TREBALL DE RECERCA

INSUFICIÈNCIA RENAL I MORTALITAT DELS PACIENTS CIRRÒTICS AMB PERITONITIS BACTERIANA ESPOTÀNIA I BAIX RISC DE MORTALITAT NO TRACTATS AMB ALBÚMINA.

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INDEX

CERTIFICAT DEL DIRECTOR DEL TREBALL DE RECERCA

German Soriano Pastor, Professor del Departament de Medicina de la Universitat Autònoma de Barcelona,

FA CONSTAR,

que el treball titulat “Insuficiència renal i mortalitat dels pacients cirròtics amb peritonitis bacteriana espontània i baix risc de mortalitat no tractats amb albúmina” ha estat realitzat sota la meva direcció per la llicenciada Maria Poca Sans, trobant-se en condicions de poder ser presentat com a treball d’investigació de 12 crèdits, dins el programa de doctorat en Medicina Interna (curs 2009-2010), a la convocatòria de juny.

Barcelona, 27 de maig de dos mil deu.

PARAULES CLAU:

Peritonitis bacteriana espontània. Albúmina. Insuficiència renal.

RESUM:

L'expansió amb albúmina disminueix la incidència d'insuficiència renal i la mortalitat dels pacients cirròtics amb peritonitis bacteriana espontània (PBE). Però no està ben establert si caldria administrar-la a tots aquests pacients. Aquest estudi determina la incidència i evolució de la insuficiència renal i mortalitat en una sèrie no seleccionada de pacients cirròtics amb PBE i baix risc de mortalitat (urea<11mmol/l i bilirrubina<68µmol/l) no tractats amb albúmina.

La baixa mortalitat i la bona evolució de la funció renal observades en els pacients amb PBE i baix risc de mortalitat no tractats amb albúmina, suggereixen que en aquests pacients no caldria administrar albúmina.

KEY WORDS:

Spontaneous bacterial peritonitis. Albumin. Renal failure.

SUMMARY:

Albumin infusion has been shown to decrease the incidence of renal impairment and mortality in cirrhotic patients with spontaneous bacterial peritonitis (SBP). However, it is not well established if albumin should be administered to all SBP patients. This study determined the incidence and outcome of renal failure and mortality in a non-selected series of cirrhotic patients with SBP and low risk of mortality (urea<11mmol/l and bilirubin<68µmol/l) non-treated with albumin.

The low mortality rates and the favourable outcome of renal function observed in patients with SBP and low risk of mortality non-treated with albumin, suggest that albumin administration does not seem to be necessary in this setting.

RENAL FAILURE AND MORTALITY IN CIRRHOTIC PATIENTS WITH SPONTANEOUS BACTERIAL PERITONITIS AND LOW RISK OF MORTALITY NON-TREATED WITH ALBUMIN.

1. Abstract

Background: Intravenous albumin infusion has been shown to decrease the incidence of renal impairment and mortality in cirrhotic patients with spontaneous bacterial peritonitis (SBP). However, it is not well established if albumin should be administered to all patients with SBP or only to those at high risk of mortality.

Aim: To determine the incidence of renal failure and mortality in a non-selected series of cirrhotic patients with SBP and low risk of mortality non-treated with albumin.

Methods: All cirrhotic patients with SBP diagnosed between 2001 and 2007 were analyzed. We considered patients al low risk of mortality when urea levels were lower than 11 mmol/l and bilirubin levels were lower than 68 µmol/l. We defined renal failure when creatinine levels were higher than 133 µmol/l. We determined in-hospital mortality, mortality at 3 months follow-up, and the incidence and outcome of renal failure at diagnosis of SBP and before SBP resolution.

Results: We included 230 SBP episodes in 180 patients, of these we excluded 14 patients. Finally we included 216 SBP episodes in 166 patients. Of these 64 patients (29.6%) were at the low risk of mortality group non-treated with albumin. And 152 patients (69%) were at the high risk of mortality group. Of these 73 (48%) were treated with albumin and 79 (52%) were not treated with albumin. Renal failure at SBP diagnosis, before SBP resolution and the in-hospital mortality and 3 months mortality in the low risk group compared to the high risk of mortality group were 0% vs 40.8% ($p< 0.0001$), 4.7% vs 25.5% ($p= 0.001$), 3.1% (2/64) vs 38.1% (58/152) ($p< 0.0001$) and 6.25% (4/64) vs 43.4% (66/152) ($p< 0.0001$).

Conclusions: The low mortality rates and the favourable outcome of renal function observed in patients with SBP and low risk of mortality non-treated with albumin, suggest that albumin administration does not seem to be necessary in this setting.

2. Introduction

Spontaneous bacterial peritonitis (SBP) is a common and severe complication that occurs in 10-30% of patients with cirrhosis and ascites[1]. Despite the infection resolution, the in-hospital mortality is still 20-30%[1].

One third of patients with SBP develop renal impairment despite successful treatment of infection. Renal failure is the most important predictor of in-hospital mortality in cirrhotic patients with SBP[2]. Furthermore, SBP precipitates hemodynamic deterioration, hepatic encephalopathy, gastrointestinal hemorrhage and hepatorenal syndrome.

Sort et al. demonstrated that intravenous albumin infusion given together with antibiotic therapy significantly decreased the incidence of renal impairment from 33% to 10% and also decreased mortality from 29% to 10%[3] in cirrhotic patients with SBP. In the same study it was observed that patients at low risk of mortality (urea < 11mmol/l, bilirubin < 68 µmol/l) did not benefit from albumin administration because the mortality was 0% in the patients treated and non-treated with albumin.

Moreover, albumin administration is not devoid of side effects and it is expensive. Two subsequent studies have therefore tried to identify which subgroup of cirrhotic patients with SBP would most benefit from albumin administration[4,5]. These two studies suggested that patients with a serum bilirubin lower than 68.4 µmol/l and creatinine lower than 88.4 µmol/l could be safety treated without albumin because they had a very low probability of death or renal failure [4, 5].

On the other hand, these previous studies included selected series of patients with SBP that do not necessarily reflect what happens in the daily clinical practice.

The objective of our study was to determine the incidence of renal failure and mortality in a non-selected series of cirrhotic patients with SBP and low risk of mortality not-treated with albumin.

3. Methods

3.1. Patients population

We reviewed all SBP episodes diagnosed in cirrhotic patients in Hospital de la Santa Creu i Sant Pau during the period between January 2001 and December 2007. We identified SBP episodes by reviewing in the Biochemistry Laboratory. Patients were considered at low risk of mortality[3] when urea was less than 11 mmol/l (BUN 30 mg/dl) and bilirubin less than 68 µmol/l (4mg/dl). In contrast patients were considered at high risk of mortality when urea was higher than or equal to 11 mmol/l and/or bilirubin higher than or equal to 68 µmol/l.

The diagnosis of cirrhosis was based on clinical, biochemical, endoscopic and ultrasonographical findings with or without liver biopsy. Diagnosis of SBP was based on the presence of polymorphonuclear cells in ascitic fluid with a cell count higher or equal than 250 cells/mm^3 in the absence of findings suggestive of secondary peritonitis[6] or peritoneal carcinomatosis. Pathogen isolation was not considered essential for SBP diagnosis. The exclusion criteria were: hemodialysis, terminal illness, being transfered to another hospital, low risk SBP treated with albumin and low risk SBP with renal failure (creatinine > 133 µmol/l) at SBP diagnosis[7]. We have excluded patients with creatinine > 133 µmol/l because these patients should receive albumin in order to treat the hepatorenal syndrome that has already been established and are not therefore candidates to renal failure prevention.

3.2. Treatment and assessments

Microbiological study of ascitic fluid was performed by bedside inoculation into two blood culture bottles (aerobic and anaerobic, 10 ml each), when possible, in view of the quantity of ascitic fluid obtained at paracentesis[8,9]. Renal failure was considered when serum creatinine values were above 133 µmol/l (1.5mg /dl)[2,3]. Septic shock was defined as a decrease in systolic blood pressure below 90 mm Hg or a reduction of

more than 40 mm Hg from baseline, despite adequate fluid resuscitation, accompanied by tachycardia and oliguria (urine output less than 20 ml/h) or anuria in the absence of other causes of shock[10]. Resolution of SBP was considered when signs and symptoms of infection had disappeared, ascitic fluid neutrophil count was <250/mm^3, and ascitic fluid culture was negative [11].

Patients were initially empirically treated with intravenous ceftriaxone 2 g daily for 7 days or until the infection was resolved. The antibiotic therapy was modified empirically or according to the in vitro susceptibility of causative microorganisms when there was an unfavourable clinical and/or analytical evolution of the infection.

Diuretic treatment was discontinued at the time of SBP diagnosis and it was not allowed until infection resolution.

All patients at low risk of mortality group were treated only with antibiotic while among the high risk of mortality group, patients received albumin infusion or not according to the medical team taking care of the patient.

Albumin was given at a dose of 1.5 g per kilogram of body weight during the first day after diagnosis, followed by 1 g per kilogram on the third day.

The main endpoints of the study were mortality and the development of renal failure.

3.3. Statistical analysis

Comparisons between groups were performed with the chi-square test or Fisher's exact test for qualitative variables and Student's t-test for quantitative variables. Probability of survival was calculated and compared by Kaplan-Meier with log rank test. Variables that reached statistical significance in univariate analyses were included in a multivariate analyses by logistic regression to identify the independent predictive factors of in-hospital mortality. A forward procedure with Wald test was used to determine the best model. Calibration was assessed using the Hosmer-Lemeshow goodness-of-fit test. Results are presented as means ± standard deviation or

frequencies. Calculations were performed with the SPSS Statistical Package (version 17.0, 2006; SPSS Inc., Chicago, IL). A p value <0.05 was considered statistically significant.

4. Results

4.1. Patients population

Two hundred and thirty SBP episodes in 180 cirrhotic patients were diagnosed in Hospital de la Santa Creu i Sant Pau during the period between January 2001 and December 2007.

We only excluded 14 patients, for the following reasons: hemodialysis (3), terminal illness (1 terminal HIV infection, 1 terminal hepatocellular carcinoma), transferred to another hospital (1), low risk SBP treated with albumin (4) and low risk SBP with renal failure (creatinine > 133 µmol/l) at SBP diagnosis (4) [7]. Therefore, we finally evaluated 216 SBP episodes in 165 patients of whom 64 (29.6%) were considered at low risk of mortality and none of them was treated with albumin. In contrast, 152 (70.4%) were considered at high risk of mortality, of these 73 (48%) were treated with albumin and 79 (52%) were not treated with albumin, according to the criteria of the medical team taking care of the patients.

4.2. Base-line patients characteristics

When comparing clinical and laboratory characteristics (see table 1), the low risk of mortality patients showed a lower Child Pugh and MELD scores and a lower urea, creatinine, bilirubin, INR and blood leukocyte count than patients at high risk. Moreover, they showed a higher sodium and mean arterial pressure than the high risk of mortality patients.

Table 1. Basal characteristics of high risk and low risk of mortality patients.

		Low risk (n=64)	High risk (n=152)	p
Age (years)		63.5 ± 13.8	63.0 ± 12.8	0.803
Sex	Male Female	42 (65.6%) 22 (34.4%)	105 (69.1%) 47 (30.9%)	0.619
Etiology	Alcohol HCV Other	17 (26.6%) 33 (51.6%) 14 (21.9%)	67 (44%) 52 (34.2%) 33 (21.7%)	0.030
Hepatocellular carcinoma		18 (28.1%)	39 (25.6%)	0.730
Previous	SBP Encephalopathy Ascites GI bleeding	11 (17.2%) 16 (25%) 45 (70.3%) 17 (26.6%)	37 (24.3%) 44 (28.9%) 115 (75.6%) 39 (25.6%)	0.248 0.554 0.413 0.911
Child-Pugh MELD MELD-Na		8.8 ± 1.7 13.2 ± 3.0 16.4 ± 3.7	9.7 ± 1.6 21.4±6.5 25.0±6.1	< 0.0001 < 0.0001 < 0.0001
HIV infection		6 (9.4%)	11 (7.2%)	0.594
Previous norfloxacin		11 (17.2%)	44 (28.9%)	0.070
Nosocomial SBP		23 (35.9%)	50 (32.9%)	0.666
Departament	Hepatology Others	52 (81.2%) 12 (18.7%)	125 (82.2%) 27 (17.8%)	0.863
Fever		27 (42.2%)	53 (34.9%)	0.309
Abdominal pain		26 (40.6%)	59 (38.8%)	0.804
Ileus		0 (0%)	3 (1.9%)	0.557
Shock		2 (3.1%)	10 (6.6%)	0.516
Encephalopathy		14 (21.9%)	52 (34.2%)	0.072
Gastrointestinal bleeding (GI)		3 (4.7%)	18 (11.8%)	0.105
Sodium (mmol/l)		135.5 ± 4.4	131.9 ± 5.9	< 0.0001
Potassi (mmol/l)		4.2 ± 0.6	4.6 ± 0.8	< 0.0001
Urea (mmol/l)		6.6 ± 2.5	14.6 ± 7.1	< 0.0001
Creatinine (µmol/l)		85.5 ± 18.5	139.3 ± 73.5	< 0.0001
Bilirubin (µmol/l)		37.9 ± 18.0	119.1 ± 127.8	< 0.0001
INR		1.39 ± 0.21	1.74 ± 0.59	< 0.0001
Blood leukocyte count (x 10^9/l)		7.93 ± 4.6	11.44 ± 9.2	< 0.0001
Mean arterial pressure (mmHg)		86.4 ± 14.2	75.9 ± 14.9	< 0.0001
Ascites neutrophil count (/mm^3)		3494 ± 5821	4159 ± 8225	0.558
Ascitic fluid total protein (g/l)		13.4 ± 8.1	13.3 ± 6.9	0.978
Positive ascitic fluid culture		19 (29.7%)	70 (46%)	0.026

When comparing high risk patients treated to non-treated with albumin (see table 2), the treated ones showed a higher MELD score and serum bilirubin levels. It was found that albumin was less frequently indicated in patients from other departments apart from the hepatology unit and also in patients with gastrointestinal bleeding.

Table 2. Basal characteristics of high risk of mortality patients treated with albumin and non-treated with albumin.

		High risk of mortality non-treated with albumin (n=79)	High risk of mortality treated with albumin (n=73)	p
Age (years)		63.6 ± 13.5	62.4 ± 12.2	0.555
Sex	Male Female	59 (74.7%) 20 (25.3%)	46 (63%) 27 (37%)	0.120
Etiology	Alcohol HCV Others	36 (45.6%) 23 (29.1%) 20 (25.3%)	31 (42.5%) 29 (39.7%) 13 (17.8%)	0.314
Hepatocellular carcinoma		19 (24%)	20 (27.3%)	0.620
Previous	SBP Encephalopathy Ascites GI bleeding	19 (24%) 25 (31.6%) 60 (75.9%) 20 (25.3%)	18 (24.6%) 19 (26%) 55 (75.3%) 19 (26%)	0.931 0.445 0.931 0.880
Child-Pugh MELD MELD-Na		9.7 ± 1.5 20.3 ± 6.5 24.1 ± 6.4	9.9 ± 1.7 22.6 ± 6.4 26.0 ± 5.8	0.555 0.030 0.059
HIV infection		8 (10.1%)	3 (4.1%)	0.153
Previous norfloxacin		22 (27.8%)	22 (30.1%)	0.756
Nosocomial SBP		30 (37.9%)	20 (27.4%)	0.166
Departament	Hepatology Others	59 (74.7%) 20 (25.3%)	66 (90.4%) 7 (9.6%)	0.011
Fever		32 (40.5%)	21 (28.8%)	0.129
Abdominal pain		25 (31.6%)	34 (46.6%)	0.059
Ileus		1 (1.3%)	2 (2.7%)	0.514
Shock		7 (8.9%)	3 (4.1%)	0.331
Encephalopathy		27 (34.2%)	25 (34.2%)	0.993
Gastrointestinal bleeding (GI)		14 (17.7%)	4 (5.5%)	0.02
Sodium (mmol/l)		132.1 ± 6.5	131.7 ± 5.3	0.696
Potassi (mmol/l)		4.7 ± 0.76	4.59 ± 0.93	0.413
Urea (mmol/l)		14.4 ± 6.3	14.8 ± 7.9	0.770
Creatinine (µmol/l)		138.7 ± 68.4	139.9 ± 79.1	0.914
Bilirubin (µmol/l)		96.6 ± 102.7	143.2 ± 147.0	0.027
INR		1.7 ± 0.7	1.8 ± 0.5	0.265
Blood leukocyte count (x 10^9/l)		10.59 ± 7.87	12.36 ± 10.48	0.239
Mean arterial pressure (mmHg)		74.7 ± 15.8	77.3 ± 13.7	0.295
Ascites neutrophil count (/mm^3)		3462 ± 4809	4904 ± 10729	0.283
Ascitic fluid total protein (g/l)		13.1 ± 7.1	13.6 ±6.7	0.649
Positive ascitic fluid culture		38 (48.1%)	31 (42.5%)	0.311

4.3. Renal failure

Data concerning renal failure are shown in figure 1. There were no statistical differences in previous renal failure between groups (we only had the data available in 188 episodes). Renal failure at SBP diagnosis was found in 112/216 (51.8%) SBP episodes: 0/64 patients in the low risk group and 62/152 (40.8%) in the high risk of mortality group ($p< 0.001$). When considering only patients at high risk of mortality we did not find statistical differences in this parameter between patients treated or not with albumin: 30/73 (41%) of the patients who were treated with albumin and 32/79 (40.5%) of the patients who were not treated with albumin presented with renal failure at SBP diagnosis ($p= 0.94$).

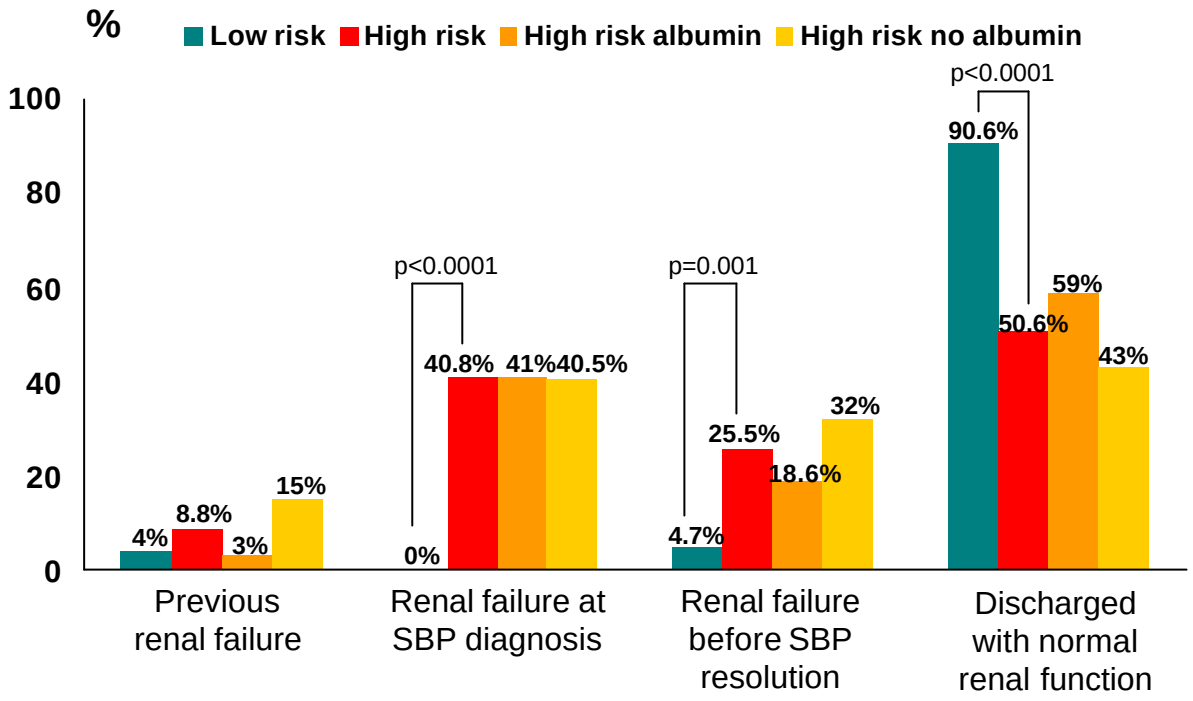
Renal failure before SBP resolution was found in 26/154 (16.8%): 3/64 (4.7%) patients in the low risk group and 23/90 (25.5%) patients in the high risk group ($p=0.001$). The patients from the low risk of mortality group who developed renal failure before SBP resolution had a favourable outcome although they were not treated with albumin: renal failure resolved in all of the patients and non of them needed to be treated with terlipressin and albumin.

There was a trend to a lower incidence of renal failure before SBP resolution among high risk patients treated than not treated with albumin (8/43, 18.6% against 15/47, 32%, $p= 0.14$, respectively).

In the low risk group 58/64 (90.6%) patients were discharged with normal renal function, compared to 71/152 (50.6%) in the high risk group ($p< 0.0001$). Among high risk patients it was higher in patients treated (43/73, 59%) than non-treated with albumin (34/79, 43%) ($p=0.051$).

The four patients in the low risk of mortality group who were discharged with impaired renal function, it was developed after the SBP was resolved.

Figure 1. Previous renal failure, renal failure ay SBP diagnosis and before SBP resolution and patients discharged with normal renal function in the whole series.

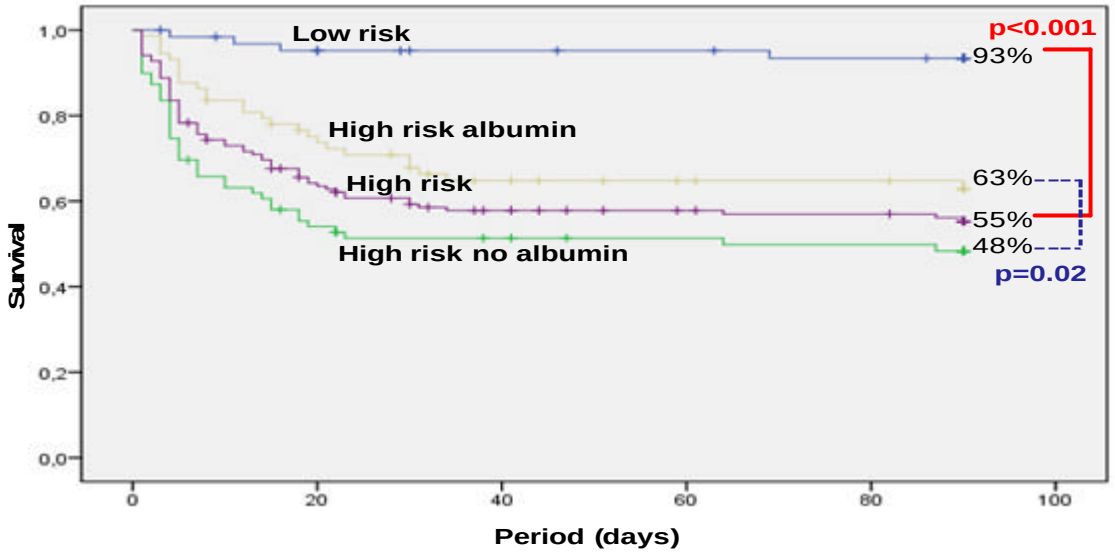


4.4. Mortality

Mortality during hospitalization was significantly lower among low risk patients than in high risk patients (3.1% versus 38.1%, p< 0.001). The causes of death in the two patients who died in the low risk group were multiorgan failure in advanced HIV infection and advanced hepatocellular carcinoma. Considering high risk patients, in-hospital mortality was lower in those receiving albumin than in those not receiving it (29% versus 47%, p=0.02).

In addition, the probability of 3-month survival was statistically higher in the low risk than in the high risk patients (93% versus 55%, p< 0.001). The causes of death in the two low risk of mortality patients at 3 months were advanced hepatocellular carcinoma and myocardial infarction. There was a higher probability of 3-month survival in high risk patients treated than non treated with albumin (62% versus 48%, p=0.02). (Figure 2).

Figure 2. Probability of survival.



Considering the whole series, the independent predictive factors of in-hospital mortality were urea, blood leukocyte count, mean arterial pressure, MELD score and nosocomial SBP. Considering only the high risk patients, the independent predictive factors of mortality were urea, blood leukocyte count, mean arterial pressure, MELD score and not being treated with albumin (tables 3 and 4).

Table 3. Independent predictive factors of in-hospital mortality in the whole series.

	OR	CI 95%	p
Urea (mmol/l)	1.117	1.049-1.189	0.001
Blood leukocyte count (x 10^9/l)	1.054	1.006-1.104	0.02
Mean arterial pressure (mmHg)	0.965	0.936-0.994	0.02
MELD	1.123	1.053-1.197	<0.001
Nosocomial SBP	2.70	1.16-6.25	0.02

Table 4. Independent predictive factors of in-hospital mortality in the high risk of mortality patients.

	OR	CI 95%	p
Urea (mmol/l)	1.117	1.046-1.192	0.001
Blood leukocyte count (x10^9/l)	1.058	1.009-1.109	0.02
Mean arterial pressure (mmHg)	0.965	0.934-0.998	0.04
MELD	1.132	1.052-1.217	0.001
No treated with albumin	4.83	1.87-12.45	0.001

5. Discussion

The main finding of the present retrospective study is the low mortality and incidence of renal failure in cirrhotic patients with SBP and low risk of mortality non-treated with albumin.

Sort et al demonstrated that albumin administration reduced the incidence of renal impairment and mortality in selected patients with SBP. However, albumin administration is not devoid of side effects and is expensive. After one study failed to find an alternative to albumin in hydroxyethyl starch [12], it has been questioned if all SBP patients need albumin treatment.

In two previous studies, *Terg et al* and *Sigal et al* showed that patients with SBP and creatinine lower than 88.4 µmol/l and bilirubin lower than 68.4 µmol/l could be treated without albumin because they had very low likelihood of death or renal failure. These two studies used creatinine and bilirubin levels to classify patients because these were the independent predictive factors of renal impairment in the study of Sort et al. In our study, we decided to classify patients as high or low risk of mortality according to urea and bilirubin levels which were the independent predictive factors of in-hospital mortality in the same study.

It should be pointed out that previous studies excluded a high number of patients in order to analyze a group as homogeneous as possible [3, 4]. We wanted however to assess a group of patients as similar as possible to the daily clinical practice, and we therefore analyzed this non-selected series. In spite of this, patients at low risk of mortality not treated with albumin showed a low in-hospital mortality (3%) and 3-month probability of mortality (6%), these figures being significantly lower than in patients at high risk of mortality. In addition, the causes of death in low risk patients were mostly not related to cirrhosis and SBP (multiorgan failure in HIV patient and advanced hepatocellular carcinoma). Low risk of mortality patients showed not only a low incidence of renal failure, but also most patients developing this complication presented

a favourable outcome. Our results therefore confirm those from the study of *Sort et al*, in which selected patients with SBP and urea < 11 mmol/l and bilirubin < 68 µmol/l did not show in-hospital mortality, independently of having been treated with albumin or not at SBP diagnosis.

Multivariate analysis in our whole series showed that in-hospital mortality was associated with worse liver and renal function (MELD, urea), more severe sepsis (blood leukocyte count) and hemodynamic impairment (mean arterial pressure), and with nosocomial SBP acquisition. This is in agreement with previous studies and point out the importance of urea in the prognosis of SBP.

In spite of patients at high risk of mortality treated with albumin presented a worse liver function compared to those at high risk non-treated with albumin, they showed a better outcome in terms of renal failure and mortality. Moreover, absence of albumin treatment was a strong independent predictive factor of in-hospital mortality in the multivariate analysis including only patients at high risk of mortality. These data strongly supports the need for albumin expansion in high risk of mortality patients.

Our study has several limitations, such as the retrospective design and that albumin administration was not decided by randomization in high risk of mortality patients. In spite of this, we think that this study provides valuable clinical information. We conclude that patients with SBP and low risk of mortality could be safely treated without albumin as they have a very low probability of mortality and renal failure. In contrast, our data suggest that patients with SBP and high risk of mortality clearly benefit from albumin administration.

6. Conclusions

- We confirm that serum bilirubin and urea are useful parameters to identify cirrhotic patients with SBP at high and low risk of mortality.
- Although it is not a randomized study, our data support that albumin administration improves survival and renal function in cirrhotic patients with SBP and high risk of mortality.
- The low mortality rates and the favourable outcome of renal function observed in cirrhotic patients with SBP and low risk of mortality non-treated with albumin, suggest that albumin administration does not seem to be necessary is this setting.

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