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Outcomes and predictors of in-hospital mortality among cirrhotic patients with non-variceal upper gastrointestinal bleeding in upper Egypt

LIVER

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Original Article

ABSTRACT

Background/Aims: Variceal bleeding is one of the most frequent causes of morbidity and mortality among cirrhotic patients. Clinical endoscopic features and outcomes of cirrhotic patients with non-variceal upper gastrointestinal bleeding (NVUGIB) have been rarely reported. Our aim is to identify treatment outcomes and predictors of in-hospital mortality among cirrhotic patients with non-variceal bleeding in Upper Egypt.

Materials and Methods: A prospective study of 93 cirrhotic patients with NVUGIB who were admitted to the Tropical Medicine and Gastroenterology Department, Assiut University Hospital (Assiut, Egypt) over a one-year period (November 2011 to October 2012). Clinical features, endoscopic findings, clinical outcomes, and in-hospital mortality rates were studied. Patient mortality during hospital stay was reported. Many independent risk factors of mortality were evaluated by means of univariate and multiple logistic regression analyses.

Results: Of 93 patients, 65.6% were male with a mean age of 53.3 years. The most frequent cause of bleeding was duodenal ulceration (26.9%). Endoscopic treatment was needed in 45.2% of patients, rebleeding occurred in 4.3%, and the in-hospital mortality was 14%. Hypovolemic shock was the most common cause of death (46.2%). Independent risk factors of in-hospital mortality among cirrhotic patients with NVUGIB in our study were bacterial infection during hospitalization [odds ratio (OR) =0.32, 95% confidence interval (CI) =0.03-0.89], shock (OR =1.12, 95% CI =0.68-1.54), early rebleeding (OR =2.26, 95% CI =1.85-3.21), low serum albumin (OR =3.81, 95% CI =2.35-4.67), low baseline hemoglobin (OR =0.714, 95% CI =0.32-1.24), and the need for endoscopic treatment (OR =2.96, 95% CI =0.62-3.63).

Conclusion: Bacterial infection during hospitalization, shock, early rebleeding, low serum albumin, low baseline hemoglobin, and the need for endoscopic treatment were independent risk factors of in-hospital mortality among cirrhotic patients with NVUGIB in Upper Egypt.

Keywords: Cirrhosis, non-variceal upper gastrointestinal bleeding (NVUGIB), endoscopic findings, mortality, predictors of mortality

INTRODUCTION

Upper gastrointestinal (GI) bleeding is a common life-threatening condition with a reported mortality rate of 4%-15% in most studies (1-5). Upper GI bleeding is classified according to the presence of a variceal or non-variceal source of bleeding. Variceal bleeding in cirrhotic patients has been studied extensively (6-8). About 30%-40% of cirrhotic patients who bleed may have non-variceal upper GI bleeding (NVUGIB), which is frequently caused by gastroduodenal ulcers (9,10). Although NVUGIB is not uncommon among cirrhotic patients, clinical features and endoscopic findings of patients with this complication have rarely been reported (6,7,11,12). The aim of the current study was to identify the outcomes and predictors of in-hospital mortality after non-variceal bleeding among cirrhotic patients in Upper Egypt.

MATERIALS AND METHODS

Patients

All cirrhotic patients with NVUGIB, who were admitted to the Department of Tropical Medicine and Gastroenterology, Assiut University Hospital (Assiut, Egypt) over

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a one-year period from November 2011 to October 2012, were included in this prospective study.

A complete history, thorough physical examination, monitoring of vital signs, establishment of an intravenous line, and resuscitation, when needed, was performed for each patient. Intravenous fluids were administered to all patients with an insufficient fluid volume status. The number of transfused blood units was indicated according to individual requirements.

Liver function and serum creatinine were assessed on admission and serially during hospitalization. Complete blood count, serum sodium, and number of units of blood received were recorded. All patients underwent upper endoscopy within 12-24 h of admission and therapy was initiated according to the endoscopic findings. For all patients, ciprofloxacin (500 mg every 12 h) was administered orally for 5 days. Patients with an actively bleeding peptic ulcer or visible vessels received an injection of adrenaline, followed by continuous omeprazole infusion at 8 mg/h for 3 days, which was then continued orally (13). Urine analysis, chest X-ray, ascitic fluid analysis, and fluid culture (if needed) were performed to detect sources of infection. All patients underwent abdominal ultra-sonography and testing for the surface antigen of the hepatitis B virus (HBsAg) and hepatitis C virus antibodies (HCV Abs).

Of 532 consecutive patients with cirrhosis and upper GI bleeding who were treated at our department over the one-year study period, 439 (82.5%) had variceal bleeding and 93 (17.5%) had NVUGIB.

Exclusion criteria

Patients with bleeding due to esophageal varices or gastric varices were excluded.

Definitions

The following definitions, used for analysis of the results, were established before collection of patient data.

Cirrhosis: Diagnosis based on a combination of physical signs, biochemical tests, and ultrasonographic findings.

Severity of liver disease: Hepatic function on admission was graded according to the Child-Turcotte-Pugh classification criteria (14).

Bleeding from a variceal source: Considered if the initial endoscopy showed any signs of variceal hemorrhage according to the Baveno Consensus Workshop guidelines (15). These patients were excluded from the study.

Early rebleeding: Defined as a new hematemesis or melena after a 24-h period of stable vital signs and hemoglobin levels, as defined by the Baveno Consensus Workshop guidelines (15).

The intensity of GI bleeding (GIB) was classified as follows: moderate, requirement of <4 U of packed red blood cells (PRBCs); **severe**, requirement of 4-6 U of PRBC; and **massive**, presence of hypovolemic shock and/or the requirement of >6 U of PRBCs. Hypovolemic shock was defined as systolic blood pressure <90 mmHg or a reduction of >40 mmHg compared with the baseline, together with signs of hypoperfusion unresponsive to the administration of plasma expanders and PRBCs (16).

In-hospital mortality: Defined as death during hospital stay. The cause of death was also determined.

Bacterial infection: Defined as spontaneous bacterial peritonitis (ascitic fluid culture and ascitic fluid polymorphonuclear cell count ≥250/mm^3), urinary tract infection (urinalysis and urine culture), and/or pneumonia (chest X-ray and sputum culture). Other infections were diagnosed according to clinical, radiological, and bacteriological data (17).

Ischemic hepatitis: Defined as an 8-fold increase or greater in aspartate transaminase and alanine transaminase levels over normal or baseline values (18).

Renal failure: Defined as an increase in serum creatinine of ≥50% with respect to the baseline value to a value >1.5 mg/dL within the first 7 days after hemorrhage or until the end of hospitalization or death, if shorter. A cut-off serum creatinine value of 1.5 mg/dL was used, because previous studies have shown that patients with cirrhosis and creatinine above this level have a markedly reduced glomerular filtration rate (19), and this value is used in the definition of hepatorenal syndrome (20).

Ethical considerations

Before enrollment, all participants submitted signed informed consent forms after receiving a detailed explanation of the study objectives. Participants were clearly informed that refusing to participate will not affect full access to available medical services and treatment. Data were collected by personal interview with participants, taking in consideration data confidentiality. The study protocol was approved by the Faculty of Medicine Ethical Committee.

Statistic analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (ver. 17; SPSS Inc., Chicago, IL, USA). All data are expressed as mean ± standard deviation (SD) or frequency. Continuous variables were compared using the Student's *t*-test and proportions were compared by chi-squared tests. Univariate analysis was performed to identify predictive factors of in-hospital mortality. Variables that reached statistical significance in the univariate analyses were subsequently included in multivariate analyses. Results are presented as mean±SD. A probability (p) value of <0.05 was considered statistically significant.

RESULTS

A total of 93 patients (65.6% males) were included in the study, of whom 84.9% were positive for HCV Abs and 80.9% were classified as Child-Turcotte-Pugh grade C. Early rebleeding occurred in 4.3% of cases. Bacterial infection during hospitalization occurred in 10.7% of cases. Spontaneous bacterial peritonitis was present in 6.4% of cases (diagnosed by ascitic fluid analysis and culture). Pneumonia was present in 2.15% of cases (diagnosed by chest X-ray and sputum culture). Urinary tract infection was present in 2.15% of cases (diagnosed by urinalysis and urine culture) (Table 1).

The most common sources of bleeding at endoscopy were duodenal ulceration (26.9%), congestive gastropathy (25.8%), gastric erosion (24.7%), and duodenal erosion (21.5%) (Table 2). Adherent blood clot (46.4%) was the most common sign of recent bleeding from an ulcer, followed by a clean ulcer base (Table 3). Proton pump inhibitors were administered to 91.4% of patients and endoscopic treatment (epinephrine injection or argon plasma coagulation) was required in 45.2% (Table 4).

In-hospital mortality among cirrhotic patients with NVUGIB was 14%. As shown in Table 5, causes of death included hypovolemic shock (46.2%), renal failure (23.1%), end-stage liver failure (23.1%), and hepatic encephalopathy/HCC (7.7 %).

Of 26 variables analyzed in regard to in-hospital mortality, 13 had predictive value according to univariate analysis (Table 6). Analysis of 13 risk factors by multivariate analysis showed that six had independent predictive value for in-hospital mortality, which included bacterial infection during hospitalization, shock, early rebleeding, baseline hemoglobin, low serum albumin, and need for endoscopic treatment (Table 7).

DISCUSSION

Non-variceal bleeding occurs in 30%-40% of all patients with upper GI hemorrhage (9,10). Hence identification of predictors of mortality among such patients may be helpful to improve treatment outcomes. Most previous studies have focused on characteristics of variceal bleeding, whereas relatively few reports have considered non-variceal and variceal bleeding together (6,11,12). Clinical and endoscopic features, as well as treatment outcomes of cirrhotic patients with NVUGIB have been rarely reported (13).

Our study disclosed several important observations. First, NVUGIB occurred in 17.5% of cirrhotic patients. Second, duodenal ulceration was the most common cause of NVUGIB. Third, the rate of in-hospital mortality because of NVUGIB among cirrhotic patients was 14%. Fourth, independent risk factors for in-hospital mortality because of NVUGIB among cirrhotic patients included bacterial infection during hospitalization, shock, early rebleeding, low serum albumin, low baseline hemoglobin, and the need for endoscopic treatment.

Table 1. Demographic, clinical, and laboratory characteristics of cirrhotic patients with non-variceal upper gastrointestinal bleeding (n=93)

Characteristics	Mean±SD n (%)
Male gender	61 (65.6%)
Age (years)	53.3±11.2
Etiology of liver cirrhosis:	
HCV Ab +ve	79 (84.9%)
HBs Ag +ve	9 (9.7%)
HCV/HBV co-infection	3 (3.2%)
Negative HCV infection and Negative HBV infection	2 (2.2%)
Child-turcotte-pugh grade	
A	6 (6.4%)
B	12 (12.9%)
C	75 (80.7%)
Hepatic encephalopathy	7 (7.5%)
Ascites on admission	25 (26.9%)
Jaundice on admission	16 (17.2%)
Hepatocellular carcinoma	7 (7.5%)
Bacterial infection during hospitalization	10 (10.7%)
Spontaneous bacterial peritonitis	6 (6.4%)
Pneumonia	2 (2.15%)
Urinary tract infection	2 (2.15%)
Comorbidities	
Diabetes mellitus	22 (23.7%)
Cardiovascular disease	10 (10.7%)
COPD	5 (5.4%)
Bleeding risk factors	
Chronic NSAID use	22 (23.7%)
Tobacco use	48 (51.6%)
History of previous bleeding	7 (7.5%)
Clinical manifestations	
Melena	53 (62.4%)
Red bright hematemesis	36 (38.7%)
Coffee-ground hematemesis	21 (22.6%)
Laboratory data on admission	
Serum hemoglobin (g/dL)	9.2±3.2
Total bilirubin (umol/L)	35.5±5.7
Serum albumin (g/dL)	2.08±0.7
Serum ALT (IU/L)	54±15
Serum AST (IU/L)	63±21
Prothrombin time (seconds)	17.1±6.6
Serum creatinine (µmol/L)	111.5±5.4
Serum sodium (mEq/L)	141.7±0.38
Platelets count (× 10^9 µ/L)	126.06±15.83
Others factors	
In-hospital bleeding	4 (4.3%)
Homodynamic instability on admission	27 (29%)
Patients requiring blood transfusions	57 (61.3%)
Blood units transfused	2.4±0.61
Rockall score	5.12±1.7

COPD: chronic obstructive pulmonary diseases; NSAID: non-steroidal antiinflammatory drugs; HBsAg: hepatitis B virus; HCV Abs: hepatitis C virus antibodies

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Table 2. Source of bleeding at endoscopy

Source of bleeding	Number (%) (n=93)
Duodenal ulcers	25 (26.9%)
Congestive gastropathy	24 (25.8%)
Gastric erosions	23 (24.7%)
Duodenal erosions	20 (21.5%)
Angiodysplasia	8 (8.6%)
Lower esophageal ulcers	5 (5.4%)
Gastric ulcers	3 (3.2%)

N.B. More than one lesion as a source of bleeding in some patients

Table 3. Stigmata of recent hemorrhage from ulcer (n=28)

Stigmata of recent bleeding	Number (%) (n=28)
Spurter	2 (7.1%)
Visible vessel	2 (7.1%)
Adherent clot	13 (46.4%)
Flat spots	0 (0%)
Clean base	6 (21.4%)
No stigmata of recent bleeding	5 (17.9%)

Table 4. Medical and endoscopic treatment of cirrhotic patients with non-variceal upper gastrointestinal bleeding

Treatment	Number (%) (n=93)
Medical treatment	
Proton Pump inhibitors	85 (91.4%)
Endoscopic treatment	42 (45.2%)
Epinephrine injection	23 (24.8%)
Argon plasma coagulation	19 (20.4%)

Table 5. Outcomes and causes of in-hospital mortality among cirrhotic patients with non-variceal upper gastrointestinal bleeding

	Number (%)
Outcomes (n=93): Clinical rebleeding	4 (4.3%)
In-hospital mortality	13 (14%)
Mortality causes (n=13): Hypovolemic shock	6 (46.2%)
Renal failure	3 (23.1%)
End-stage liver cell failure	3 (23.1%)
Hepatic encephalopathy plus HCC	1 (7.7%)

Liver cirrhosis is a clinically labile condition, so NVUGIB certainly has particular implications in the clinical evolution of cirrhosis as compared with non-cirrhotic patients (12). Our in-hospital mortality rate was similar to that reported by González-González et al. (13) (14% vs. 13.8%, respectively) in spite of the differences in patient-related factors in the two studies, such as the ratio of patients with a Child-Turcotte-Pugh grade of C (80.7% vs. 26%, respectively) and ulceration as the primary source of bleeding (30.1% vs. 50.6%, respectively). In addition, the primary etiology of cirrhosis in our cohort was HCV infection (84.9%), whereas alcohol consumption was the main cause of cirrhosis (63.8%) reported by González-González et al. (13).

The frequency of duodenal ulcers in our study was similar to that reported in non-cirrhotic patients (2,21) and was considered the most common cause of non-variceal bleeding in cirrhotic patients, followed by gastropathy, gastric erosion, duodenal erosion, angiodysplasia, lower esophageal ulcers, and gastric ulcers. Peptic ulcers in cirrhotic patients may increase the risk of bleeding because of coagulation disorders and thrombocytopenia, which is frequently observed in these patients (22).

In our study, the rebleeding rate was slightly higher than that reported in non-cirrhotic patients (4.3% vs. 3.2%) (2) and also higher than that reported by González-González et al. (13) among cirrhotic patients with non-variceal bleeding (4.3% vs. 1.9%), which may be explained by patient-related factors.

In-hospital mortality was significantly higher in our study than that reported for non-cirrhotic patients in three previous studies (14% vs. 5.4 %, 4.5 %, and 4.6 %, respectively) (2,21,23), but similar to that reported in cirrhotic patients (14% vs. 13.8%) (13).

Hypovolemic shock was the most common cause of death (46.2%) in our study, whereas the remaining causes of deaths were associated with end-stage liver failure (23.1%), renal failure (23.1%), and hepatic encephalopathy plus hepatocellular carcinoma (7.7%). Death was directly related to a bleeding episode in 29.2% of non-cirrhotic patients, and comorbidities had a fundamental role in the occurrence of death in the remaining cases (4). González-González et al. (13) reported that the most common causes of death in cirrhotic patients with non-variceal bleeding were hypovolemic shock (36.4%), renal failure (36.4%), and liver failure (13.6%).

Predictors of in-hospital mortality among cirrhotic patients with NVUGIB in our study were bacterial infection during hospitalization, shock, early rebleeding, low serum albumin, low baseline hemoglobin, and endoscopic treatment, whereas the following predictors were observed in the non-cirrhotic patients: severity of a bleeding episode, functional class, in-hospital bleeding, number of comorbidities, and advanced age (2,12,21,24,25).

Cryptogenic etiology of cirrhosis, low serum albumin, and active bleeding at the ulcer base were independent predictors of in-hospital mortality among cirrhotic patients with NVUGIB (13), although these predictors differed from those of in-hospital mortality in our study, with the exception of low serum albumin, which was an independent predictor of in-hospital mortality in both studies. The need for endoscopic treatment was an independent predictor of in-hospital mortality among

Table 6. Univariate analysis of risk factors for in-hospital mortality

Variables	Death (n=13)	No death (n=80)	p value
Sex			
Male	9 (69.2%)	52 (65%)	0.766
Female	4 (30.8%)	28 (35%)	
Age, years (mean±SD)	56.5±12.4	52.2±10.2	0.333
Renal failure	3 (23.1%)	0 (0%)	0.000*
Encephalopathy on admission	1 (7.7%)	6 (7.5%)	1.000
Presence of jaundice	6 (46.1%)	10 (12.5%)	0.010*
Presence of ascites on admission	10 (76.9%)	15 (18.7%)	0.000*
Bacterial infection during hospitalization	7 (53.9%)	3 (3.7%)	0.000*
Hepatocellular carcinoma	1 (7.7%)	6 (7.5%)	0.981
Intensity of GIB (severe or massive)	10 (76.9%)	15 (18.7%)	0.000*
Shock	6 (46.1%)	9 (11.25%)	0.000*
Child-Turcotte-Pugh grade C	13 (100%)	62 (77.5%)	0.127
Early rebleeding	4 (30.8%)	0 (0.0%)	0.000*
Ischemic hepatitis	8 (61.5%)	10 (12.5%)	0.000*
Baseline hemoglobin (g/dL)	8.1±0.55	9.51±0.17	0.000*
Total bilirubin (μmol/L)	40.11±8.25	34.17±5.12	0.612
Serum albumin (g/dL)	1.81±0.13	2.23±0.05	0.000*
Prothrombin time (s)	21.84±1.27	16.32±0.64	0.062
Number of units of blood transfused	2.8±0.45	2.3±0.24	0.000*
Platelet count ($\times 10^9$ u/L)	119.02±18.11	128.80±5.01	0.732
Serum sodium (mEq/L)	132.15±2.35	135.41±1.02	0.436
Etiology of cirrhosis			
HCV Ab +ve	11 (84.6%)	68 (85%)	0.972
HBs Ag +ve	2 (15.4%)	7 (8.75%)	0.746
HCV/HBV co-infection	0 (0%)	3 (3.75%)	0.712
Negative for HCV and HBV infection	0 (0%)	2 (2.5%)	0.852
Comorbidities:			
Diabetes mellitus	4 (30.8%)	18 (22.5%)	0.836
Cardiovascular disease	1 (7.7%)	9 (11.25%)	0.913
COPD	1 (7.7%)	4 (5%)	0.823
Ulcer as source of bleeding	10 (76.9%)	18 (22.5%)	0.02*
Stigmata of recent bleeding from ulcer	9/10 (90%)	14/18 (77.7%)	0.726
The need for endoscopic treatment	13 (100%)	29 (36.25%)	0.03*
Rockall's score	5.22±1.2	5.08±1.9	0.634

* Statistically significant difference ($p<0.05$)
COPD: chronic obstructive pulmonary disease

Table 7. Multivariate analysis of risk factors for in-hospital mortality

Variables	Death (n=13)	No death (n=80)	OR	95% CI	p value
Bacterial infection during hospitalization	7 (53.9%)	3 (3.7%)	0.32	0.03-0.89	0.000
Shock	9 (69.2%)	11 (13.7%)	1.12	0.68-1.54	0.04
Early rebleeding	4 (30.8%)	0 (0.0%)	2.26	1.85-3.21	0.018
Baseline hemoglobin (g/dL)	8.1±0.55	9.51±0.17	0.714	0.32-1.24	0.035
Serum albumin (g/dL)	1.81±0.13	2.23±0.05	3.81	2.35-4.67	0.006
The need for endoscopic treatment	13 (100%)	29 (36.25%)	2.96	0.62-3.63	0.002

CI: confidence interval; OR: odds ratio

cirrhotic patients with NVUGIB in our study (45.2%), although this factor was not significant in the multivariate analysis performed by González-González et al. (13).

Two limitations to this study that should be addressed include the small number of patients in our cohort and the lack of a control group of non-cirrhotic patients.

The in-hospital mortality rate among cirrhotic patients with NVUGIB was greater than that of non-cirrhotic patients. Duodenal ulcers, congestive gastropathy, gastric erosion, and duodenal erosion were the most common causes of NVUGIB among cirrhotic patients. Hypovolemic shock was the most common cause of in-hospital mortality among cirrhotic patients with NVUGIB. Bacterial infection during hospitalization, shock, early rebleeding, low serum albumin, low baseline hemoglobin, and the need for endoscopic treatment were independent risk factors for in-hospital mortality among cirrhotic patients with NVUGIB.

Ethics Committee Approval: Ethics committee approval was received for this study.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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