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Scientific Research

Predictors of Intra-Hospital Mortality in Patients with Cirrhosis

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Abstract

Intra-hospital mortality in cirrhotic patients is variable depending on the studies reported in literature. Several studies have demonstrated independent predictors of mortality. The aim of this work is indeed to identify these predictors. Patients and Methods: We conducted a retrospective study of 1080 cirrhotic patients hospitalized in our department of gastroenterology and hepatology between January 2001 and August 2010. A descriptive study of the study population was performed, and a univariate analysis looking for an association between intra-hospital mortality, and clinical, biological, etiological and socio-demographic characteristics of our patients. Results: The average age of our patients was 54 years, with an equal number of men and women. 41.1% of patients had cirrhosis secondary to hepatitis C and 18.5% had cirrhosis secondary to hepatitis B. 26.1% of our patients were CHILD C. Intra-hospital mortality was 8.7% (97 deaths) with a mean of 23.4 ± 35.8 months. Univariate analysis showed that the intra-hospital mortality was significantly associated with higher age ($p = 0.049$) as well as the reasons for admissions like hepatic encephalopathy, and hematemesis ($p < 0.0001$), melena, jaundice and ascites ($p = 0.001$). Among the biological parameters analyzed in univariate analysis, significant associations with mortality were objectified for high white blood cell count ($p = 0.035$), and high serum bilirubin and creatinine ($p < 0.0001$); low rate of prothrombin time (PT) ($p < 0.0001$), of albumin ($p = 0.0001$) and of serum sodium ($p < 0.0001$). Among the complications analyzed, significant associations with mortality were objectified for jaundice, ascites ($p = 0.001$), hemorrhagic decompensation, hepatic encephalopathy, and spontaneous bacterial peritonitis ($p < 0.001$). Univariate analysis of the etiology of cirrhosis objectified significant associations for cirrhosis secondary to hepatitis B ($p = 0.001$) and hepatitis C ($p = 0.022$). Multivariate analysis objectified four independent predictors of mortality: hepatic encephalopathy, infection (hyper leukocytosis ≥ 10,000/mm^3), renal failure (serum creatinine ≥ 15 mg/l) and hyponatremia. Conclusion: In our series, we identified four independent predictors of intra-hospital mortality in cirrhotic patients: hepatic encephalopathy, infection, renal failure and hyponatremia.

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Keywords

Cirrhosis; Portal Hypertension; Intra-Hospital Mortality

1. Introduction

The search for risk factors that stratify cirrhotic patients into subgroups with different survival rates is of great prognostic value for the clinician. Many studies have focused on the search for predictors of mortality in cirrhotic patients, and their use to develop a reliable model of survival. In these studies, the study populations were cirrhotic patients [1]-[5], patients with alcoholic cirrhosis [6] [7], and cirrhotic patients after an episode of variceal bleeding [8]-[12]. The Child-Turcott score [1] and its subsequent modifications by Pugh [8] are old empirical methods used to assess the degree of liver failure in candidate patients for porto-systemic shunt. Although the statistical accuracy of the Child-Pugh score (CPS) was not assessed, it was long considered to be an adequate method to determine the degree of liver failure, and the probability of survival [13]-[15]. However, two of its elements are very subjective (ascites and encephalopathy) [5]. In some studies, the prognostic value of CPS has been described as incomplete. In addition, several other clinical and biological variables not included in the CPS were demonstrated to have prognostic significance [16]. In our study, the principal etiology of cirrhosis in our patients is hepatitis B and C. It seemed, therefore, interesting to investigate the factors involved in the short-term survival in these cirrhotic patients.

2. Patients and Methods

• Study population

We present a retrospective study of cirrhotic patients admitted in our department of hepatology and gastroenterology at the University Hospital of Fez, between January 2001 and January 2010. The diagnosis of cirrhosis was based on the combination of clinical, biological, endoscopic and ultra-sonographic criteria.

• Variables studied

All patients had received a biological assessment within 24 hours of admission. The variables studied were: age, sex, presence of ascites, encephalopathy, presence of hemorrhage, jaundice, hepatocellular carcinoma (HCC), platelet count, white blood cells, transaminases, prothrombin time, bilirubin, albumin, creatinine, serum sodium, spontaneous bacterial peritonitis, the etiology of cirrhosis and CPS.

• Statistical Methods

A descriptive study of our population was conducted, as well as univariate and multivariate analysis looking for an association between mortality and clinical, biological and socio-demographic characteristics of our patients. We used standard descriptive statistics to characterize the population studied: mean, standard deviation, median, range. Comparison of two independent variables with normal distribution was performed using the Student test (t) whereas comparisons of more than two means were based on analysis of variance (ANOVA). A multivariate analysis was performed using a technique of logistic regression stepwise including all variables and significance level was defined as a value less than 0.2 in univariate analysis. In all statistical tests, the risk of error α was set at 0.05. Data were analyzed using Epi Info™ 3.5.1 software.

3. Results

Between January 2001 and January 2010, 1080 patients were included in this study. The clinical characteristics of patients are shown in **Table 1**. The average age was 54 years, sex ratio M/F was 1.05 with 555 (51.3%) men and 525 (48.6%) women. Ninety-six percent (N = 746) of patients had ascites, 46.5% (N = 503) had a hemorrhagic decompensation and 12.3% (N = 12.3) had hepatic encephalopathy. Forty-two percent (N = 463) of patients had cirrhosissecondary to hepatitis Cand 19.9% (N = 215) secondary to hepatitis B. Twenty-six percent of patients were Child C, and 7% (N = 75) had a HCC.

The hospital mortality was 8.7% (97 deaths).

In univariate analysis, factors associated with intra-hospital mortality in cirrhotic patients (**Tables 2** and **3**) were older age ($p = 0.049$), and reasons for admission: hepatic encephalopathy and hematemesis ($p < 0.0001$),

Table 1. General data of patients (N = 1080).

Mean age	54 ans
Men	555 (51.3%)
women	525 (48.6%)
Ascites	746 (96%)
Variceal bleeding	503 (46.5%)
Hepatic encephalopathy	133 (12.3%)
Cirrhosis secondary to hepatitis	
C	463 (42.8%)
B	215 (19.9%)
CHILD	
A	19.2%
B	54.6%
C	26.1%
HCC	75 (6.9%)

Table 2. Comparison of sex and age between patients who died and survivors.

	Survivors (n = 984)	Deads (n = 96)	p
Sex ratio (M/F)	0.9	1.2	0.178
Age	52.2 ± 17.17	55.8 ± 14.39	0.049

Table 3. Comparison of reasons for hospitalization among patients who died and survivors.

	Survivors (n = 984)	Deads (n = 96)	p
Asthenia	17.1%	18.8%	0.678
Fever	12.3%	16.7%	0.219
Hematemesis	38.0%	59.4%	<0.0001
Melena	27.2%	42.7%	0.001
Jaundice	20.6%	35.4%	0.001
Ascites	53.7%	71.9%	0.001
Edema of the lower limbs	17.3%	21.9%	0.260
Hepatic encephalopathy	6.4%	21.9%	<0.0001

melena, jaundice and ascites (p = 0.001). Among the biological parameters (**Table 4**), significant associations with mortality were objectified for high levels of white blood cell count (p = 0.035), of serum bilirubin (p < 0.0001), and of serum creatinine (p < 0.0001); low rates of PT (p < 0.0001), of albumin (p = 0.000) and of serum sodium (p < 0.0001). Complications of cirrhosis were analyzed also in univariate analysis (**Table 5**), and significant associations with mortality were objectified for jaundice, ascites (p = 0.001), hemorrhagic decompensation, hepatic encephalopathy and spontaneous bacterial peritonitis (p < 0.0001). Concerning the etiology of cirrhosis (**Table 6**) significant associations with mortality were found forcirrhosis secondary to hepatitis B (p = 0.001) and hepatitis C (p = 0.022). The multivariate analysis (**Table 7**) has objectified four independent predictors of mortality, which are hepatic encephalopathy (OR = 14.9), infection (leukocytosis ≥ 10,000/mm^3) (OR = 6.9), renal failure (Creatinine ≥ 15 mg/l) (OR = 10.8) and hyponatremia (OR = 15.3).

4. Discussion

In our series, the intra-hospital mortality was 8.7%, a figure much lower than the literature data. However, the

Table 4. Comparison of biological parameters between patients who died and survivors.

	Survivors		Deads		p
	n	Average ± SD	N	Average ± SD	
Hb (g/l)	865	9.6 ± 3.05	87	9.1 ± 3.16	0.126
GB (10^3/mm^3)	918	6.2 ± 11.61	90	8.8 ± 5.43	0.35
Platelets (10^3/mm^3)	867	129.3 ± 99.92	85	133.8 ± 83.31	0.689
PT (%)	912	69 ± 20.93	81	56.1 ± 23.47	<0.0001
Albumine (g/l)	168	31.8 ± 7.55	17	24.5 ± 5.5	0.000
Bilirubin (mg/l)	541	26.6 ± 43.73	56	58.9 ± 70,79	<0.0001
Creatinine (mg/l)	740	9.3 ± 7.39	72	14.6 ± 11.91	<0.0001
Natremia (meq/l)	525	136.3 ± 5.74	58	131.5 ± 9.02	<0.0001

Table 5. Comparison of the occurrence of complications of cirrhosis between patients who died and survivors.

	Survivors (n = 984)	Deads (n = 96)	p
Variceal bleeding	44.8%	66.6%	<0.0001
Ascites	67.7%	84.3%	0.001
Hepatic encephalopathy	10.1%	36.4%	<0.0001
SBP	3.3%	12.5%	<0.0001
Jaundice	20.6%	35.4%	0.001
HCC	6.9%	9.3%	0.370

SBP: spontaneous bacterial peritonitis, HCC: Hepatocellular carcinoma.

Table 6. Comparison of etiology of cirrhosis between patients who died and survivors.

	Survivors (n = 984)	Deads (n = 96)	p
Cirrhosis secondary to hepatitis C	41.4%	58.7%	0.022
Cirrhosis secondary to hepatitis B	17.8%	42.2%	0.001
Alcoholic cirrhosis	2.1%	3.1%	0.530

Table 7. Multivariate analysis of in-hospital mortality in cirrhotic.

	OR (IC 95%)	p
Leucocytes		
<10,000/mm^3	1	
>10,000/mm^3	6.9 (1.39 - 34.07)	0.018
Creatinine		
<15 mg/l	1	
>15 mg/l	10.8 (1.9- 59.49)	0.006
Natremia		
>130 meq/l	1	
>130 meq/l	15.3 (3.13 - 74.93)	0.001
Hepatic encephalopathy		
Absent	1	
Present	14.9 (2.20 - 101.16)	0.006

medical structures of admission of cirrhotic patients with complications are variable, making it difficult to compare mortality figures observed. It may be a hepatology and gastroenterology service or intensive care units [17].

Several studies had studied prognostic factors in patients with cirrhosis, and elaborated a survival models, easy to use in routine practice.

According to the findings of the international consensus conference of Baveno IV [18], there is no adequate prognostic model of portal hypertension in patients with cirrhosis, and individual characteristics are insufficient to establish a prognosis. However, four clinical stages of portal hypertension, of increasing severity were identified.

In addition, the CPS, active bleeding at endoscopy, the portosystemic pressure gradient, infection, renal failure, the severity of the initial bleeding episode, vein thrombosis and HCC were identified as indicators of poor prognosis [19] [20].

The older age was significantly associated with mortality in our series, this was also reported in the series of Luca. A *et al.* [21], in contrast to several studies that have not objectified significant association between age and mortality [22] [23].

The circumstances of admission of cirrhotic patients with complications in intensive care units such as gastrointestinal bleeding, sepsis, impaired consciousness associated with encephalopathy, acute respiratory distress syndrome or acute renal failure have been associated with high mortality in these patients [24]. In our study, variceal bleeding, jaundice, ascites and hepatic encephalopathy were significantly associated with mortality, which was similar to the literature data [24].

Gastrointestinal bleeding due to rupture of esophageal varices is the second leading cause of cirrhosis mortality [25]. Twenty to 40% of deaths occur in the following year of the bleeding episode and the mortality rate is 15% to 30% at 6 weeks [26] and 50% in patients with Child C [27]. The severity of variceal bleeding cannot be dissociated from the severity of cirrhosis that is appreciated by the degree of liver failure. The bleeding episode may worsen liver function and the underlying liver disease. The death is not related to hemorrhage itself (initial blood loss), because there is rarely an acute and massive hypovolemia, but due to complications such as infections, hepatic encephalopathy, severity of liver failure and kidney failure. Survival after bleeding episode has improved in 40 years, going from 45% to 60%. This result was due to a rapid assessment of the gravity (identified prognostic factors), non-specific intensive care, and the early introduction of a specific medical treatment of variceal bleeding (vasoactive drogues) [28] [29]. In our series, hemorrhagic decompensation was significantly associated with mortality in univariate analysis.

Several parameters were associated with intra-hospital mortality in cirrhotic patients, the most important being the degree of liver failure, since the bilirubin and prothrombin time were associated with a greater risk of mortality in several studies [30]. In our study, a prothrombin time < 45%, serum bilirubin > 50 mg/l, and serum albumin < 28 g/l were significantly associated with mortality , confirming the data of literature.

The prospective study of Singh and al shows that liver failure assessed by CPS and the model for end stage liver disease (MELD) are the main prognostic factor for short-term survival and the occurrence of complications [31].

Other factors of severity seem to be independent prognostic factors; these factors are active bleeding, renal function, a massive transfusion of more than 5 red blood cells, an initial state of shock and tracheal intubation [32].

In our study, we found that kidney failure was a poor prognostic factor in patients with cirrhosis, and serum creatinine at admission was higher in cirrhotic patients who died than in survivors, findings that are consistent with previous studies [33].

According to some studies, hyponatremia is associated with higher mortality [22]. In our series, serum sodium ≤ 130 meq/l was a poor prognostic factor in these patients. We also identified leukocytosis > 10,000/mm^3 as a poor prognostic factor and this leukocytosis is usually incorporated in severe sepsis. In a meta-analysis [34], the occurrence of infection was associated with recurrent bleeding and a higher mortality.

The etiology of cirrhosis does not appear to be independent prognostic factors [33]. In our study, the viral origin of cirrhosis emerged as a predictor of mortality, which confirms its more virulent and aggressive character than other liver diseases.

Ascites occurs in 30% of patients with cirrhosis. The occurrence of ascites is a major event in the natural history of cirrhosis, and survival rates at 1 and 5 years, are respectively 50% and 20%. Ten percent of patients develop refractory ascites which is a reflection of severe liver failure. The survival of these patients is 40% to 60%

at 1 year and 20% - 40% at 2 years [35]. In our series, ascites was also associated with a high mortality in cirrhotic patients. This has been reported in many other studies [24] [36].

Spontaneous bacterial peritonitis is a frequent and serious complication. It occurs in 8% - 25% of patients hospitalized for ascites. The prognosis is much improved over the past 20 years. The rate of healing is about 80% and hospital mortality is below of 30% [35]. This complication was found in 4.1% (N = 45) of patients, and always appears as a predictor of mortality in our study.

Hepatocellular carcinoma has became the most common fatal complication of cirrhosis. In France, the mortality rate of HCC has been multiplied by 4. This is explained primarily by the conjunction of two factors: in one hand, a decrease in mortality due to other complications of cirrhosis (like spontaneous bacterial peritonitis and bleeding due to portal hypertension) and in the other hand an increase in frequency of HCC related to cirrhosis secondary to hepatitis C [37]. In our series, this complication was not identified as a predictor of intrahospital mortality in cirrhotic patients p = 0.370).

Unlike other complications, there are very few studies that have focused on specific prognosis of hepatic encephalopathy, although it is a common and potentially serious complication of cirrhosis. It is estimated that the survival of cirrhotic patients after a first episode of hepatic encephalopathy, with or without other complication, is about 40% at one year and 15% to 20% in three years [37]. The short-term prognosis of cirrhotic patients admitted to intensive care unit has not been specifically studied. The difficulty of conducting this type of study is that the hepatic encephalopathy is usually associated with one or more severe complications of cirrhosis, and the prognosis is then more directly related to intercurrent complications.

In our study, hepatic encephalopathy was significantly associated with intra-hospital mortality in univariate and multivariate analysis.

Several studies have highlighted in multivariate analysis independent predictors of mortality in patients with cirrhosis: kidney failure (serum creatinine), serum bilirubin, prothrombin time, leukocytosis, cirrhosis decompensation [33] [24]. In our series, we identified in multivariate analysis four independent predictors of intra hospital mortality in patients with cirrhosis, which are hepatic encephalopathy, infection, renal failure and hyponatremia. These result joined the data of literature [24].

5. Conclusion

In conclusion, advanced patient age, severity of liver failure, viral origin of cirrhosis, variceal bleeding, ascites, and spontaneous bacterial peritonitis, were predictors of intra-hospital mortality in cirrhotic patients. Adding to this, hepatic encephalopathy, infection, renal failure and hyponatremia were meanwhile, independent predictors of this mortality.

Conflicts of Interest

No conflicts of interest.

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