Original Article

Factors predicting in-hospital mortality in patients with cirrhosis hospitalized with gastro-esophageal variceal hemorrhage

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Aim: To identify factors at the time of admission that predict in-hospital mortality in patients with gastro-esophageal variceal hemorrhage. **Methods**: Case records of patients admitted with gastro-esophageal variceal hemorrhage between January 1998 and October 2003 were retrospectively analyzed. Relevant clinical and laboratory parameters, and their relationship to mortality, were studied. Clinical parameters assessed included Child-Pugh class, ascites, portosystemic encephalopathy (PSE), and occurrence of rebleed within 24 hours of esophago-gastroduodenoscopy. The laboratory parameters assessed were: hemoglobin, prothrombin time, serum bilirubin, creatinine, and albumin. **Results**: Of the 343 patients admitted during the study period, 30 (8.7%) died in hospital. Serum bilirubin (2.4 versus 1.6 mg/dL) and serum creatinine (2.1 vs 1.1 mg/dL) levels were higher among non-survivors than among survivors. Non-survivors were also more likely to suffer from PSE (53%) than survivors (17%), while rebleeding within 24 hours of endoscopy occurred in 40% and 5% of these groups, respectively. On multivariate analysis, serum creatinine >1.5 mg/dL at the time of admission ($p<0.001$), serum bilirubin >3 mg/dL ($p<0.001$), presence of PSE ($p=0.003$), and rebleed within 24 hours of endoscopy ($p<0.001$) were significant predictors of mortality. **Conclusion**: Serum creatinine and bilirubin levels, presence of PSE, and rebleeding within 24 hours of initial endoscopy are independent predictors of mortality in patients with gastro-esophageal variceal bleeding. [*Indian J Gastroenterol* 2006;25:240-243]

Gastro-esophageal variceal (GEV) hemorrhage is a major complication of portal hypertension resulting from cirrhosis of the liver.[1] It occurs in 30% of patients with cirrhosis, and accounts for 80%-90% of bleeding episodes in these patients. GEV hemorrhage is associated with higher morbidity, mortality and hospital costs than other causes of upper gastrointestinal tract bleeding.[2,3]

Approximately 30%-50% of patients with liver cirrhosis die within six weeks of the first variceal bleeding episode.[4,5] Though the mortality rate has decreased with advances in the management of GEV hemorrhage, it continues to be unacceptably high.[3] In patients admitted with GEV hemorrhage, increasing age, advanced Child-Pugh class, hepatocellular carcinoma, early re-bleeding after endoscopy, presence of hepatic encephalopathy, and renal failure have been shown to influence mortality; however, the factors predicting prognosis have varied between studies.[3,4]

Pakistan has a large burden of chronic liver disease (CLD),[5] and GEV hemorrhage is a common cause of admission to our hospital. In-hospital mortality is very high in these patients, ranging from 8%-50%.[2] The aim of this study was to identify factors that predict death during the index admission in cirrhotic patients admitted to our hospital with GEV hemorrhage.

Methods

Case records of patients admitted to our hospital with GEV hemorrhage due to cirrhosis of the liver between January 1998 and October 2003 were analyzed retrospectively. The study was approved by the hospital ethics review committee.

In our hospital, all patients with GEV hemorrhage are admitted to a dedicated Gastrointestinal Bleeding Control Unit, which is an intensive care area equipped with hemodynamic monitors, pulse oxymeters, trained nurses and physicians, and a 24-hour endoscopy service. Splanchnic vasoconstrictors like terlipressin and octreotide are regularly used, when indicated. Sengstaken-Blakemore tube is used for emergency hemostasis, in patients with exsanguinating and uncontrollable upper GI hemorrhage. Variceal band ligation is the treatment modality of choice, except when visibility is poor due to torrential bleed, in which case ethanolamine oleate sclerotherapy is performed. In patients with significant rebleed, defined as frank hematemesis, new onset of melena, fresh blood in nasogastric tube aspirate, or hemodynamic compromise, with a drop in hemoglobin level of >2 g/dL, re-endoscopy is done.

All patients are assessed by a surgical team at admission; surgical intervention is advised if adequate

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hemostasis is not achieved at initial endoscopy, or for re-bleeding after two sessions of endoscopic treatment within 48 hours. In patients with high operative risk, transjugular intrahepatic portasystemic shunt (TIPSS) procedure is performed provided no contraindications exist.

The relationship of various clinical and laboratory parameters at admission to mortality was assessed. The clinical parameters were: age, gender, diagnosis (cirrhosis alone, cirrhosis with hepatocellular carcinoma [HCC], cirrhosis with portal vein thrombosis [PVT], cirrhosis with HCC and PVT), Child-Pugh class, presence of ascites, presence of portosystemic encehalopathy (PSE) according to the West Haven criteria,[6] and presence of spontaneous bacterial peritonitis. Occurrence of a re-bleed within 24 hours of endoscopy was also assessed. The laboratory parameters assessed were: hemoglobin concentration, prothrombin time, serum bilirubin, serum creatinine and serum albumin.

Diagnosis of cirrhosis was based on biochemical parameters and imaging studies and liver biopsy, where available. HCC was diagnosed when two of the following three were present: a space-occupying lesion on ultrasonography and/or CT scan, liver biopsy, or raised serum alpha fetoprotein level. PVT was diagnosed on ultrasound Doppler scanning or CT. Ascites was graded as 'absent', 'easily controlled' (if not associated with distress or easily treated with diuretics), or 'tense' (if associated with respiratory or abdominal distress). PSE was categorized as absent, stage 1-2, or stage 3-4. Spontaneous bacterial peritonitis was defined as absolute neutrophil count >250/mL in the ascitic fluid.[3]

In patients with multiple admissions for GEV hemorrhage, each admission was treated separately. In case of death in the second or subsequent admission, the patient's data were analyzed as 'survivor' in the initial admission(s) and as 'non-survivor' in the last admission.

Statistical analysis

Data were analyzed using the Statistical Package for Social Science (SPSS; Release 11.5, standard version). Data on quantitative variables are presented as mean (SD), and numbers and percentages are reported for qualitative variables. Differences in means between the survivors and non-survivors were tested using the independent sample *t* test and differences in proportion were assessed by using chi-squared or Fisher' exact test where appropriate. Variables with a p value of <0.25 on univariate analysis were included in step-wise multiple logistic regression analysis to identify independent risk factors for mortality. Wald statistics was used to assess the importance of each variable in the model, with p values <0.05 taken as significant.

Results

A total of 343 patients (207 men) had 382 admissions during the study period (13 had 2 admissions each, and 4 had 3 admissions each). The etiology of cirrhosis was hepatitis C virus (HCV) in 328 patients, hepatitis B virus (HBV) in 7, HBV and hepatitis D virus (HDV) coinfection in 3, infection with HBV, HCV and HDV in 2, and unknown in 2 patients. Thirty patients (8.7%) died in hospital.

Tables 1 and 2 show clinical and laboratory parameters in survivors and non-survivors. The mean age and gender distribution were similar in the two groups. Both HCC and PVT co-existing with liver cirrhosis, Child-Pugh class C, tense ascites, PSE and re-bleeding within 24 h of the initial endoscopy were more common in the non-survivors. The type of endoscopic therapy (band ligation 228, injection sclerotherapy 103, both 12 patients) did not influence mortality.

The non-survivors had higher serum bilirubin (2.4 [1.4] vs. 1.6 [0.3] mg/dL; p=0.032) and serum creatinine (2.1 [1.1] vs. 1.1 [0.6] mg/dL; p=0.02) (Table 2). Serum creatinine level exceeding 1.5 mg/dL was more common in non-survivors (13/30 [43%]

Table 1: Clinical variables at time of admission in survivors and non-survivors

Parameter	Survivors (n=313)	Non-survivors (n=30)	p value
Age (years)	52.1 (4.2)	56.0 (3.4)	0.098
Male gender	190 (61%)	17 (57%)	0.092
Diagnosis			
Cirrhosis alone	228 (73 %)	21 (70 %)	0.089
Cirrhosis + HCC	62 (20 %)	5 (17 %)	0.088
Cirrhosis + PVT	12 (4 %)	1 (3%)	0.099
Cirrhosis + HCC + PVT	11 (3%)	3 (10%)	0.049
Child-Pugh class			
A	38 (12%)	0 (0%)	0.059
B	72 (23%)	4 (13 %)	0.064
C	203 (65 %)	26 (87%)	0.049
Ascites			
Absent	79 (24%)	4 (13%)	0.068
Easily controlled	216 (70%)	14 (47%)	0.060
Tense	18 (6%)	10 (33%)	0.038
PSE			
Absent	261 (83%)	14 (47%)	0.032
Stage 1 or 2	35 (11%)	12 (40%)	0.047
Stage 3 or 4	17 (6%)	4 (13 %)	0.042
Re-bleeding within 24 h	16 (5%)	12 (40%)	0.021

HCC: Hepatocellular carcinoma; PVT: Portal vein thrombosis

Table 2: Laboratory parameters at time of admission in survivors and non-survivors

Parameter	Survivors (n=313)	Non-survivors (n=30)	p value
Hemoglobin (g/dL)	10.4 (2.5)	9.1 (2.9)	0.071
Prothrombin time (s)*	19.0 (4.2)	21.5 (5.2)	0.065
S. bilirubin (mg/dL)	1.6 (0.3)	2.4 (1.4)	0.032
S. creatinine (mg/dL)	1.1 (0.6)	2.1 (1.1)	0.027
S. albumin (g/dL)	2.5 (1.4)	2.7 (1.9)	0.082

* Control value 12 s

than in survivors (38/313 [12%]; p=0.027), as was serum bilirubin level exceeding 3 mg/dL (19/30 [63%] vs. 62/313 [20%]; p=0.032).

On multiple logistic regression analysis, the independent predictors of mortality were: serum creatinine >1.5 mg/dL, serum bilirubin >3 mg/dL, presence of PSE and re-bleed within 24 h of endoscopy (Table 3).

Discussion

Gastrointestinal hemorrhage is a major complication of cirrhosis and portal hypertension, and is responsible for significant morbidity and mortality.[1] In recent years, improvements in patient management, including the use of terlipressin, prophylactic antibiotics, variceal band ligation and TIPSS, have resulted in a decline in in-hospital mortality.[7-11]

Our in-hospital mortality rate of 8.7% is consistent with the experience from other centers. Pauwels *et al* showed that in-hospital mortality in cirrhotic patients admitted with variceal bleeding has decreased by 50% over the past 15 years.[12] In 1986, Chojkier and colleagues reported a bleeding-related mortality rate of 35%,[13] whereas Afessa and Kubilis in the year 2000 reported an in-hospital mortality rate of 21% in bleeding cirrhotics.[14] More recently, Chalasani *et al* in a large study over 3 years reported the in-hospital mortality to be 14.2%.[15] In another large series of 403 patients with liver cirrhosis and variceal bleeding, Del Olmo and colleagues reported a mortality rate of 7.4%.[16] Similar decline in hospital mortality has been reported in other studies too.[17]

Table 3: Independent predictors of mortality on multiple logistic regression analysis

Parameter	Adjusted OR	95% CI	p value
Re-bleed within 24 h	40.9	11.7-14.31	<0.0001
PSE			
Stage 1 or 2	3.9	1.2-12.9	0.026
Stage 3 or 4	8.9	2.1-37.9	0.003
S. creatinine >1.5 mg/dL	5.3	2.3-12.2	<0.001
S. bilirubin >3.0 mg/dL	7.9	3.2-19.7	<0.001

Our results revealed that serum creatinine >1.5 mg/dL, serum bilirubin >3 mg/dL, presence of PSE, and re-bleeding within 24 hours of endoscopy were independent predictors of mortality. These results are in line with previously published data.[13,14,18]

In an early study, in-hospital status, co-morbid conditions and greater transfusion requirements showed a striking association with mortality, whereas age, presence of cirrhosis, and recent excessive alcohol intake did not.[13] Magliocchetti and colleagues further showed that Child-Pugh score, albumin level, encephalopathy, and GEV hemorrhage correlated with survival.[19] Patch *et al* found six factors to have independent prognostic value for death: moderate to severe ascites, need for ventilation, white blood cell count, platelet count, partial thromboplastin time, and creatinine.[20] In a study of 56 patients, Chalasani reported emergency TIPSS placement, serum bilirubin concentration >3 mg/dL, ALT levels, and encephalopathy as factors predicting mortality.[21] In a large retrospective study of 403 cirrhotics with variceal bleed, renal failure with raised serum creatinine, post-gastroscopy re-bleeding, and presence of HCC and PSE were found to be independent predictors of mortality.[6] Serum bilirubin and creatinine levels have been shown to predict survival in the Malinchocs model.[22] Other studies too have shown serum bilirubin level >3 mg/dL and serum creatinine level >1.7 mg/dL as predictors of mortality.[16,20,21]

In our study, high bilirubin levels, high creatinine levels, presence of PSE, and occurrence of rebleeding after endoscopy were shown to independently predict mortality. Though we did not find Child-Pugh score to be a predictor of mortality, two of its constituents, namely, serum bilirubin and presence of PSE, were found to independently predict mortality.

In conclusion, serum creatinine levels >1.5 mg/dL, serum bilirubin levels >3 mg/dL, presence of PSE, and re-bleeding within 24 hours of gastroscopy were independent predictors of mortality in our patients with liver cirrhosis and GEV bleeding.

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