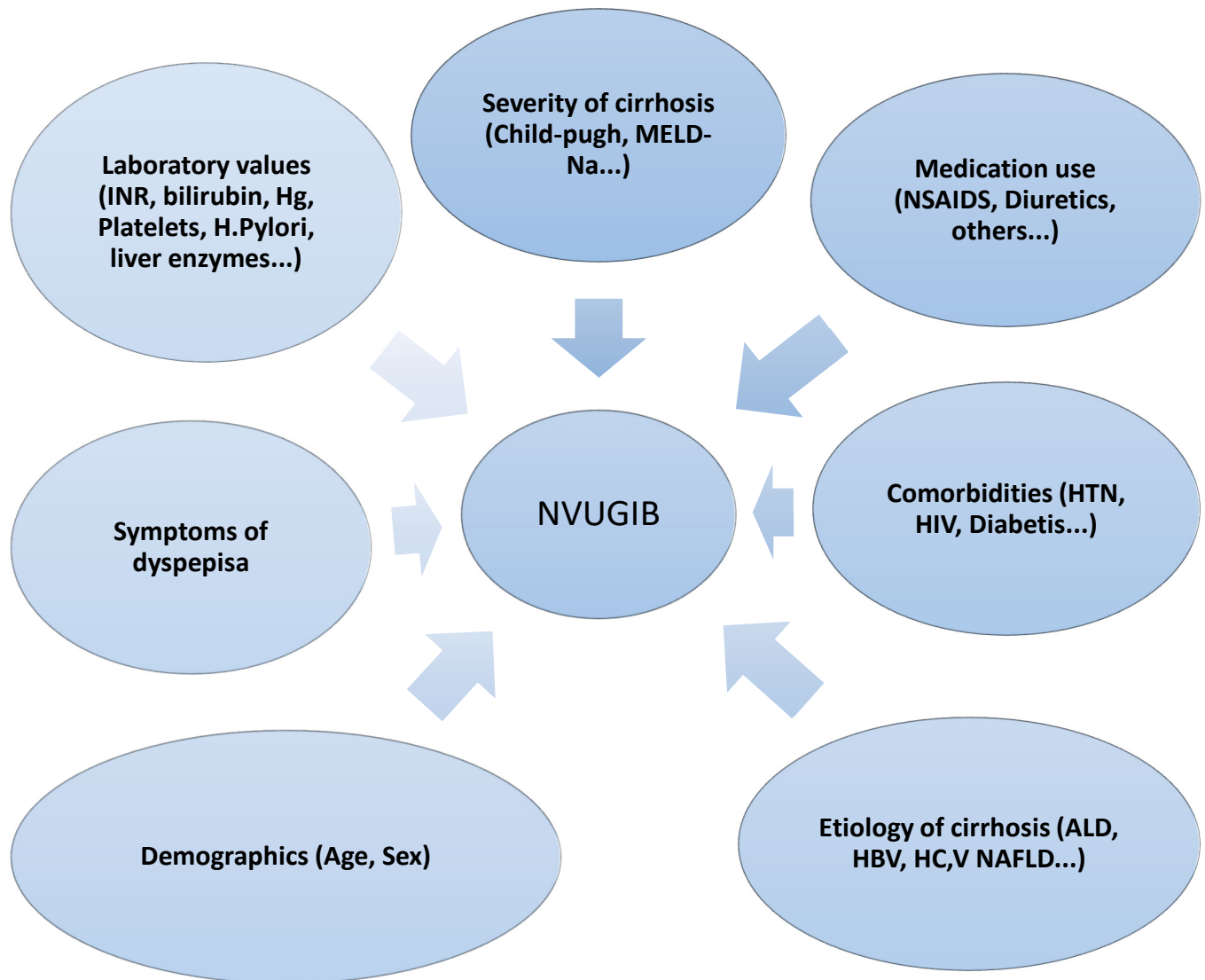


Figure 1 Conceptual framework for factors affecting NVUGIB in patients with cirrhosis

3 Objectives

3.1 General objective

To assess prevalence, clinical characteristics, treatment outcome and associated factors of non-variceal upper gastrointestinal bleeding, among patients with cirrhosis having follow up at gastroenterology and hepatology clinic in SPHMMC, Addis Ababa-Ethiopia, from December, 2020 to December, 2023.

3.2 Specific objectives

- ◆ Determine the prevalence of non-variceal upper gastrointestinal bleeding in patients with cirrhosis with follow up at gastroenterology and hepatology clinic in SPHMMC
- ◆ Assess factors that are associated with NVUGIB in patients with cirrhosis
- ◆ Assess clinical characteristics
- ◆ Determine treatment outcome of NVUGIB in those groups of patients

4 Methods

4.1 Study setting

The study was conducted at St. Paul's Hospital Millennium Medical College, one of the largest governmental tertiary care hospital located in Gulele sub-city, Addis Ababa, Ethiopia(36).

The college currently has 250 faculty members, and more than 2800 clinical, academic and administrative and support staffs that provide medical specialty services to patients who are referred from all over the country, in addition to teaching medicine and other health science students and doing basic and applied researches. On average, the college gives service to 1200 clients at emergency and outpatient clinics daily and has an inpatient capacity of more than 700 beds(36).

Gastroenterology and Hepatology unit, one of the subunits of internal medicine, has re-started fellowship program by 2021, after it was discontinued previously due to resource limitations, and currently has 6 senior gastroenterologist and hepatologists, and 4 fellows under it. It provides services for about 1300 patients as shown in the college registries.

4.2 Study design

A hospital based cross-sectional study was conducted on the Prevalence and associated factors of non-variceal upper gastrointestinal bleeding among patients with cirrhosis.

4.3 Study period

The study was conducted at SPHMMC at GI clinic from December 2020 to December 2023.

4.4 Study population

4.4.1 Source population

All patients with cirrhosis attending SPHMMC gastroenterology and hepatology follow up clinic

4.4.2 Study population

All cirrhosis patients attending SPHMMC gastroenterology and hepatology follow up clinic within the study period from December 2020 – December 2023, presenting with UGIB.

4.4.3 Inclusion criteria

- ◆ Age ≥ 18 years
- ◆ Patients with diagnosis of cirrhosis attending gastrointestinal and hepatology follow up clinic during the study period of December 2020 – December 2023.
- ◆ Patients with cirrhosis presenting with upper gastrointestinal bleeding

4.4.4 Exclusion criteria

- ◆ Patients with incomplete data with incomplete clinical or imaging evidence of cirrhosis
- ◆ Patients with subsequent bleeding episodes after the first GI bleeding (only the first episode during the study period was be taken)
- ◆ Patients who do not have endoscopy

4.5 Sample size determination and sampling technique

4.5.1 Sample size determination

The sample size was calculated using the estimation proportion formula with estimated proportion assumed to be 50% Since there is no previous study done to estimate the prevalence of non-variceal bleeding in cirrhosis patients.

$$n = z^2 p (1-p) / w^2$$

Key

n = sample size, p = estimated proportion take p as 50% to get maximum sample size, Z = level of confidence. It is 95%, W = margin of error; it is 5%.

$$n = (1.96) * (1.96) * (0.5(1-0.5)) / (0.05) * (0.05)$$

$$n = 384.16 \sim 384$$

Our study population (N = 592 cirrhosis patients obtained from the hospital's Health Management Information System [HMIS] registry) is < 10,000 and it needs some arrangement. By using correction formula, the final sample size(nf) is calculated as:

$$nf = \frac{n}{1 + \frac{n}{N}} = nf = \frac{384}{1 + \frac{384}{592}} = 232$$

10% contingency is added and the final sample size will be 255.

- Sample size calculation for selected potential variables of associated factors is calculated as:

		Assumptions					
Variable	Odds ratio	Proportion	Ratio	Power	Confidence interval	Sample size	Reference
Ulcerogenic drug use	5	42.8%	1:1	80%	95%	374	(9)

Child pugh score	4.6	46.3%	1:1	80%	95%	91	(13)
Alcohol consumption	4.9	69.4%	1:1	80%	95%	328	(10)

The maximum calculated sample size using Epi Info software 374 which is greater than the calculated sample size for prevalence, so this is the final sample size calculated for this study.

4.5.2 Sampling technique and procedures

All cirrhotic patients on follow up at gastroenterology and hepatology clinic of SPHMMC during the study period presenting with upper gastrointestinal bleeding were undertaken into the study.

4.6 Study variables

4.6.1 Dependent variables

- Non-variceal gastrointestinal bleeding
- Treatment outcome (Death or alive)

4.6.2 Independent variables

- Socio-demographic variables:(Age, sex)
- Clinical and laboratory variables:
 - o Clinical presentation (ascites, UGIB [Hematemesis/melena], Blood pressure records, and other comorbid illness like Diabetes Mellitus [DM], Heart failure [HF], Chronic Kidney Disease (CKD)
 - o Laboratory variables: (Complete blood count [CBC], Renal function test [RFT], Liver function test [LFT] (albumin, bilirubin, International normalized ration

- [INR]), Liver enzymes, Child-Pugh score, Model for end-stage liver disease [MELD] score, Serum Sodium [Na] level)
 - Platelet count/spleen diameter ratio
 - Helicobacter pylori test
 - Non-steroidal anti-inflammatory drugs (NSAIDs), Aspirin or steroid use, diuretics
- Imaging and endoscopy variables:
 - abdominal U/S findings (cirrhosis, mass, ascites, splenomegaly, portal hypertension)
 - Esophagogastroduodenoscopy (EGD) findings: (Esophageal/Gastric varices, esophagitis /Gastritis/ Duodenitis, peptic ulcer disease or Mass)
 - Timing of endoscopy and time after the onset of bleeding
- Treatment related variables: (Beta blockers, PPIs, transfusions, endoscopic interventions)
- Outcome variables (death or alive)

4.7 Operational definitions

- Upper gastrointestinal bleeding - is bleeding from the upper part of GI (proximal to ligament of Treitz) manifested by melena, hematemesis confirmed endoscopically or clinically.
- Variceal bleeding – spurting or oozing varix, or varix with nipple sign or a varice and no other cause of bleeding.
- Non-variceal gastrointestinal bleeding – all other causes of bleeding other than variceal bleeding, if spurting, oozing, adherent clot or red or blue spot was observed or if it is the only lesion detected in UGI tract or the endoscopist diagnosis of NVUGIB
- Cirrhosis – a pathological diagnosis by fibrosis and nodule formation of the liver secondary to chronic injury, leading to alteration of the normal lobular organization of the liver diagnosed with clinical features, laboratory parameters of deranged liver functions and ultrasound features of small nodular liver, with/without biopsy.

4.8 Data collection methods and procedures

Data was collected from December 2020 to December 2023 G.C. Data collection checklist prepared in English was used to gather information of socio-demographic variables, baseline characteristics of the subjects (Clinical and laboratory variables, abdominal ultrasound and endoscopic findings) and treatment related variables.

4.9 Data quality management

Training was given to seven data collectors (General Practitioners and residents of SPHMMC) on the components of the checklist, and training for one person on how to fill the data into a computer. Records of the study population was assessed for completeness before data entry and the entered data was checked by the data supervisor for any incompleteness and/or inconsistency.

4.10 Data processing and analysis

Data was checked manually for completeness before analysis. The data was entered into a computer using Statistical Package for Social Sciences (SPSS) version 26.0. Categorical variables was put as percentages and frequency and was compared by chi square test. Continuous variables were recorded as mean, and standard deviation and were compared by binary logistic regression. Frequency tables and descriptive summary were done for the study variables. Bivariate logistic analysis was performed, and those variables in bivariate analysis with p value ≤ 0.2 were taken as a candidate for multivariate logistic analysis. Multivariate logistic regression analysis as used to identify associated factors for the prevalence of NVUGIB in cirrhosis patients. Adjusted odds ratio (AOR) along with 95% CI was estimated to see strength of association and p-value of <0.05 was used for statistical significance.

4.11 Ethical considerations

Ethical clearance was obtained from the Institutional Review Board of St. Paul's Hospital Millennium Medical College and then permission was sought from the school administration through the academic provost of the school to carry out the study. Identifiers of patients were kept anonymous and confidential. Obtained data will be used for study purpose only.

4.12 Dissemination of results

The final result of the study will be communicated to SPHMMC department of internal medicine and public health in partial fulfilment of the requirement for a specialty certificate in internal medicine. Finally, attempts will be made to present in scientific journals and then to be published in reputable journals.

5 Results

During the study period, a total of 646 patients with cirrhosis visited Gastroenterology and Hepatology clinic at Saint Paul's Hospital Millennium Medical College from December 2020 to December 2023 G.C. Of those patients with cirrhosis 255 (39.4%) patients presented with Upper gastrointestinal bleeding. Of those, 21 patients were excluded due to incompleteness of documentation. From the remaining 234 patients, missing data was 7% for the laboratory parameter Total and Direct bilirubin levels, and imputation with the mean value was used for analysis and finally data from 234 patients was analyzed.

5.1 Sociodemographic results

Of the 234 cirrhotic patients presenting with Upper Gastrointestinal Bleeding (UGIB), the Mean age was 40 ± 14 years, ranging from 18 – 87 years of age. Mean age for Non-variceal upper

gastrointestinal bleeding (NVUGIB) was 39±14 and for variceal UGIB was 41±14 years. A total of 158 (67.5%) were male and the remaining 76 (32.5%) were female (Table 1).

Table 1 Age and sex distribution of cirrhotic patients with UGIB at St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia, 2020 to 2023 (N=234)

Category	Sex				Age	
Variable	Male		Female			
	Count (n)	Percent (%)	Count (n)	Percent (%)	Mean	SD
Study Participants	158	67.5	76	32.5	40	14
Variceal UGIB	106	66.3	54	33.8	41	14
Non-Variceal UGIB	52	70.3	22	29.7	39	14

5.2 Clinical characteristics of patients with UGIB

Hepatitis B virus (HBV) was the most common etiology of cirrhosis identified in patients NVUGIB (48.6%), followed by Hepatitis C virus (HCV) (16.2%), and Alcoholic liver disease (ALD) (13.5%), wherein patients with Variceal UGIB, the most common causes were HBV

(27.5%), followed by Alcohol-related cirrhosis (21.3%) and HCV (15.0%). Significantly less patients had Hepatosplenic schistosomiasis reported as a cause of cirrhosis in the NVUGIB group (2.7%) than the variceal group (21.3%) ($p<.001$). In addition, Hepatocellular carcinoma (HCC) was found among approximately 11.3% patients with variceal UGIB, while it was found in approximately 13.5% patients in the Non-Variceal UGIB group.

In the study of severity of cirrhosis, Child-Turcotte-Pugh (CTP) Class A cirrhosis was relatively uncommon in both groups but slightly higher in the NVUGIB group (8.1%) compared to the Variceal (3.8%), and similarly CTP Class B cirrhosis was more common in the NVUGIB group (37.8%) compared to the Variceal UGIB group (30.0%). Lesser patients in NVUGIB group had CTP Class C cirrhosis (54.1%) compared to the Variceal UGIB group (66.3%), although in both groups CPT Class C was more prevalent than CTP Class A and B.

Regarding comorbidities, a slightly higher number of patients had Retroviral Infection in NVUGIB group (6.8%) compared to the Variceal UGIB group (3.1%), whereas more patients had Chronic Kidney Disease (CKD) in the Variceal group (10.0%) compared to patients with NVUGIB (5.4%). Prevalence of Hypertension (HTN) was comparable in both groups.

Assessment of prior Medication use revealed that NSAID use was common in both groups, with similar percentages (55.0% in Variceal UGIB and 56.8% in Non-Variceal UGIB). Beta-Blocker (BB) use was more common in the Variceal UGIB group (47.5%) compared to the Non-Variceal UGIB group (24.3%). Proton Pump Inhibitor (PPI) use was relatively low in both groups but slightly higher in the Variceal UGIB group (8.8%) compared to the Non-Variceal UGIB group (5.4%). Aspirin use was identified in around 2.7% of the NVUGIB group (Table 3).

Table 2 Clinical characteristics of cirrhotic patients with UGIB at St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia, 2020 to 2023 (N=234)

		Study Participants		Variceal UGIB		Non-Variceal UGIB		
Variable	Category	Total (n)	Percent (%)	Count (n)	Percent (%)	Count (n)	Percent (%)	P value
Cause of Cirrhosis	HBV	80	34.2	44	27.5%	36	48.6%	<.001
	HCV	36	15.4	24	15.0%	12	16.2%	
	Alcohol	44	18.8	34	21.3%	10	13.5%	
	MAFLD	0	0	0	0.0%	0	0.0%	
	Schistosomiasis	36	15.4	34	21.3%	2	2.7%	
	Others	38	16.2	24	15.0%	14	18.9%	
Severity of Cirrhosis	CTP Class A	12	5.1	6	3.8%	6	8.1%	.13
	CTP Class B	76	32.5	48	30.0%	28	37.8%	
	CTP Class C	146	62.4	106	66.3%	40	54.1%	
Comorbidities	DM	12	5.1	8	5.0%	4	5.4%	.89
	HTN	16	6.8	11	6.9%	5	6.8%	.97
	HF	2	0.8	2	1.3%	0	0.0%	.33
	CKD	20	8.5	16	10.0%	4	5.4%	.23
	RVI	10	4.3	5	3.1%	5	6.8%	.02

	Others	18	7.6	14	8.8%	4	5.4%	.45
	HCC	28	12	18	11.3%	10	13.5%	.62
Previous GI bleeding	No	182	77.8	122	76.3%	60	81.1%	
	Yes	52	22.2	38	23.8%	14	18.9%	.41
Prior medication use	NSAIDS	130	55.5	88	55.0%	42	56.8%	.80
	Aspirin	2	0.8	0	0.0%	2	2.7%	.03
	BB	94	40.1	76	47.5%	18	24.3%	<.001
	Diuretics	117	50.0	81	50.6%	36	48.6%	.78
	PPI	18	7.6	14	8.8%	4	5.4%	.37
	Others	40	17.1	24	15.0%	16	21.6%	.62
Duration of cirrhosis	Mean	21		18		26		.015
	SD	37		25		54		
MELD score	Mean	17		17		17		.76
	SD	7		7		7		
Systolic blood pressure	Mean	114		116		111		.05
	SD	19		19		18		

Diastolic blood pressure	Mean	71	71	70	.51
	SD	13	13	14	

HBV: Hepatitis B virus, HCV: Hepatitis C virus, MAFLD: Metabolic associated fatty liver disease, CTP: Child Turcotte Pugh, DM: Diabetes Mellitus, HTN: Hypertension, HF: Heart Failure, CKD: Chronic Kidney Disease, RVI: Retroviral Infection, HCC: Hepatocellular Carcinoma, NSAIDs: Non-steroidal Anti-inflammatory drugs, BB: Beta-blockers, PPI: Protein pump inhibitors, MELD: Model for End-stage Liver Disease

Around 23.8% of patients with Variceal UGIB had a previous history of GI bleeding compared and 18.9% of patients in the Non-Variceal UGIB group (18.9%). The duration of cirrhosis varied widely among participants in both groups. Patients with NVUGIB had median of 5 months (SD 54), showing greater variability than patients in the variceal group that had median duration of 6 months (SD 25). MELD score was comparable between the two groups.

Assessment of blood pressure at presentation showed median SBP 112 mmHg (SD 18) among Non-variceal groups and 112mmHg (SD 19) in patients variceal UGIB (Table 2).

5.3 Laboratory parameters

On measurements of laboratory parameters, patients with NVUGIB had a mean WBC count of 6525 cells/mm³ (SD 3864) and 6028 cells/mm³ (SD 4455) in patients in the variceal group. The post-bleeding Hg in the Non-variceal group was 11.9 g/dl (SD 2.2) and the variceal group had Hg of 10.9 (SD 3.1). INR measurements showed mean value of 1.84 (SD .93) among non-variceal bleeders where as the mean INR value of variceal UGIB was 2.08 (SD 1). Serum creatinine levels were a mean of 1.04 (SD 0.63) in the NVUGIB patients which showed similar values in the variceal groups as well (Table 3).

Table 3 Laboratory parameters of of cirrhotic patients with UGIB at St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia, 2020 to 2023 (N=234)

Variable	Study Participants		Variceal UGIB		Non-variceal UGIB		P-value	Missing
	Mean	SD	Mean	SD	Mean	SD		
WBC (/mm ³)	6185	4274	6028	4455	6525	3861	.409	<.5%
Post-bleeding Hemoglobin	11.2	3.1	10.9	3.4	11.9	2.2	.022	<.5%
Platelets (/mm ³)	129376.1	98082.6	124362.5	98310.0	140216.2	97367.9	.251	<.5%
AST Value	109.05	173.55	105.79	189.98	116.11	132.06	.673	<.5%
ALT Value	63.5	136.7	67.3	160.6	55.2	58.0	.541	<.5%
ALP Value	181.6	153.9	171.1	142.5	204.3	175.1	.602	<.5%
TB Value	2.691	3.434	2.698	3.535	2.676	3.226	.849	7%
Albumin Value	2.54	.76	2.57	.76	2.49	.76	.48	1%
INR	2.01	.99	2.08	1.00	1.84	.93	.070	<.5%
Creatinine	1.01	.62	1.00	.62	1.04	.63	.680	<.5%
Serum Sodium	135.3	6.8	135.7	6.6	134.5	7.1	.20	1.1%
WBC: White Blood cell, AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, ALP: Alkaline Phosphatase, TB: Total bilirubin, INR: International Normalized ratio								

WBC: White Blood cell, AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, ALP: Alkaline Phosphatase, TB: Total bilirubin, INR: International Normalized ratio

5.4 Endoscopic findings and causes of Upper Gastrointestinal Bleeding in cirrhotic patients

Of patients presenting with UGIB the prevalence of Non-Variceal Upper Gastrointestinal bleeding (NVUGIB) reached 31.6% (95% Confidence Interval 26% - 37.8%), and the majority of the remaining patients had Variceal bleeding (67.1%), and 1.3% of the patients had normal Endoscopic findings. The commonest etiology identified was Duodenal Ulcer accounting for 48.6% of all NVUGIB, followed by Gastric ulcer (16.2%), Gastritis (12.2%), both Gastritis and Duodenitis (5.4%), Esophagitis (4.1%), both Gastric and Duodenal ulcer (1.4%). Less common etiologies included such as Portal Hypertensive gastropathy, Cameroon ulcer and previous ligation site ulceration accounted for the remaining 10.2% (Table 4).

Table 4 Causes of Non-variceal bleeding in cirrhotic patients with UGIB at St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia, 2020 to 2023 (N=234)

Variables	Category	Count (n)	Percent (%)
Non-variceal upper gastrointestinal bleeding	Duodenal ulcer	36	48.6
	Esophagitis	3	4.1
	Gastritis	9	12.2
	Both Gastritis and Duodenitis	4	5.4
	Duodenitis	3	4.1
	Gastric ulcer	12	16.2

	Gastric and Duodenal ulcer	1	1.4
	Ligation site ulcer	3	4.1
	Cameroon ulcer	2	2.7
	Portal Hypertensive gastropathy	1	1.4

5.5 Interventions and outcomes

Among the 234 participants presenting with UGIB, 41 patients (17.5%) died and 193 patients (82.5%) of patients were alive. Of these mortality in NVUGIB was 20.3% (n=15), and VUGIB was 17.5% (n=41). Mortality was the highest in patients with Duodenal ulcer (29.3%, n=12), followed Gastritis (9.7%, n=4) and both Gastritis and Duodenitis (2.4%, n=1). Regarding interventions, 26.5% (n=62) required transfusion of blood products, of which around 21.4% (n=50) were transfused with Packed Red Blood Cells (PRBC) or whole blood. 4.3% (n=10) required Fresh Frozen Plasma (FFP) transfusion and another 3.4% (n=8) patients were transfused with platelets. Endoscopic interventions were done for more than half of the patients with UGIB (57.7%, n=135) (Table 7).

Table 5 Interventions and Outcomes of of cirrhotic patients with UGIB at St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia, 2020 to 2023 (N=234)

		Study Participants		Variceal UGIB		Non-Variceal UGIB		
Variable	Category	Total (n)	Percent (%)	Count (n)	Percent (%)	Count (n)	Percent (%)	P value
Interventions	Endoscopic	150	57.7	106	66.3%	44	59.5%	.001

	Blood transfusion	62	26.5	50	31.3%	12	16.2%	.015
RBC transfusion	0-1	192	82.1%	124	77.5%	68	92%	.047
	2	22	9.4%	22	13.8%	0	0.0%	
	>2	20	9.1%	14	8.9%	6	8.1%	
Platelets	0-1	226	96.6%	152	95.0%	74	100.0%	.28
	2	4	1.7%	4	2.5%	0	0.0%	
	>2	4	1.8%	4	2.6%	0	0.0%	
Fresh Frozen Plasma (FFP)	0-1	224	95.7%	154	96.3%	70	94.6%	.26
	2	4	1.7%	4	2.5%	0	0.0%	
	>2	6	2.7%	2	1.3%	4	5.4%	
Treatment outcome	Alive	193	82.48%	134	83.8%	59	79.7%	.452
	Dead	41	17.5%	26	16.3%	15	20.3%	

5.6 Factors associated with NVUGIB

Binary logistic regression was used to determine the association of variables with the Dependent variable NVUGIB. With this, Schistosomiasis and Hepatitis C as the cause of cirrhosis, Prior use

of Aspirin, use of Beta-blockers, presence of Chronic kidney disease (CKD) and Retroviral Infection (RVI) as comorbidities, Duration of Cirrhosis, Systolic blood pressure, post-bleeding Hemoglobin, requirement for transfusion of blood products, International Normalized Ratio (INR), and serum Sodium (Na) level were found to have associations of P Value < .25 and were analyzed with Multivariable logistic regression.

Longer duration of Cirrhosis ($p = .03$, AOR = 1.01, 95% CI [1.001-1.019], and the presence of RVI as a comorbid condition ($p < .001$, AOR = 51.72, 95% CI [5.65-471.8]) were strong predictors of NVUGIB, whereas patients with relatively older age ($p = .007$, AOR = 0.96, 95% CI [0.93-0.99], patients with Hepatitis C virus ($p = .009$, AOR = .118, 95% CI [.05-.66], and Schistosomiasis ($p < .001$, AOR = 0.34, 95% CI [0.01-0.19]), as the cause of cirrhosis, patients with prior use of Beta blockers ($p = .005$, AOR = 0.32, 95% CI [0.14-0.70]), and with higher INR ($p = .014$, AOR = 0.57, 95% CI [0.36-0.89], were less likely to develop NVUGIB as compared to Variceal bleeding. In addition, patients with NVUGIB had a relatively lower Systolic Blood Pressure (SBP) measurements at presentation ($p = .010$, AOR = 0.97, 95% CI [0.95-0.99], however they had lesser requirement of blood products ($p = .009$, AOR = 0.25, 95% CI [0.08-0.71] (Table 8).

Table 6 Multivariable binary logistic regression analysis of cirrhotic patients with UGIB at St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia, 2020 to 2023 (N=234)

				95% C.I.		
Categories	Variables	OR	AOR	Lower	Upper	P value
Demographics	Age	.98	.963	.937	.990	.007
Cause of Cirrhosis	HBV	1.00	1.00			
	HCV	.61	.188	.053	.661	.009

	ALD	.35	.379	.140	1.024	.056
	Schistosomiasis	.07	.034	.006	.193	.001
	Others	.71	.507	.187	1.379	.184
Severity of cirrhosis	CTP Class A	1.00	1.00			.166
	CTP Class B	.58	.261	.049	1.389	.115
	CTP Class C	.38	.191	.034	1.064	.059
Clinical parameters	Systolic Blood Pressure	.98	.973	.953	.993	.010
	Duration of Cirrhosis	1.01	1.010	1.001	1.019	.037
	Beta-blockers	2.81	.316	.142	.706	.005
	Aspirin			.000		.999
	Blood Transfusion	2.35	.251	.088	.713	.009
Laboratory parameters	Post-bleeding Hemoglobin	1.12	1.120	.980	1.279	.096
	INR	.76	.570	.363	.893	.014
	Serum Sodium (Na ⁺)	0.97	.959	.906	1.015	.149
Comorbidities	CKD	1.94	.547	.129	2.311	.411
	RVI	99	51.720	5.669	471.826	.001
HCV: Hepatitis C virus, CTP: Child Turcotte Pugh, INR: International Normalized Ratio, CKD: Chronic Kidney Disease, RVI: Retroviral Infection						

6 Discussion

The findings of this study showed a significant number of patients with cirrhosis present with Non-variceal causes of upper gastrointestinal bleeding with a prevalence of 31.6%, in a sample of 234 patients. This finding of the prevalence of NVUGIB is slightly higher than Indian study that showed prevalence of 24.5% (8), however is lower than the Pakistan study that showed a prevalence of 56.93% (26), and the study in Thailand (51%) (16). This lower prevalence may be explained with the relatively longer time to endoscopy after bleeding episodes in our study, which might have resulted in healing of ulcers, underestimating the true prevalence. In addition, Patients included in the Pakistan study were relatively younger, ranging from 18-65 years, and the relatively older age of patients in our study, as well as the negative association we found with NVUGIB and increasing age might have contributed to the relatively lower prevalence we found. In addition, they had excluded patients who have received sclerotherapy or band ligation for varices within the past 30 days, which might have contributed for the increased proportion of NVUGIB than variceal.

Peptic ulcer disease was found to be the most common etiology of NVUGIB in our finding, which was present in around two-third of our patients (68.9%). Although at a relatively higher prevalence in our study, the finding of peptic ulcer causing the majority of NVUGIB in cirrhosis patients is similar with most studies such as the Czech study of 108 patients (26) and the Indian study of 550 patients which reported incidence of 40.5% of gastroduodenal ulcers (8). This

relatively higher number in our study might in part be associated with the high prevalence of *Helicobacter pylori* (H. Pylori) in our country, which is reported in 52.2% in a meta-analysis done of 18,890 patients (37). Less common etiologies such as PHG is found in only 1.4% of our study, which may show PHG is an uncommon etiology as a cause of acute UGIB among cirrhotic, as supported by other studies which reported an incidence between 2 and 12 %, albeit it plays a major role in the pathophysiology of ulcer formation and poor gastric mucosal healing (17,33).

Longer duration of cirrhosis was shown to have a strong positive association with NVUGIB in our study with mean duration found to be 2 ± 4.5 years. Longer duration of cirrhosis is correlated with increased severity of cirrhosis, and with the development and progression of portal Hypertension and portal Hypertensive Gastropathy (38). Considering the pathophysiology of NVUGIB including peptic ulcer, mechanisms suggested in liver cirrhosis include portal hypertension-induced impairment of the gastric mucosal defenses(32), reduced prostaglandins, decreased gastric acid secretion, elevated serum gastrin concentration, impaired mucus secretion, a reduction in potential difference of the gastric mucosa (30)

Certain comorbidities such as RVI are also identified as strong predictors of NVUGIB in our findings. This might be a result of multiple factors, such as the presence of opportunistic infections such as Herpes simplex virus (HSV), cytomegalovirus (CMV), typical or atypical mycobacterium infections that are ulcerogenic or causing esophagitis, as stated in literatures (39).

Lower INR values were seen with NVUGIB in our study, than the higher values seen with the variceal group. This finding is different from the study done in china that compared variceal UGIB with peptic ulcer bleeding, which found higher INR, bilirubin, and creatinine values in non-variceal groups (13). This may be in part that, higher INR values might implicate a worse decompensation of liver function, which is one factor for the development of varices. It may also be due to other etiologies in NVUGIB that were not addressed in their study. In addition, although there was a slightly increased number of patients with Hepatocellular carcinoma in the NVUGIB, it was not statistically significant, unlike the study in china.

Schistosomiasis is an uncommon cause of cirrhosis. The main pathophysiologic mechanism of developing UGIB in schistosomiasis is the causation of pre-sinusoidal portal Hypertension, which in turn will result in increased splanchnic vasodilation and formation of varices (40). Therefore, variceal bleeding is the more common presentation of UGIB, as shown in our study with the significant negative association with NVUGIB.

The incidence of NVUGIB in cirrhotic patient had significant negative association with the use of Beta-blockers in our study, compared to variceal groups. This may be due to that patient are started on Beta-blockers for primary or secondary prophylaxis for variceal bleeding from prior screening with presence of varices or prior episodes of bleeding, hence, this increased incidence of varices may predispose them to variceal UGIB than Non-variceal (13).

In addition, patients with NVUGIB were less likely to require blood product transfusions, similar to the study done in china (13). Mortality was 17.5% in our patients with UGIB, and 20.3% in those with NVUGIB, which we did not find to differ significantly among our two groups of patients. Relatively similar mortality rates were recorded in other studies, of mortality 23.5% - 25% (6, 21).

7 Strength and limitations

7.1 Strength

- This type of research has not been conducted in our country, to the researcher's knowledge. It will be the first of its type and can be establish a baseline data for future research and comparisons.
- Overall, a reasonable number of samples were undertaken in this study, and patients can be representative of their source population.

7.2 Limitations

- Access to endoscopy during acute bleeding episodes were somehow limited, resulting in prolonged time to endoscopy. This might have resulted in healing of ulcers and the true prevalence of NVUGIB might be higher than reported.
- A few of the variables might have a small number of participants, which might make some of the data difficult to interpret.
- As the study is a retrospective analysis, only associations may be derived, and not causative relationships could be identified.

8 Conclusion

In patients with cirrhosis, NVUGIB can be a significant concern. The prevalence of NVUGIB in cirrhotic patients can vary depending on the population studied and the underlying risk factors. Peptic ulcer disease is one of the most common causes of NVUGIB in cirrhotic patients, accounting for a significant proportion of cases. Younger age, presence of comorbidities, and longer duration of cirrhosis have a strong positive association, whereas higher INR, use of Beta-blockers, and certain causes of cirrhosis were seen to have negative associations with the development of NVUGIB in cirrhotic patients.

9 Recommendations

Based on the findings of this research, the recommendations forwarded:

For Clinicians,

- To note that NVUGIB is a major cause in cirrhotic patients presenting with upper gastrointestinal bleeding, and Prompt evaluation and management are crucial to improve patient outcomes.

- Clinicians should consider the duration of cirrhosis as a potential risk factor and closely monitor patients with longer disease duration.
- Early detection and management of comorbid conditions such as RVI should be undertaken.
- Earlier time to endoscopy, including during after-hours is a necessary step in early detection and intervention of UGIB in patients and improving resource availability and utilization is recommended.

For researchers,

- Other predictor models of Non-variceal bleeding as compared to cirrhotic patients with no UGIB might be an area of research in the future.
- Increasing the sample size for some of the parameters might yield a stronger association between the parameters.

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11 Annexes

11.1 Information sheet

Research title: Prevalence and associated factors of non-variceal upper gastrointestinal bleeding among Cirrhotic patients on follow up at Gastroenterology and hepatology follow up clinic, SPHMMC.

Principal investigator: Dr. Mahlet Mitiku (Internal Medicine Resident)

Name of organization: St. Paul's Hospital Millennium Medical College

Introduction: Greetings, My name is Dr. Mahlet Mitiku, and I am a medical resident in the Department of Internal Medicine of St. Paul's Hospital Millennium Medical College. As part of my postgraduate study, I had undertaken this research project on “Prevalence and associated

factors of non-variceal upper gastrointestinal bleeding among cirrhotic patients on follow up at Gastroenterology and Hepatology follow up clinic, SPHMMC”.

Purpose of the research project: The aim of this research was to describe the prevalence and assess the factors that are associated with non-variceal upper gastrointestinal bleeding among patents with cirrhosis. The findings will aid physicians in clinical practice and clinical recommendations. This study was a cross-sectional design, and had included cirrhotic patients on follow up clinic over a period of 14 months.

Procedure: The data collection was conducted in SPHMMC. Standard questionnaire was prepared to collect necessary information from patient charts and registries. The questionnaire will include questions about sociodemographic, clinical and laboratory data, along with imaging and endoscopy findings, interventions provided and outcomes.

Risk and Benefit: The results of this study will benefit in advancing clinical practice, as well as serve as an input for policy makers in putting forth guidelines in improving patient cares. There are no anticipated risks from inclusion in this study.

Confidentiality: During data collection the patient’s name were not be documented on questionnaires. All information gathered was confidential and will only be used for research and afore mentioned purposes.

Person to contact: If you have further inquiries about this study please contact:

Principal investigator: Dr. Mahlet Mitiku (Internal Medicine Resident)

- Phone number: +251936983080
- Email address: malidmitik@yahoo.com

Advisors: Dr Henok Fisseha (Assistant professor of Internal Medicine, Gastroenterology and Hepatology Fellow)

:Mr. Aman Yesuf (MPH/Epidemiology)

Sponsor: St. Paul's Hospital Millennium Medical Collage

11.2 Data collection checklist

Card number					
1. Sociodemographic					
1.1 Age					
1.2 Sex	1. Male				
	2. Female				
2. Clinical and laboratory characteristics					
2.1 Duration of cirrhosis					
2.2 Cause of Cirrhosis	1. HBV	2. HCV	3. Alcohol	4. NAFLD	5. Others (specify)
2.3 Severity of Cirrhosis	1. Child-Pugh class A		2. Child-Pugh class B		3. Child- Pugh class C
2.4 Comorbid illness	1.DM	2. HTN	3. HF	4. CKD	5. Others (Specify)

2.5 Previous GIB					
2.6 Blood pressure					
2.6 CBC parameters	1. WBC		2. Hg		3. Platelet
	Neutrophil	Lymphocyte	Pre-bleeding	Post-bleeding	
2.7 Liver biochemical tests	Value		X upper limit normal (ULN)		
AST					
ALT					
ALP					
TB					
DB					
PT					
Albumin					
Serum Na					
MELD score					
3. Abdominal ultrasound findings					
3.1 Cirrhosis					
3.2 Ascites					
3.3 Splenomegaly					
3.4 Portal hypertension					

3.5 HCC						
3.6 Others (Specify)						
4. Endoscopic findings						
4.1 Normal findings						
4.2 Esophageal/ gastric varices (Specify grade)						
4.3 Gastric ulcer						
4.4 Duodenal ulcer						
4.5 Both gastric and duodenal ulcer						
4.6 Esophagitis/ Gastritis/Duodenitis						
4.7 Mass						
4.8 Others (specify)						
5. Timing of endoscopy after bleeding onset (in hours)						
6. Medication use	1. NSAIDS	2. Steroids	3. Aspirin	4. Beta- Blockers	5. Diuretics	6. Others (specify)
7. Interventions provided	1. Endoscopic		2. PPI		3. Blood transfusion (specify amount)	
8. Treatment outcome	1. Dead (state date)			2. Alive		

11.3 Assurance of the investigator

I the undersigned resident agree to accept all responsibilities for the scientific, ethical and technical conduct of the research project and for provision of required progress reports as per terms and conditions of the Research and Publication Directorate and /or Department of Public Health of St. Paul's Hospital Millennium Medical College.

Name of the Resident:_____

Signature:_____

Date: _____

Approval of Advisors

Name of Public Health Advisor:_____

Signature:_____

Date:_____

Name of Clinical Advisor: _____

Signature: _____

Date: _____
