Original Article

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Incidence and predictors of acute oesophageal variceal haemorrhage in patients with spontaneous bacterial peritonitis

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Abstract

Background: Rupture oesophageal varices (REV) is a life-threatening complication of liver cirrhosis. Bacterial infection is linked with the risk of variceal bleeding through complex pathophysiologic pathways. Spontaneous bacterial peritonitis (SBP) is the commonest well-known bacterial infection in patients with cirrhosis. the aim of this study is to estimate the incidence and predictors of REV in cirrhotic patients with SBP.

Patients and methods: 389 patients with cirrhotic ascites out of 2880 patients with ascites and/or acute gastrointestinal bleeding were divided into two groups, group 1 included 189 patients with SBP and group 2 included 200 patients without SBP. Routine clinical and laboratory data were collected. **Results:** Compared to patients without SBP, patients with SBP had significant higher incidence of oesophageal variceal hemorrhage (25.4% in patients with SBP versus 14% in patients without SBP (P =0.004). multivariate analysis for factors associated with oesophageal variceal haemorrhage in patients with SBP demonstrated that, the independent predictors for rupture oesophageal varices in patients with SBP were, increased age (p value= 0.001) with EXP(B) 1.068; 95.0% C.I. was (1.026-1.113), presence of fever (p value= 0.005) with EXP(B) 3.433; 95.0% C.I. was (1.458-8.083) and hepatic encephalopathy (p value= 0.039) with EXP(B) 3.159; 95.0% C.I. was (1.060-9.421). **Conclusion:** Spontaneous bacterial peritonitis increases the risk of oesophageal variceal haemorrhage. Increased age, presence of fever and hepatic encephalopathy were independent predictors of acute oesophageal variceal haemorrhage in patients with SBP.

Introduction

Liver cirrhosis is a chronic disease of the liver which s commonly complicated by increased portal venous pressure and formation of esophageal varices [1]. The incidence of esophageal varices in cirrhotic patients is around 5% at the end of one year and 28% at the end of three years. Small varices progress to large varices at a rate of 10% to 12% annually [2]. Approximately 50% of all patients with a new diagnosis of cirrhosis have gastrointestinal varices [3].

The rate of acute oesophageal variceal haemorrhage (AEVH) is 5–15%/ year and the risk of bleeding increases in presence of larger varices, red-signs and advanced liver disease [4-7]. Despite improvement in therapy, overall mortality with each episode of variceal haemorrhage remains around 15% to 25% at six weeks. Such risk is much higher in patients who develop variceal hemorrhage (VH) in combination with other forms of decompensation than in those presenting with VH as an isolated decompensating event [9-10].

Ascites is a grave complication of decompensated liver cirrhosis with about 75% occur as a result of portal hypertension and the remainder because of infectious, inflammatory and infiltrative conditions [10-15]. In cirrhotic patients, bacterial infections are a public complication and connected with increases the morbidity and mortality [16-18]. Furthermore, bacterial infections can lead to acute kidney injury, jaundice, coagulopathy and encephalopathy that result from worsening vasodilatation and a systemic inflammatory state [19].

Spontaneous bacterial peritonitis (SBP) is a grave complication that occurs amongst cirrhotic patients with ascites. This infection develops in approximately 10-30% of cirrhotic ascetic patients [20]. Bacterial infections are frequently associated with upper gastrointestinal bleeding in cirrhotic patients. The impact of SBP on rate of oesophageal variceal haemorrhage in studies is scarce. Therefore, the aim of this study is to evaluate the incidence and risk factors of oesophageal variceal haemorrhage in patients with spontaneous bacterial peritonitis.

Patients and methods

This is a retrospective observational cohort study including patients with cirrhotic ascites and/or with upper gastrointestinal bleeding (UGIB) referred to Tropical and Internal Medicine Departments, Mansoura University from October 2020 to June 2022. At time of admission all patients presented with UGIB were recorded and immediately received standard conservative therapy (plasma volume expanders, blood transfusion, vasoactive drugs, and ceftriaxone (1 g/24 hours) followed by endoscopic interventions (8-12 hours following admission).

Directly following admission, all patients were subjected to complete history taking, physical examination

Keywords: Acute oesophageal variceal haemorrhage, oesophageal varices, spontaneous bacterial peritonitis, liver cirrhosis.

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and laboratory investigations including, albumin, total bilirubin, liver enzymes, creatinine, sodium, potassium, haemoglobin levels, leukocytic count, platelet count, prothrombin time, and INR. Abdominal ultrasonography was done to define hepatic cirrhosis, ascites and portal hypertension.

Inclusion criteria: Cirrhotic ascites patients presented with upper gastrointestinal bleeding due to rupture esophageal varices.

Exclusion criteria: Patients who had taken antibiotics former to hospital admission or on prophylactic antibiotics for SBP or on anticoagulant medications, non-cirrhotic ascites (cardiac, renal and malignant), secondary bacterial peritonitis, unrelated infection (e.g., skin and lung infection. Similarly, patients unable to tolerate endoscopy (e.g. comatose patients), patients who had withdrawn their informed consent to participate in the study. Besides, patients with causes of upper GIT bleeding other than ruptured oesophageal varices (e.g., isolated gastric varices, malignancy, portal hypertensive gastropathy.

Patient classification: After exclusion of the patients presented with upper gastrointestinal bleeding who were not fulfilled the inclusion criteria for the study, 389 patients with cirrhotic ascites and/or UGIB due to rupture oesophageal varices were included in the study. The patients were divided into two groups, the first group was patients with spontaneous bacterial peritonitis (included 189 patients) and the second group was patients with cirrhotic ascites without spontaneous bacterial peritonitis (included 200 patients).

Diagnosis of spontaneous bacterial peritonitis: Immediately following admission, 15 ml ascitic fluid samples were aspirated under the complete aseptic state at the bedside. 10 ml were directly inoculated in aerobic and anaerobic blood culture bottles. The remaining amount of ascitic fluid was used for biochemical and cytological investigation in tubes containing EDTA and analyzed in 3 hours of aspiration. Ziehl-Neelsen staining of the ascitic fluid was done when required. SBP was diagnosed if the polymorph nuclear neutrophil cell count in the ascitic fluid is ≥250/mm3 with positive culture of ascitic fluid (culture positive SBP) or culture negative neutrocytic ascites with PMN > 250/mm3 and a negative ascitic fluid culture in the absence of other causes of peritonitis and hemorrhagic ascites. The study was approved by our university Institutional ethical Committee and carried out in accordance with the guidelines of the Helsinki Declaration (1975).

Results

Out of 2880 patients with ascites and or acute gastrointestinal bleeding included in this study. 389 patients with cirrhotic ascites and/or UGIB due to rupture oesophageal varices were included in the study **Figure 1**. In this study, we found a significant increase in incidence of rupture oesophageal varices among cirrhotic ascetic patients with spontaneous bacterial peritonitis 25.4% (48/189 patients) versus patients without spontaneous bacterial peritonitis 13.5% (28/200 patients) (p value=0.004).

Table 1 shows demographic, clinical and biochemical details of studied groups. The two groups were matched for age, sex and etiology of cirrhosis. Compared to patients without SBP, patients with SBP showed a significant increase as regards, ROV, fever, serum creatinine, CRP and blood WBC and significant non-significant differences were found between both groups regarding, INR, HE, serum albumin, bilirubin, AST, ALT, hemoglobin and platelets.

Table 2 shows that, among the 189 patients with SBP, 48 patients had oesophageal variceal haemorrhage (EVH). Compared to patients with SBP without EVH, patients with SBP and EVH showed a significant increase as regards, age, fever, HE and serum CRP. However, non-significant differences were found as regarding other studied parameters between both groups.

To determine predictive parameters for oesophageal variceal haemorrhage among patients with SBP, variables with significant associations on univariate analysis were subjected to multivariate analysis. Increased age (p value= 0.001) with EXP(B) 1.068; 95.0% C.I. for EXP(B) (1.026-1.113), presence of fever (p value= 0.005) with EXP(B) 3.433; 95.0% C.I. for EXP(B) (1.458-8.083) and hepatic encephalopathy (p value= 0.039) with EXP(B) 3.159; 95.0% C.I. for EXP(B) (1.060-9.421) were independent predictors of oesophageal variceal haemorrhage in patients with SBP **Table 3**.

Discussion

Oesophageal variceal haemorrhage is a medical emergency [21]. In cirrhotic patients, bacterial infection increases the morbidity and mortality [22-24]. Among bacterial infection in cirrhotic patients, SBP is the most serious and most common form of infection with hospital-mortality rate about 20%. However, nowadays the mortality from spontaneous bacterial peritonitis may be decreasing because of advances in its diagnosis and treatment [25-28].

In this study, we aimed to estimate the incidence of oesophageal variceal haemorrhage in patients with spontaneous bacterial peritonitis. We found that, the incidence of EVH in patients with SBP was 25.4% which is more significant higher than that was found in cirrhotic ascetic patients without SBP (14%).

Previous study found that, bacterial infections in cirrhotic patients are common. There is a tendency to intestinal bacterial overgrowth, intestinal dysmotility, and increased intestinal permeability, all leading to an increase in bacterial translocation. Bacterial translocation is the probable mechanism for spontaneous bacterial peritonitis and source of bacterial byproducts such as endotoxin which can cause an increase in portal pressure, impairment of liver function, and worsening of haemostasis [29]

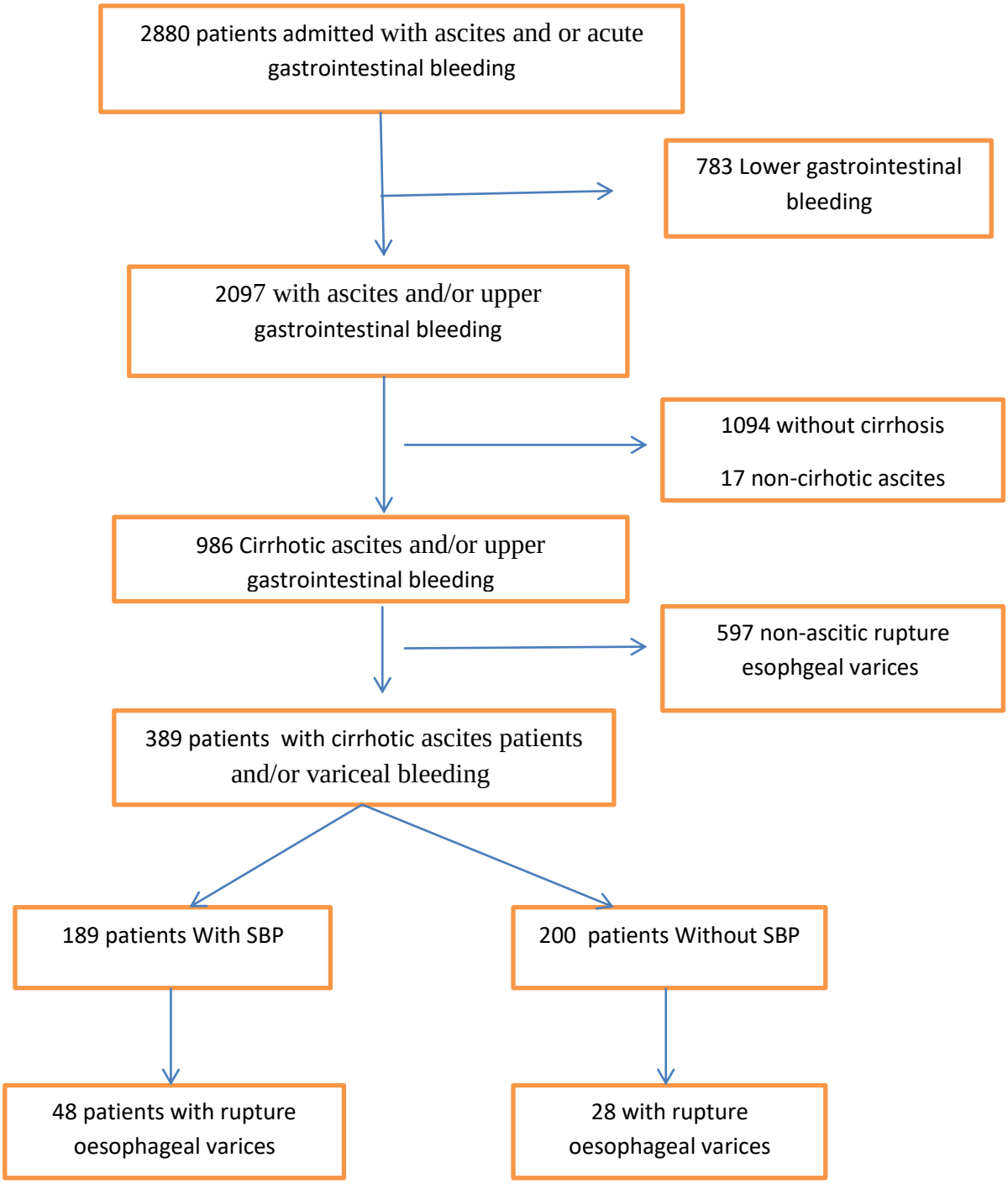

Figure 1: Flow diagram of the patient study.

Table 1. Demographic, clinical and biochemical characteristic of studied patient.

Parameters	SBP (N=189)	Non-SBP (N=200)	P value
Age	55.63±8.99	55.42±9.04	0.64
Sex: M/F	126/63	(84/57	0.113
HCV (N/%)	135(71.4%)	142(71.0%)	0.5
HBV (N/%)	33(17.5%)	28(14.0%)	0.212
DM: (N/%)	66(34.9%)	80(40.0%)	0.17
REV(N/%)	48 (25.4%)	28 (14%)	0.004
Fever: (N/%)	105 (55.6%)	68 (34.0%)	0.001
Albumin: g/dl	2.32± .6	2.36±0.63	0.41
Bilirubin: mg/dl	2.32± .60	2.36±0.63	0.46
AST(U/L)	63(37.37-104.50)	60(29-107)	0.68
ALT(U/L)	30.5(21.22-41.7)	34(21-48)	0.158
INR	1.60±0.55	1.62±0.48	0.59
CPS (N): B/C	25/164	23/177	0 .604
Creatinine: mg/dl	1.4(.9-2.1)	1.2(.80-1.97)	0.05
CRP: mg/dl	24(7 -84)	48(12-96)	<0.001
WBC (10^3/cmm)	8530 (5280-13100)	6500 (4460-1.2400)	0.003
Hemoglobin: g/dl	10.49±2.148	10.36±2.02	0.57
Platelets (10^9/L)	79000 (46000-12900)	79000 (48000-12800)	0.711

HCV, hepatitis C virus**; HBV,** hepatitis B virus**; DM,** diabetes mellitus**; REV**, Rupture oesophageal varices**; HE,** hepatic encephalopathy**; ALT,** alanine aminotransferase**; AST,** aspartate aminotransferase**; CPS,** Child–Pugh score; **CRP,** C reactive protein.

Table 2: Comparison between patients with spontaneous bacterial peritonitis with and without acute oesophageal variceal haemorrhage.

	Oesophageal variceal haemorrhage (48)	Without oesophageal variceal haemorrhage (141)	P value
Age	58.31±11.44	54.72±7.83	0.023
Sex: M/F	33/15	93/48 (66.0%)	0.43
HCV: (N/%)	33(68.8%)	102(72.3%)	0.38
HBV: (N/%)	9(18.8%)	24(17.0%)	0.47
DM: (N/%)	18(37.5%)	48(34.0%)	0.39
HE: (N/%)	42(87.5%)	105 (74.5%)	0.04
Fever : (N/%)	36(75.0%)	69(48.9%)	0.001
Albumin: g/dl	2.37±0.68	2.33±0.44	0.62
Bilirubin: mg/dl	3.65(1.85-5.05)	3.40(1.8-7)	0.41
AST(U/L)	60.5(43.5-94.5)	66.5(37-110.75)	0.96
ALT(U/L)	32(21-40.25)	29.5(21.92-42.75)	0.81
INR	1.65±0.55	1.66±0.48	0.87
CPS (N): B/C	8/40	17/124	0.415
Creatinine: mg/dl	1.4(1.1-2.02)	1.4(.8-2.2)	0.42
CRP: mg/dl	63(24-96)	48(12-48)	0.01
WBC (10^3/cmm)	8795(5025-17950)	8530(5280-13100)	0.52
Hemoglobin: g/dl	9.73±1.87	10.57±2.04	0.07
Platelets (10^9/L)	65500(50000-124000)	79000(45200-136000)	0.9

HCV, hepatitis C virus**; HBV,** hepatitis B virus**; DM,** diabetes mellitus**; REV,** Rupture oesophageal varices**; HE,** hepatic encephalopathy**; ALT,** alanine aminotransferase**; AST,** aspartate aminotransferase**; CPS,** Child–Pugh score**; CRP,** C reactive protein.

Table 3. multivariate analysis of risk factors associated with acute oesophageal variceal haemorrhage among patients with spontaneous bacterial peritonitis.

	B	Sig.	Exp (B)	95.0% C.I. for EXP(B)	
				Lower	Upper
Age	.066	.001	1.068	1.026	1.113
CRP	.010	.108	1.010	.998	1.022
Fever	1.233	.005	3.433	1.458	8.083
HE	1.150	.039	3.159	1.060	9.421
Constant	-6.320-	.000	.002		

CRP, C reactive protein**; HE,** hepatic encephalopathy

There are several mechanisms suggested for the increased incidence of EVH in patients with SBP; first is that, infection contribute worsening of liver function which is a recognized risk factor for variceal bleeding, or indeed be a trigger for variceal haemorrhage, particularly as the liver damage occurring in sepsis may itself contribute to an acute increase in portal hypertension that is a major risk factor for AEVH in additions to liver dysfunction, and to the variceal size [30].The second is that, bacterial translocation and gut barrier impairment are common phenomena in cirrhotic ascitic patients with SBP has been associated with hemodynamic changes and portal hypertension[31-33] and directly related to the risk of variceal bleeding via increased release of endotoxin and viable bacteria into the portal and systemic circulation leads to increase in nitric oxide and TNF-α producing a reduced response to vasoconstrictors and increasing risk of variceal bleeding [29,34].

The third is that, endotoxaemia secondary to bacterial infection may indeed be the critical trigger for variceal haemorrhage as it produces a wide series of effects that may predispose the cirrhotic patient to bleeding such as impairment of primary and secondary haemostasis, increase in portal pressure, and worsening of liver function [35]. The fourth is, in patients with large varices and a high wall tension, the release of endotoxin into the systemic circulation during episodes of bacterial infection results in a further increase in portal pressure through the induction of endothelin and possibly vasoconstrictive cyclo-oxygenase products. The subsequent contraction of hepatic stellate cells causes a rise in intrahepatic vascular resistance, Furthermore, endotoxin-induced nitric oxide and prostacyclin could inhibit platelet aggregation, thus resulting in variceal bleeding [35, 36]. In addition, the presence of bacterial infection in cirrhotic patients has been associated with increased endogenous heparin-like activity, which inhibits platelet aggregation and leads to a higher risk of bleeding [37].

In this study, compared to patients with SBP without AEVH, patients with SBP and AEVH showed a significant increase as regards, age, fever, HE and serum CRP.

In this study, multivariate analysis demonstrated that, increasing age, presence of fever and hepatic encephalopathy were independent predictors of oesophageal variceal haemorrhage in patients with SBP. Study found a non-significant association between age and AEVH in cirrhotic patients [38]. A previous study identified hepatic encephalopathy as a risk factor of acute variceal bleeding in patients with SBP [39]. However, another study found no relation between fever and acute oesophageal variceal haemorrhage [40].

Conclusion

Spontaneous bacterial peritonitis is a risk factor for acute oesophageal variceal haemorrhage. In patients with SBP, increased age, presence of fever and hepatic encephalopathy were independent predictors of oesophageal variceal haemorrhage.

Ethical approval.

The Ethical Committee at Mansoura University, Egypt, approved the study protocol for this study.

This research has received no outside funds.

Conflict of interest

There are no conflicts of interest declared by the authors.

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