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Research Article

Prevalence of Upper Gastrointestinal Bleeding and Associated Factors Among Patients with Chronic Liver Disease Admitted to the Medical Emergency Department of Hawassa University Comprehensive Specialized Hospital, Hawassa, Sidama, Ethiopia

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Abstract

Background: Upper gastrointestinal bleeding is a common medical emergency associated with significant morbidity and mortality. At present, there is limited epidemiological data on gastrointestinal bleeding due to chronic liver disease and associated factors in Ethiopia. *Objective:* To assess the prevalence of upper gastrointestinal bleeding and associated factors among patients with chronic liver disease (CLD) admitted to the medical emergency department at HUCSH, Hawassa, Sidama Region, Ethiopia. *Methods:* An institutional-based cross-sectional study design was employed on a total of 166 patients' record charts reviewed at Hawassa University Comprehensive Specialized Hospital from December 1st to 15th, 2023. The data were collected using a pre-tested and structured checklist through chart review by three pre-trained BSc nurses. The data were entered into Kobo Toolbox data collection software, then exported, cleaned, and analyzed using SPSS version 26. A descriptive summary of the data and logistic regression were used to identify possible predictors using odds ratios with a 95% confidence interval and a P-value of 0.05. *Result:* The prevalence of Upper gastrointestinal bleeding was found to be 32.5% (95% CI: 25.3–39.7). The mean (SD) age of patients was 39.8 ±14.51. HBsAg positive [AOR: 2.3; 95%CI (1.06–5.15)], male gender [AOR: 4; 95% CI: 1.60–10.1], heavy alcoholic [AOR: 3.2; (1.05–10.0)], urban residence [AOR: 2.79; 95% CI: 1.23–6.31] and platelet count below 150 thousand [AOR: 2.40; 95%CI (1.06–5.24)] were independent risk factors upper gastrointestinal bleeding. *Conclusion:* The study found that the magnitude of UGIB was high among patients with CLD. Hepatitis B-positives, heavy alcohol drinkers, male gender, urban residents, and low platelet counts are associated with a higher occurrence of bleeding. Therefore, care providers should encourage HBV screening and vaccination, and provide emergency endoscopic therapy and medications to halt the progression of bleeding.

Keywords

UGIB, Emergency Endoscopy, CLD, Variceal, HUCSH

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1. Background

Upper gastrointestinal bleeding (UGIB) is defined as blood loss from the gastrointestinal tract, originating proximal to the ligament of Treitz, i.e., from the esophagus to the third part of the duodenum, characterized by hematemesis, tarry black stool, and bleeding per anus or rectum [1]. UGIB can be variceal or nonvariceal, with nonvariceal causes accounting for 80-90%, and variceal bleeding originating from gastric or esophageal varicosities, often in portal hypertension [2]. Patients with liver cirrhosis may experience upper gastrointestinal hemorrhage from various lesions, including gastroesophageal varices and portal hypertensive gastropathy, and may experience hemorrhage from varices equally or more frequently [3]. Portal hypertension-related gastrointestinal bleeding, a common acute GI emergency, can lead to severe hemodynamic compromise and mortality in patients with liver cirrhosis [4, 5]. Chronic liver disease (CLD) patients face significant complications and high mortality rates, leading to the development of national and international guidelines for safe risk stratification and timely emergency department management [6]. Acute UGIB mortality globally ranges from 5% to 10%, with more cases in variceal etiologies than non-variceal ones [7].

Schistosoma, a prevalent disease in Africa, causes non-cirrhotic portal hypertension, with esophageal varices common in 54-67% of upper GI endoscopy patients, causing complications and a high mortality rate [8]. Esophageal varices are present in 30-40% of liver-compensated cirrhosis patients and 60% of ascites patients, with an annual incidence of 5-10% for new varices in liver cirrhosis patients without varices [4].

The prevalence of UGIB substantially varied globally; it was 27% in Romania [9] and 48% in Pakistan [10]. Studies reported from Ethiopia reported that the magnitude of the problems varies from setting to setting: 10% at St. Paul's Hospital, Addis Ababa, and 51.9% at the University of Gondar Hospital, Northwest Ethiopia [2, 5]. Some risk factors increase the risk of upper GI bleeding due to chronic liver diseases (cirrhosis), such as the severity of liver disease, size of varices, and presence of red wale markers/signs, as well as infection, grade of varices, duration of illness, and poor adherence to beta-blockers [11].

Rebleeding risk is high (60-70%) until gastroesophageal varices are removed, but can be reduced through endoscopic therapy, nonselective beta-blockers, cigarette smoking, excessive alcohol consumption, and traditional medication usage [12]. Over 50% of patients experience spontaneous variceal bleeding, but those with continued bleeding have a mortality rate of 70-80% [13]. Each episode of variceal hemorrhage is linked to a 30% risk of mortality [14].

UGIB patients should be managed with resuscitative measures, such as intravenous crystalloids or colloids, and endoscopic treatments like esophageal band ligation and cyanoacrylate for gastric varices. Variceal bleeding despite endoscopic variceal ligation (EVL) and beta-blockers may be due to suboptimal doses or other factors [3, 15, 16]. The data on the magnitude and contributing factors to the occurrence of UGIB in Ethiopia are limited. Therefore, the study aims to assess the prevalence of upper gastrointestinal bleeding and its associated factors among patients with chronic liver disease admitted to the medical emergency department at Hawassa University Comprehensive Specialized Hospital.

2. Method and Materials

2.1. Study Area and Period

The study was conducted at Hawassa University Comprehensive Specialized Hospital in Hawassa City, which is the capital city of the Sidama region and is located 275 km from Addis Ababa. There are 12 hospitals in the city: four government hospitals and eight private hospitals. Hawassa Comprehensive Specialized Hospital serves approximately 18 million people from the Sidama region, the Southern Nations Nationalities and Peoples Region (SNNPR), and the neighboring Oromia region. It has major departments such as internal medicine, surgery, pediatric and child health, obstetrics and gynecology, as well as ophthalmology, dermatology, oncology, ENT, radiology, psychiatry, anesthesiology, emergency and critical care departments, laboratories, and pharmacy. The Gastroenterology and Hepatology unit provides follow-up services for patients with chronic liver disease as well as other gastrointestinal diseases at the Medical Referral Clinic (MRC). A total of 174 CLD patients were admitted to the medical emergency department between January 2020 and November 2023. The study was conducted from December 1st to 15th, 2023.

2.2. Study Design and Participants

An institution-based cross-sectional study was conducted from January 2020 and November 2023. All patients with chronic liver disease (CLD) who were admitted to the medical emergency department of Hawassa University Comprehensive Specialized Hospital were the source population. All 174 CLD patients who were admitted to the medical emergency department from January 2020 to November 2023 were included in the study. CLD patients who had incomplete baseline information were excluded from the study.

2.3. Variables of the Study

The outcome variable for this study was the occurrence of Upper GI bleeding among CLD patients. The independent variables included socio-demographic characteristics (age,

sex, and, residence), health and disease-associated characteristics (HBV, HCV, alcohol consumption, beta blockers, duration of illness, grade of varices, smoking, ALD and HSS), and clinical/laboratory characteristics (albumin level, bilirubin (Total/Direct), INR/PT, comorbidity, H. Pylori infestation, NSAIDS usage).

2.4. Data Collection Instrument

A data extraction checklist was developed from the literature [2, 5]. A structured questionnaire was used to be filled out by reviewing the patient's charts as well as the Kobo toolbox software. The structured questionnaire includes the socio-demographic characteristics of the patient's chart, clinical characteristics like hematemesis, melena, hematochezia, and previous history of liver disease and UGIB, risk behaviors like Smoking, alcohol consumption, chronic use of anticoagulants, steroids, NSAIDS.

2.5. Data Collection Procedure

Data was collected by three medical interns by reviewing each patient's register charts and observing with supervision by the investigators, codes or charts of all UGIB Patients with CLD were selected from the Health Management Information System (HMIS) and patient's medical record logbook, then the charts were revised and any additional information asked if not available on charts at a medical emergency, the necessary data on clinical predictors, associated factors and data on risk behaviors was obtained by careful review of the chart.

2.6. Data Quality Control

The measures that were undertaken to ensure the quality of data include Pre-testing of the data collection instrument on 30 patients (charts), Training for data collectors on data collection, the relevance of the study, and confidentiality of information was conducted for 2 days in form of the workshop before data collection for the study was started and supervision of the data collection process, data storage, and management was taken seriously.

2.7. Data Analysis

Data were collected using Kobo and analyzed using SPSS version 26. Descriptive analyses were carried out using frequency distributions, central tendency, and dispersion measures. The presence of a statistical association between dependent and independent variables was assessed using the chi-square. Binary logistic regressions were used to identify statistically significant independent variables. Variables having a p-value <0.25 in the bivariate analysis were analyzed in multivariate analysis, and finally adjusted odds ratio along with a 95% confidence interval and a p-value of less than 0.05 was reported as having a significant association between explanatory variables and outcome variables. The goodness of the model was checked by using the Hosmer and Lemeshow test (p=0.215).

2.8. Operational Definitions

UGIB- is bleeding that originates proximal to the ligament of Treitz; in practice, from the esophagus, stomach, and duodenum.

CLD inflammatory injury of the liver parenchyma, which has persisted for six or more months and may progress to end-stage liver disease and mortality.

Cirrhosis- a final pathway for a variety of chronic liver diseases, is a pathologic entity defined as diffused hepatic fibrosis with the replacement of the normal liver architecture by nodules.

Hematemesis- Vomiting of blood (coffee-ground vomitus).

Melena is the passage of black, tarry stools.

Hematochezia is the passage of fresh or altered blood per rectum.

Shock is circulatory insufficiency resulting in inadequate oxygen delivery, leading to global hypoperfusion and tissue hypoxia, with MAP <65 mmHg or BP<90/40 mmHg.

Varices are abnormal distended veins usually in the esophagus (esophageal varices) or in the stomach (gastric varices).

Alcohol use code (2004–forward, Adult Health Behaviors Section, SAMADULT.DAT).

1) No use of alcohol
2) Occasional drinker (+)- a subject who took alcohol during social events
3) Daily drinker (++) subject who takes alcohol daily for more than two

Standard drinks.

Heavy drinker (+++), a subject who took alcohol to the level that the subject is considered drunk by society

Smoker code (2004–forward, Adult Health Behaviors Section, SAMADULT.DAT).

1) None
2) Occasional smoker (+)-smokes during recreation
3) Light smoker (++)-smokes <5-10 cigarettes per day
4) Heavy smoker (+++)-smokes> 10 cigarettes per day

2.9. Ethics Consideration

The study used the routine existing patient record data from the chart. Ethical clearance was obtained from the Hawassa University College of Medicine and Health Sciences ethical review committee (Ref No IRB/ 013/16), and permission was obtained from Hawassa University Comprehensive Specialized Hospital. As the study used existing admission data and patient records, and there was no direct contact with patients, the committee waived the requirement for patient consent. The personal informant was kept anonymous throughout the investigation, and information concerning particular personal identifiers like patient names were not collected.

3. Results

3.1. Socio-demographic and Lifestyle Characteristics

A total of 166 patients with CLD were included in this study. The mean (SD) age of patients was 39.8 ±14.51 years, and over three-quarters (81.3%) of patients were aged 18 to 50 years. More than half of the respondents were males, and 108 (65.1%) came from rural areas. Forty-six (27.7%) were former smokers, and one-fourth of the patients were heavy drinkers (Table 1).

Table 1. *Socio-demographic characteristics of UGIB with CLD patients in Hawassa University Comprehensive Specialized Hospital, Sidama, Ethiopia, 2023 N=166.*

Variables	Category	Frequency	Percentage
Age	>18-50 years	135	81.3
	>50 years	31	18.7
Sex	Male	98	59
	Female	68	41
Residency	Urban	58	34.9
	Rural	108	65.1
Smoking habit	Former smoker	46	27.7
	Never smoker	61	36.7
	Unknown	59	35.5
Alcohol habit	Heavy drunker	43	25.9
	Daily drunker	50	30.1
	Never drunker	73	44.0

3.2. Clinical Characteristics/Diagnosis

About a third (31.3%) of patients had a history of previous UGIB, and the esophageal varices were the most common, with 31 (18.7%), followed by duodenal ulcer (4.8%). Upon presentation, weight loss was the most common clinical feature (43.4%), followed by yellowish discoloration of the eye (42.2%). The commonest cause of CLD was hepatitis B (68 (41%) (Figure 1), and 154 (92.8%) patients had abdominal ultrasounds. The majority have no endoscopy, about sixty-three percent. Regarding treatment, 40 (24.1%) were treated with proton-pumping inhibitors (PPI), and 35 (21.1%) received beta-blockers (Table 2).

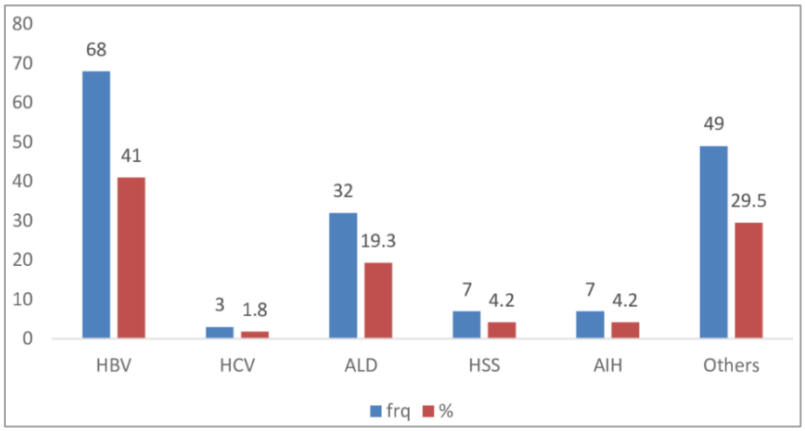

Figure 1. *Risk factors of CLD among patients admitted to HUCSH, 2023.*

Table 2. Clinical and comorbidity characteristics of UGIB with CLD patients in Hawassa University Comprehensive Specialized Hospital, Sidama, Ethiopia, 2023 N=166.

Variables	Category	frequency	Percent
Previous History of UGIB	Yes	52	31.3
	No	114	68.7
H. pylori Test	Yes	18	10.8
	No	148	89.2
Alarming symptoms/signs of CLD	Yellowish discoloration of the eye	70	42.2
	Weight loss	72	43.4
	Epigastric mass	16	9.6
		8	4.8
Abdominal ultrasound	No	12	7.2
	Yes	154	92.8
duration of illness	<4 years	26	15.7
	>4 years	140	84.3
Endoscopy	No	105	63.3
	Yes	61	36.7
endoscopy findings (n=61)	Duodenal ulcer	10	16.7
	Gastric ulcer	6	10.0
	Esophagitis	3	5.0
	Esophageal varices	54	90.0
	Others	4	6.5
Grade of GEV	Garde I	4	2.4
	Grade II	15	9
	Grade III	35	21.1
Treatment	Beta-blockers	35	21.1
	EVL	27	16.3
	Antibiotics	27	16.3
	PPI	40	24.1
	Other	37	22.3
Severity of CLD	CTP class A	42	25.3
	CTP class B	94	56.6
	CTP class C	30	18.1

3.3. Laboratory Characteristics of Patients

About a third (31.3%) of patients have hemoglobin <7 mg/dl, and more than 55 (33.1%) have a platelet count of less than <150,000/µl. One hundred (60.8%) were HBsAg, and 25 (16.9%) had INR<1.12 (Table 3).

Table 3. Laboratory characteristics of UGIB with CLD patients in Hawassa University Comprehensive Specialized Hospital, Sidama, Ethiopia, 2023, N=166.

Variables	Category	Frequency	percent
Hgb (mg/dl)	<7	52	31.3
	7-12	62	37.4
	>12	52	31.3
BUN/Cr (mg/dl)	<1.32	133	80.1
	>1.32	33	19.9
Platelets in thousands	>150,000/µl	111	66.9
	<150,000/µl	55	33.1
Albumin	<3.5	122	73.5
	>3.5	44	26.5
INR/PT	<1.12	28	16.9
	>1.12	138	83.1
Total Bilirubin	<2	74	44.6
	>2	92	55.4
HBsAg	Positive	101	60.8
	Negative	65	39.2
HCV antibody	Positive	3	1.2
	Negative	163	98.2
HIV serology	Reactive	2	1.2
	Non-reactive	67	40.4
	Not done	97	58.4

3.4. Prevalence of UGIB

In this study, 54 (32.5%; 95% CI: 25.3–39.7) of CLD patients admitted had UGIB (Figure 2).

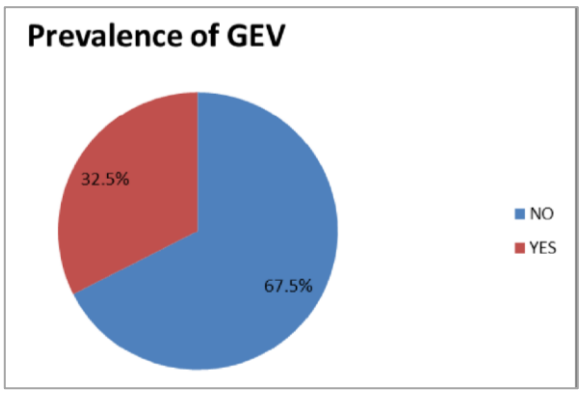

Figure 2. Magnitude of UGIB among CLD patients admitted to the medical emergency at HUCSH.

3.5. Factors Associated With UGIB

In the bivariable analysis, nine variables (heavy alcohol drinker, former smoker, younger age, male sex, short duration of illness, stage of disease, HbsAg positive, previous history of UGIB, urban residency, and platelet count< 150 thousand) were found to be significantly associated with the occurrence of UGIB. In multivariable analysis, five variables were found to be significantly associated with variceal bleeding. These were: heavy alcohol drinker, male sex, HbsAg positive, low platelet count, and urban residency.

The odds of UGIB for males were 4 [AOR: 4.0; 95% CI: 1.60–10.1] times more likely to develop compared to females. Similarly, patients dwelling in the urban area were nearly three [AOR: 2.79; 95% CI: 1.23–6.31] times more likely to develop UGIB than rural-dwelling patients.

The odds of developing UGIB for heavy alcoholic patients were 3.2 [AOR: 3.2; (1.05–10.0)] times more likely than those of non-alcoholic patients. In addition, hepatitis B-positive patients had 2.3 [AOR: 2.3; 95%CI (1.06–5.15)] higher odds of developing UGIB as compared to their coun-

terparts. Furthermore, patients with a platelet count below 150 thousand were 2.4 [AOR: 2.4; 95%CI (1.06–5.24)] times more likely to develop UGIB than those with a platelet count of more than 150 thousand (Table 4).

Table 4. *Binary logistic regression analysis of factors associated with UGIB in patients with CLD at Hawassa University Comprehensive Specialized Hospital, Sidama, Ethiopia, 2023.*

Variable	Category	UGIB		COR (95% CI)	AOR (95%CI)
		Yes, n (%)	No, n (%)		
Age	18-50	47 (34.8)	88 (65.2)	1.83 (0.73, 4.56)	2.51 (0.75, 8.42)
	>50	7 (22.6)	24 (77.4)	1	1
Sex	Male	29 (42.6)	39 (57.4)	2.17 (1.12, 4.20)	4.0 (1.60, 10.1)**
	Feamle	25 (25.5)	73 (74.5)	1	1
Alcohol	Heavy drunker	18 (41.9)	25 (58.1)	2.20 (0.98, 4.92)	3.2 (1.05, 10.1) *
	Daily drunker	18 (36.0)	30 (64.0)	1.71 (0.78, 3.76)	2.1 (0.80, 5.41)
	Never drunker	18 (24.7)	57 (75.3)	1	1
Smoking	Former smoker	21 (45.7)	25 (53.4)	2.57 (1.13, 5.86)	2.1 (0.77, 6.15)
	Never smoker	18 (30.5%)	41 (69.5)	1.34 (0.60, 3.00)	1.08 (0.39, 2.96)
	Unknown	15 (24.6)	46 (75.4)	1	1
Residency	Urban	25 (43.1)	33 (56.9)	2.06 (1.05, 4.04)	2.79 (1.23, 6.31)*
	Rural	29 (26.9)	79 (73.1)	1	1
Duration of illness	<4 years	11 (42.3)	13 (57.7)	1.65 (0.70, 3.89)	2.2 (0.75, 6.23)
	>4 years	43 (30.7)	99 (69.3)	1	1
HbsAg	Positive	28 (43.1)	37 (56.9)	2.18 (1.12, 4.23)	2.3 (1.06, 5.15)*
	Negative	26 (25.7)	75 (74.3)	1	1
Previous history of UGIB	Yes	22 (42.3)	30 (57.7)	1.87 (0.94, 3.72)	2.4 (0.93, 6.04)
	No	32 (28.1)	82 (71.9)	1	1
Serum Albumin in mg/dl	<3.5	12 (27.3)	32 (72.7)	0.71 (0.33, 1.52)	
	>3.5	42 (34.4)	80 (65.6)	1	
Platelets in thousands	<150	28 (50.9)	27 (49.1)	3.39 (1.70, 6.74)	2.4 (1.06, 5.24)*
	>150	26 (23.4)	85 (76.6)	1	1
CTP class	A	11 (26.8)	30 (73.2)	1	1
	B	30 (31.9)	64 (68.1)	1.27 (0.56, 2.89)	2.1 (0.78, 6.11)
	C	13 (41.9)	18 (58.1)	1.97 (0.73, 5.31)	2.8 (0.84, 9.85)

*Significate at a p-value<0.05 level and ** significant at a p-value <0.001 level; AOR: adjusted odds ratio; HBsAg: Hepatitis B surface antigen; COR: crude odds ration; CTP: Child-Turcotte-Pugh; UGIB; Upper Gastrointestinal bleeding

4. Discussion

The study found that the prevalence of UGIB among patients with CLD was 32.5%. Hepatitis B-positives, heavy alcohol drinkers, male gender, urban residents, and low platelet counts are associated with a higher occurrence of bleeding. This finding was lower than a study conducted in the University of Gondar Hospital, Northwest Ethiopia, Gonder (51.9%) [2], Pakistan (48%) [10], and Ghana (90.60%). The variation might be due to sample size, differ-

ences in clinical profiles of patients, like the proportion of thrombocytopenia, serum album level, and measurement of outcome, as well as the high burden of hepatosplenic schistosomiasis in northern Ethiopia.

However, the finding was higher than a study done at St. Paul's Hospital Millennium Medical College, Addis Ababa (10.2%) [5]. This is because the study reported that upper gastrointestinal bleeding upon admission could underestimate the prevalence because the study did not include patients who had experienced bleeding during hospitalization.

The study found a significant association between gender and UGIB, with males being 4 times more likely to develop it compared to females. This is because males are more likely to engage in alcoholism and tobacco use, which negatively impact liver function and can lead to alcohol-associated liver disease or alcoholic hepatitis (AH), fibrosis progression, and hepatocellular carcinoma, increasing the risk of upper gastrointestinal bleeding [17]. Similarly, urban residents are at a higher risk of upper gastrointestinal bleeding, with variceal bleeding being three times more common than in rural patients.

Alcohol consumption significantly increases the risk of upper gastrointestinal bleeding, with heavy drinkers 3.2 times more likely to develop variceal bleeding compared to non-alcoholics. This is the fact that due to Ethanol metabolism, enzymes are highly expressed in hepatocytes, leading to harmful effects on the liver. Chronic alcohol consumption leads to various hepatic lesions, including steatosis, hepatitis, and fibrosis/cirrhosis. The fibrotic response starts with active pericellular fibrosis, progressing to cirrhosis, characterized by liver scarring and vascular alterations, increasing the risk of upper GI bleeding [18].

Hepatitis B infection increases the risk of UGIB, with patients with the virus having about three times higher likelihood of developing upper GI bleeding. This is explained by the fact that Hepatitis B (HBV) patients often experience liver cirrhosis, portal hypertension, and hypersplenism, leading to upper gastrointestinal bleeding due to varicose vein rupture [19]. HBX protein levels can infect the gastric mucosa and worsen gastric mucosal injury by affecting apoptosis, gene expression, cell cycle, and proliferation in host cells, and its expression is linked to atrophy, metaplasia, and bleeding [20].

Furthermore, the study revealed that patients with thrombocytopenia are at a higher risk of upper gastrointestinal bleeding. Those patients with a platelet count below 150 thousand are 2.4 times more likely to experience variceal bleeding. The finding was supported by a study done at the University of Gondar Hospital, Northwest Ethiopia [2]. Platelet count is linked to Child-Turcotte-Pugh score and CTP grade B/C. Patients with chronic hepatitis B and cirrhosis have lower platelet counts and higher aspartate transaminase-to-platelet ratio index (APRI) and fibrosis index based on four factors (FIB-4) [21]. The stage of compensated cirrhosis increases the risk of varices, overt clinical decompensation (ascites, variceal hemorrhage, hepatic encephalopathy), post-surgical decompensation, and hepatocellular carcinoma [22].

Strengths and limitations of this Study

1) Since the study's design was retrospective cross-sectional, it cannot establish causal relationships between dependent and independent variables.
2) The reason why most patients were on low doses of beta blockers or even taking beta blockers was not assessed and hence requires further investigation.
3) Most patients never underwent upper GI endoscopy screening because of a lack of affordability before the resumption of our endoscopy services.
4) Liver biopsy and elastography were not used because of a lack of expertise and unavailability, respectively.
5) There is a possibility that many of the unknown liver diseases might have NAFLD, which needs further study.

5. Conclusion and Recommendations

The study found that the magnitude of UGIB was high among patients with CLD. Hepatitis B-positives, heavy alcohol drinkers, male gender, urban residents, and low platelet counts are associated with a higher occurrence of bleeding. Therefore, care providers should encourage HBV screening and vaccination, and provide emergency endoscopic therapy and medications to halt the progression of bleeding.

Abbreviations

AUGIB	Acute Upper Gastrointestinal Bleeding
ACG	American College of Gastroenterology
CLD	Chronic Liver Disease
GERD	Gastroesophageal Reflux Disease
GEV	Gastroesophageal Varices
GEV	Gastroesophageal Variceal Hemorrhage
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
H	PYLORI -Helicobacter Pylori
HSS	Hepatosplenic Schistosomiasis
INR/PT	International Normalization Ratio/Prothrombin Time

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Author Contributions

All authors have made substantial intellectual contributions to the conception and design of the study, and the acquisition, analysis, and interpretation of data. They have also been involved in drafting the manuscript, approved

the final manuscript, and agreed to be accountable for all aspects of this work.

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Data Availability

The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare no conflicts of interest.

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