Open Journal of Gastroenterology, 2013, 3, 317-321 **OJGas**
http://dx.doi.org/10.4236/ojgas.2013.37056 Published Online November 2013 (http://www.scirp.org/journal/ojgas/)

Predictors of early rebleeding and mortality after acute variceal haemorrhage in patients with cirrhosis*

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Received 25 September 2013; revised 26 October 2013; accepted 14 November 2013

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ABSTRACT

The upper gastrointestinal bleeding from esophageal or gastric varices is the most dangerous complication of portal hypertension. The purpose of this study was to identify the predictors of early rebleeding and mortality after a bleeding episode. Patients and Methods: It was a retrospective study including 215 patients admitted in our department of hepatology and gastroenterology at the Hassan II University Hospital of Fez, from January 2001 to January 2010. Results: The mean age of our patients was 51 years. Thirty percent of patients had cirrhosis due to virus (B or C). The majority of patients (79%) had only esophageal varices. Fifty patients (23%) had a bleeding recurrence. Twenty-five patients (11.5%) died during the first ten days, of which 52% had presented rebleeding (p = 0.01). In 30% of cases, the rebleeding was secondary to a fall of pressure ulcers. Univariate analysis showed that early mortality of patients was significantly associated with advanced age (p = 0.018), low prothrombin time (PT) (p = 0.022), low serum sodium (p = 0.03), low platelet count (p = 0.05), and elevated transaminases (p = 0.02). Conclusion: The survival of cirrhotic patients after a bleeding episode was influenced by advanced age, a low rate of PT, of serum sodium, and of the platelet count, and elevated transaminases.

Keywords: Cirrhosis; Portal Hypertension; Gastrointestinal Bleeding; Esophageal Varices

1. INTRODUCTION

The upper gastrointestinal bleeding from esophageal varices is one of the most dangerous complications of portal hypertension, with a consistently high morbidity and mortality [1,2]. Despite advances in the management of variceal bleeding, mortality following a bleeding episode in cirrhotic patients has decreased by only 20% [3,4]. Several risk factors associated with mortality after a bleeding episode were identified. These factors are: active bleeding during the initial endoscopy, venous pressure gradient, portal vein thrombosis, alcoholic liver disease, bilirubin, albumin, hematocrit, transaminases, encephalopathy, hepatocellular carcinoma and Child Pugh score [5,6]. Many of these data were collected from retrospective studies where mortality after variceal bleeding was greater than 50%. But these studies have included a relatively small number of patients, or groups with no standard treatment especially concerning the use of antibiotics [5,7,8]. Several prognostic scores have been developed in cirrhotic patients with variceal bleeding. Currently, the most used are the Child-Pugh score and MELD. Recent studies have demonstrated the ability of these scores to predict early mortality in these patients [9]. Given the significant changes in the natural history of cirrhosis from the broad and standardized use of antibiotic prophylaxis and endoscopic treatment, and given the etiological feature of cirrhosis in our population characterised by the high prevalence of viral cirrhosis, we have found that it is very interesting to investigate predictor factors of rebleeding and those involved in the short-term survival of cirrhotic patients with variceal bleeding.

2. PATIENTS AND METHODS

2.1. Study Population

We present a retrospective study of patients with cirrhosis and variceal bleeding, admitted in our department of hepatology and gastroenterology at the University Hos-

*Conflicts of interest: No conflicts of interest.
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pital of Fez, between January 2001 and January 2010. We have included only patients presenting a first bleeding episode. The diagnosis of cirrhosis was based on the combination of clinical, biological, endoscopic and ultrasonographic criteria. The diagnosis of variceal bleeding was confirmed by the presence of hematemesis and/or melena at admission of our patients, and the presence of varices at endoscopy with or without active bleeding and without any other causes of bleeding highlighted in the endoscopy. All patients were treated by esophageal varices ligature associated with an antibiotic prophylaxis based on cephalosporins, and transfusion if necessary. During the study period, no patients had received treatment with vasoactive drugs. We did not take into account the experience of the operator who performed the haemostatic action.

2.2. Variables Studied

All patients had received a biological assessment within 24 hours after the bleeding episode.

The variables studied were: age, sex, presence of ascites, encephalopathy, the presence of active bleeding, lesions found at endoscopy, the platelet count, transaminases, prothrombin, the etiology of cirrhosis and child.

Rebleeding was defined according to the criteria of Baveno V [10].

Early mortality was defined as death within 6 weeks after the bleeding episode.

2.3. Statistical Methods

We conducted a descriptive analysis of data using the Epi Info system and analytical one using the "t" Student test. We have considered $p < 0.05$ as a significant value.

3. RESULTS

Between January 2001 and January 2010, 215 patients with cirrhosis were included. The clinical characteristics of patients are shown in **Table 1**. The average age was 51 years old, with an equal number of men and women. Forty-one percent of patients had viral cirrhosis B and 18% had viral cirrhosis C, 67% of patients had Child B and 22% had Child C. Forty-nine percent of patients had ascites. The majority of patients (82%) had esophageal varices alone, and 18% had esophageal varices associated with gastric varices. Active bleeding at initial endoscopy was found in 66 patients (30%). The mean hemoglobin level at admission was 8.7 g/dl, 42% of patients had received a blood transfusion during the first 24 hours of hospitalization (**Table 1**).

Fifty patients (23%) had rebleeding. Univariate analysis showed that rebleeding was significantly associated with the presence of a lowered prothrombin time ($p = 0.05$). Ascites was noted in 40% of patients with recurrence of bleeding ($p = 0.1$). The mean hemoglobin level was 8.7 ($p = 0.2$), with an average number of units transfused 2 ($p = 0.1$). The mean bilirubin was 16.85% ($p = 0.41$). 60% of patients with recurrence had a Child B ($p = 0.2$). Active bleeding at initial endoscopy was noted in 34% of cases ($p = 0.3$) (**Table 2**).

Twenty five (11.5%) patients died during the first ten days, whose 52% had presented rebleeding ($p = 0.01$); 30% were secondary to an ulcer fall ($p = 0.4$). Univariate analysis showed also that early mortality of patients was significantly associated with advanced patients age ($p = 0.018$), low prothrombin time ($p = 0.022$), low serum sodium ($p = 0.03$), low platelet count ($p = 0.05$), and elevated transaminases ($p = 0.02$) (**Table 3**).

4. DISCUSSION

The rate of rebleeding in our study was 23% , this rate is lower than that reported by Wang M *et al*. [11] in 2011 (35.8%) and Ben-Ari Z *et al*. [12] in 1999 (44%), but approximately equal to that reported in the study of Krig JE *et al*. [13] in 2009 (24%). This difference could be due to a difference in treatment methods. Ben-Ari Z and colleagues [12] treated their patients by blood transfu-

Table 1. Clinical and biological characteristics of the study population (N = 215).

Number of patients	215
Male	107 (50%)
Mean age	51 ans
Child	
A	24 (11%)
B	145 (67%)
C	48 (22%)
Cause of bleeding	
Esophageal varices	215 (82%)
Gastric varices + esophageal varices	37 (18%)
Clinical caracteristics of bleeding	
Melena	13
Hematemesis	75
Hématemesis + melena	127
Etiology of cirrhosis	
Virus B	89 (41%)
Virus C	38 (18%)
Others	88 (41%)
Mean Hemoglobin (g/dl)	8.7
Natremia (meq/l)	135.7
Ascites	105
Transfusion in the first 24 hours	92 (24%)
Average number of units transfused	1.17
Varices with red signs	149
Varices with actif bleeding	66 (30%)

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Table 2. Predictors of rebleeding: univariate analysis.

	No rebleeding: N = 165	Rebleeding: N = 50	p
Mean age (an)	51 ans	50 ans	0.7
Male (%)	50%	50%	0.5
Ascites	85 (51%)	20 (40%)	0.1
Hepatic encephalopathy	11 (6%)	3 (6%)	0.5
Active bleeding	49 (29.7%)	17 (34%)	0.6
Esophageal varices grade III	68 (41%)	18 (36%)	0.5
Gastric varices	27 (16%)	10 (20%)	0.5
Platelets	107,805	109,608	0.8
Glutamopyruvate Transférase (GPT)	48	68	0.2
Prothrombin time	70%	59%	0.05
Child A Child B Child C	17 (10%) 107 (64%) 43 (26%)	6 (12%) 34 (68%) 6 (12%)	0.6 0.2 0.03

Table 3. Predictors of early mortality: univariate analysis.

	Patients survived N = 190	Patients died N = 25 (11.6%)	p
Age (an)	50.53	58.84	0.018
Male (%)	51%	40%	0.3
Ascites	91 (48%)	14 (56%)	0.5
Hepatic encephalopathy	10 (5.2%)	4 (16%)	-
Rebleeding	37 (19.5%)	13 (52%)	0.01
Platelets	132,590	105,053	0.05
Prothrombin time	69%	57%	0.02
Glutamopyruvate Transférase (GPT)	44.6	114	0.02
Serum albumin	30	25	0.19
Serum creatinine	9.68	11.39	0.45
Natremia	136	132	0.03
Child A Child B Child C	245 (13.2%) 126 (96.6%) 31 (17%)	2 (14.2%) 6 (42.8%) 6 (42.8%)	0.5

sions and vasoactive drugs, and if failure, sclerosis of esophageal varices was performed. In the study of Wang M *et al*. [11], patients were also treated with blood transfusions, vaso active drugs and anti acids. However, Krige JE and colleagues [13] treated their patients by sclerosis of esophageal varices. In our study, all patients were treated by endoscopic band ligation. The comparison between these series allows us to conclude that endoscopic therapy may be effective in cirrhotic patients with bleeding esophageal varices, this should be confirmed by other studies. In the study by Wong *et al*. [11], univariate analysis revealed that a low albumin levels, high white blood cell count, score of Child B and C, the presence of ascites, and encephalopathy were predictors of rebleeding in cirrhotic patients, these results were similar to those found in several studies [14-18]. In our study, these factors were not significantly associated with rebleeding, and only a low rate of prothrombin was a predictor of recurrence. This result implies that the severity of coagulopathy may play a critical role in rebleeding. In the series of K Bambha *et al*. [19], the MELD score and the presence of platelet plug on varicose veins in the initial endoscopy were predictive of rebleeding. Stratification of patients according to the MELD score (MELD ≥ 18 points, MELD < 18 points) revealed a significant increase in the risk of rebleeding in patients with a MELD score ≥ 18 points. Currently, there is no well-established model to accurately predict the survival of cirrhotic patients after an episode of gastrointestinal bleeding due to rupture of esophageal varices. One of the difficulties is that the prognosis for these patients is influenced not only by the severity of the bleeding episode itself, but also by the severity of the underlying liver disease. In our series, the advanced age of patients was predictive of mortality in the first six weeks after the bleeding episode, this was consistent with the series of Sempere L *et al*. [20] who found that age ≥ 65 years was significantly associated with early mortality. This factor is probably related to some factors found in the elderly population, mainly the duration of progression of liver disease, and the greater difficulty of management of recurrent decompensation [21]. In this series, the presence of HCC, the incidence of infection during the bleeding episode, a Child score ≥ 10 and MELD score ≥ 18 were also associated with early mortality. Some authors suggest that the development of HCC may accelerate the course of liver disease [22]. These patients often have a portal vein thrombosis, rebleeding after endoscopic treatment and thus a higher risk of early mortality. This high mortality rate is probably secondary to the advanced state of the underlying cirrhosis and the difficulty of mastering portal hypertension resulting [23-25]. In the series of Bamba K *et al*, advanced Child score, MELD score ≥ 18, the number of units transfused during the first 24 hours, the presence of ascites, an active bleeding at initial endoscopy, high transaminase levels and low serum sodium were predictive of early mortality. The last two parameters were also found in our study, which was consistent with other studies [26]. The occurrence of rebleeding during the first five days after the bleeding was significantly associated with early mortality in our series, a

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factor also reported in the series of Kamba *et al*. [19].

5. CONCLUSION

The degree of liver cell failure influenced the occurrence of rebleeding after an episode of variceal bleeding in cirrhotic patients. The advanced age of patients, low prothrombin time, low rates of serum sodium and of platelets count, and high transaminase rate were predictors of early mortality in these patients.

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