In-hospital mortality risk factors in patients with ascites due to cirrhosis

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Summary

Introduction: ascites is one of the most common complications of cirrhosis associated with a high rate of mortality. Although several scores have been developed in order to assess the prognosis of the disease, they were designed for predicting liver transplantation requirements and mortality in the short term, but not while in hospital. The aim of this study was to weigh risk factors for in-hospital mortality in adult patients with ascites due to alcoholic cirrhosis.
Material and methods: we performed a cross-sectional study in 180 adult patients with diagnosis of cirrhosis with portal hypertension associated with high alcohol intake. The diagnosis of cirrhosis was made by liver echography and portal hypertension was defined by clinical features plus *serum*-ascites albumin gradient. Sampled individuals were subjected to complete clinical examination. Child Pugh and the MELD scores were applied in all the patients.
Results: nineteen patients died while in-hospital. Mortality was associated with increased levels of *serum* white blood cell, *urea*, creatinine, prolonged prothrombin time, aspartate aminotransferase and alanine aminotransferase. We conducted a multiple binary logistic to predict in-hospital mortality which yielded that *serum urea*, creatinine and prothrombin time made a significant contribution to prediction with an OR 14 (95% CI 12.8 - 16.7 p = 0.03), 2 (95% CI 0.5 - 3.47, p = 0.04), and 2 (95% CI 1.03 - 2.31, p = 0.01) linearly-related.
Conclusions: our results suggest that acute renal failure and prolonged prothrombin time are predictors of in-hospital mortality in patients with portal hypertension due to alcoholic cirrhosis.

Keywords: ascites, alcoholic, liver cirrhosis, hospital mortality.

Study conducted at the Internal Medicine Department, Hospital J. B. Iturraspe, Santa Fe, Argentina

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Introduction

The three most common complications of cirrhosis are ascites, hepatic encephalopathy and variceal hemorrhage.[1] Ascites usually develops within 10 years during the course of the disease in the 60% of the patients with compensated cirrhosis,[2] and it is associated with poor prognosis with a rate of mortality of approximately 40% after 1 year.[3-7] The related factors for mortality prediction in patients with ascites include hyponatremia, high *serum* creatinine and low arterial blood pressure.[3-9] These patients also have high risk for other complications such as spontaneous bacterial peritonitis (SBP), hyponatremia and hepatorenal syndromes, which increase the risk of fatal outcome.[1,3,7-16]

Several scores have been developed in order to predict severity of the disease and prognosis in order to consider liver transplantation as a potential treatment option.[2] These scores are Child Turcotte Pugh and MELD; however, they were designed for predicting liver transplantation requirements and mortality in the short term, but not while in hospital.[3,14-21] The present study was carried out in order to evaluate risk factors for in-hospital mortality in adult patients with ascites due to alcoholic cirrhosis.

Materials and methods

Study population and subject evaluation

We performed a cross sectional study including 180 adult patients with diagnosis of cirrhosis with portal hypertension associated with high alcohol intake. They were all recruited at the Internal Medicine Service of a teaching Hospital in Santa Fe, Argentina, from January of 2008 to

December of 2010. The diagnosis of cirrhosis was made by liver echography and portal hypertension was defined according to clinical features plus *serum*-ascites albumin gradient. Sampled individuals were subjected to a complete clinical examination including chest X-ray, and biochemical tests. Exclusion criteria comprised: age <18 years, coronary artery disease or history of other cardiac diseases, chronic renal disturbances, immunosuppression or ongoing use of immunosuppressant agents, diabetes, positive serology for viral hepatitis A, B and C, autoimmune hepatitis, hepatorenal syndrome and other systemic complaints. The data recorded included clinical and demographic characteristics of each patient and the variables needed to determine the Child Pugh categories and MELD scores.

The study was approved by the Ethics Review Board of National Coastal University. Informed consent was obtained from all participants. All patients were treated according to local practice and international established guidelines.

Statistical analysis

Data were analyzed by using MedCalc version 12.2.1. Normal distributions of the continuous variables were tested by Kolmogorov-Smirnov method. The data are expressed as means ± SD or median and interquartile range. Chi-square test or Fisher's exact were used for categorical variables, whereas the one-way Anova was used to compare means. A multiple binary logistic regression model was used to assess the impact of variables associated with in-hospital mortality. The Hosmer-Lemeshow test was employed for goodness of fit of the logistic regression model. A p value <0.05 was considered significant.

Results

General population

We included 180 patients aged 53.6±10.3 years (means ± SD), 140 males and 40 females, with ascites due to portal hypertension. There were no age differences between genders. Nineteen patients died while in hospital. The median time of the admission period of the whole sampled individuals was 41 days. The mean age of the patients who died was 52.8 ± 11.1 years (range 43-71). There was no relation between the Child Pugh and MELD scores. In regard to the complications of portal hypertension, 32 individuals presented spontaneous bacterial peritonitis (SBP) and 18 esophageal variceal bleeding. Prolonged prothrombin time was not related with variceal bleeding. The features of the patients stratified by the Child Pugh score are summarized in Table 1.

As shown in Table 1, mortality was not related with age, sex or clinical complications such as SBP or esophageal variceal bleeding. Furthermore, this group presented lower casuistic of spontaneous bacterial peritonitis (p <0.0001), esophageal variceal bleeding (0.05) and encephalitis (p <0.0001). From the whole sampled individuals with SBP, only 17 presented positive ascites cultures to *Escherichia coli* (n = 10), *Klebsiella pneumoniae* (n = 4), *Streptococcus viridans* (n = 2) and *Enterococcus faecalis* (n = 1). No particular microbe was related to fatal outcome. On the other hand, Child Pugh C group presented higher rate of mortality (p = 0.04).

TABLE 1 Characteristics of the patients. Quantitative variables are expressed as means ± SD

	Low risk (n = 41)	Intermediate risk (n = 105)	High risk (n = 34)	p
Age	43.9 ± 11.8	51.3 ± 11.2	67.7 ± 13.4[1]	< 0.001
Gender (n)				
Male	29	90	21	NS
Female	12	15	13	
Systolic blood pressure	123.8 ± 15.5 mmHg	117.2 ± 16.4 mmHg	106 ± 20 mmHg[2]	0.001
Diastolic blood pressure	77.6 ± 8 mmHg	70 ± 10 mmHg	60 ± 5 mmHg[3]	<0.001
Sepsis (n)				
Non-septic	13	16	6	<0.05
Sepsis	28	76[4]	23	
Severe sepsis	-	13[5]	5	
Admission in the intensive care unit (n)	6	23[6]	7	0.001
Mortality rate (n)	1[7]	9	13	0.001

NS: Not significant.
Patients with high risk according to the Child Pugh score were older[1] and presented lower levels of systolic[2] and diastolic blood[3] pressure compared to the remaining groups. On the other hand, those who were stratified as intermediate risk, showed a higher rate of sepsis[4] and severe sepsis[5] with more frequent admission in the intensive care unit.[6] However, there was no difference in the mortality proportion between individuals grouped as intermediate risk and those in the group of high risk.[7]

Prediction of in-hospital mortality

As mentioned above, SBP was not related to in-hospital mortality. We evaluated if SBP caused by microbes isolated from culture was associated with fatal outcomes, yielding negative results. In relation to biochemical tests, patients who died presented increased levels of *serum* white blood cell, *urea*, creatinine, prothrombin time, aspartate aminotransferase and alanine aminotransferase. Also, they had lower ascites albumin concentration and decreased *serum*-ascites albumin gradient. Then we analyzed the area under the curve (AUC) for each of them, leading to the conclusion that only *serum urea*, creatinine and prothrombin time had statistically significant AUC of 87% (95% CI 81.6 to 91.7, p <0.0001), 75% (95% CI 68.9 to 81.7, p = 0.0014) and 69% (95% CI 62.2 to 75.9, p = 0.007), respectively (Figure 1).

Multiple binary logistic regression was conducted to predict in-hospital mortality using the categorical variable Child Pugh, and the continuous variables MELD score, level of *serum urea*, *serum* creatinine and prothrombin time. The Wald criterion demonstrated that *serum urea*, *serum* creatinine and prothrombin time made a significant contribution to prediction with OR: 14 (95% CI 12.8 - 16.7 p = 0.03), 2 (95% CI 0.5 - 3.47, p = 0.04), and 2 (95% CI 1.03 - 2.31, p = 0.01) linearly-related. The overall model fit Chi-squared was 46.3 (p<0.0001) with a Hosmer-Lemeshow test of 4.54 p = 0.8, indicating a good logistic regression model fit. The area under the receiver operating characteristic (ROC) curve of the model was 92% (95% CI 87.6 - 95.8).

Discussion

Ascites develops in approximately 60% of the patients with cirrhosis within 10 years during the course of the disease. Its very presence is an indicator of poor prognosis with a mortality approximately of 40% after 1 year, and it is suggested that if ascites is diagnosed, liver transplantations should be considered as a treatment option.[1,5] Furthermore, scores were developed in order to forecast the requirement of liver transplantation or the mortality risk; however, they were designed for short term predictions and not for in-hospital death outcome.[2,18-21] In our work, we analyzed these variables related to the adverse outcome on admission.

None of the scores were useful to predict in-hospital mortality. Also, despite hyponatremia is described as one of the mortality risk factors,[5,15,21] it was not related to this outcome in our casuistic. On the other hand, as it was observed previously,[5,21-24] high *serum* creatinine presented a significant contribution to prediction. We did not included patients with diagnosis of hepatorenal syndrome, which presents a high mortality rate by itself; however, despite these exclusions, *serum* creatinine persisted as an

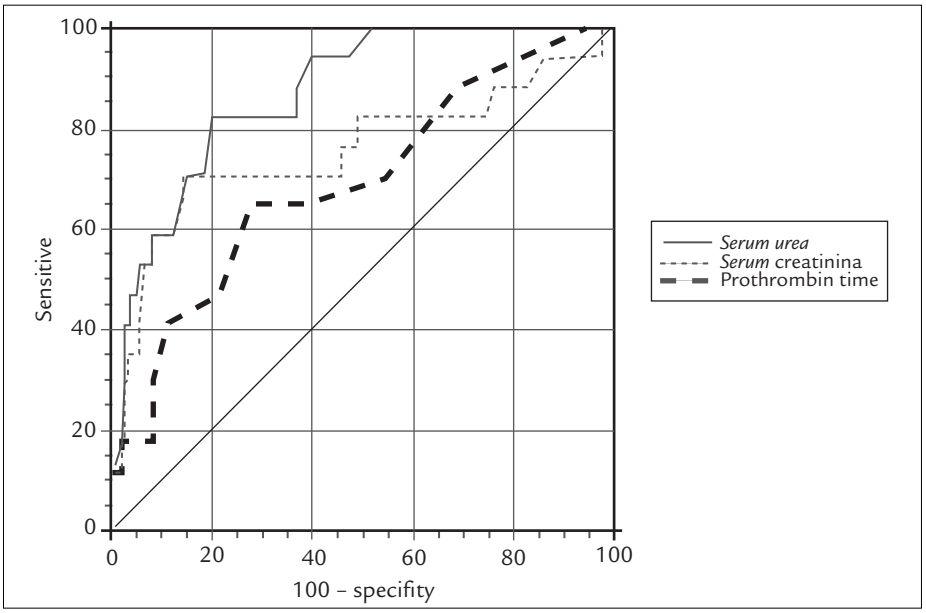

FIGURE 1 Area under the ROC curve for mortality by *serum urea*, creatinine and prothrombin time.

The associated criterion for *serum urea* was 0.42 g/L, with sensitivity of 82.4% (95% CI 56.6 to 96.2), specificity of 79.9% (95% CI 73 to 85.6) and positive likelihood ratio of 4. In the case of serum creatinine criterion value was 1.28 mg/dL with sensitivity of 70.6% (95% CI 44 to 89.7), specificity of 86.4% (95% CI 80.3 to 91.2) and positive likelihood ratio of 5. Finally for prothrombin time the cut off value was 17 seconds with sensitivity of 64.7% (95% CI 38.3 to 85.8), specificity of 72.2% (95% CI 64.8 to 78.8) and positive likelihood ratio of 2.

indicator of adverse outcome. This variable is used to calculate the MELD score; nevertheless, it has limitations as an estimate of glomerular filtration rate in cirrhosis, so the score possible underestimates the mortality risk in patients with ascites.

Although, similarly to other authors, we observed that *serum* creatinine is related to mortality, we found two other variables related to the adverse outcome. Prolonged prothrombin time presented a low AUC of 69% with an odds ratio of 2. This risk factor was not related to esophageal variceal bleeding but it is associated with liver dysfunction, which increases the probability of death in the short term. Last, the other risk factor with a great AUC of 87% and an odds ratio of 14, was higher level of *serum urea*. This variable was not described previously as a predictor of mortality in patients with ascites caused by cirrhosis and it is not included in the scores. Despite *serum urea* level might increase due to hemorrhage, in our casuistry only 18 individuals presented digestive bleeding (esophageal variceal bleeding), most of them in the surviving patient group.

Considering our results, in-hospital mortality was related to acute renal failure with increased levels of *serum urea* and creatinine and prolonged prothrombin time.

Conclusion

Our results suggest that acute renal failure and prolonged prothrombin time are predictors of in-hospital mortality in patients with portal hypertension due to alcoholic cirrhosis, despite Child Pugh category or clinical presentation.

Limitation of the study

Our study was performed in a single center with a relatively reduced sample size. Also, because it is a cross-sectional study, it is difficult to establish the role of the determined variables as risk factors for in-hospital mortality.

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Resumo

Fatores de risco de mortalidade intra-hospitalar em pacientes com ascite por cirrose hepática.

Introdução: ascite é uma das complicações mais comuns de cirrose associadas a uma elevada taxa de mortalidade. Embora vários escores tenham sido desenvolvidos a fim de avaliar o prognóstico da doença, eles foram concebidos para prever requisitos de transplante de fígado e mortalidade a curto prazo, mas não durante a internação. O objetivo deste estudo foi o de pesar fatores de risco para a mortalidade intra-hospitalar em pacientes adultos com ascite decorrente de cirrose alcoólica.

Material e métodos: foi realizado um estudo transversal em 180 pacientes adultos com diagnóstico de cirrose com hipertensão portal, associada à alta ingestão de álcool. O diagnóstico de cirrose foi feita por ecografia hepática e a hipertensão portal foi determinada por características clínicas e pelo gradiente de albumina soro-ascite. Indivíduos avaliados foram submetidos a exame clínico completo. A classificação de Child-Pugh e a escala MELD foram aplicadas em todos os pacientes.

Resultados: dezenove pacientes morreram durante a internação. A mortalidade foi associada ao aumento dos níveis de glóbulos brancos, ureia, creatinina, aspartato aminotransferase, alanina aminotransferase e tempo de protrombina prolongado. Realizamos uma logística binária múltipla para prever a mortalidade intra-hospitalar, que confirmou que ureia, creatinina e tempo de protrombina contribuíram significativamente para a previsão, com uma OR = 14 (IC 95% 12,8-16,7 p = 0,03), 2 (IC 95% 0,5-3,47, p = 0,04), e 2 (IC 95% 1,03-2,31, p = 0,01), relacionada linearmente.

Conclusões: nossos resultados sugerem que a insuficiência renal aguda e de tempo de protrombina prolongado são preditores de mortalidade intra-hospitalar em pacientes com hipertensão portal decorrente de cirrose alcoólica.

Palavras-chave: ascite, alcoólico, cirrose hepática, mortalidade hospitalar.

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