Predictors of hepatorenal syndrome in alcoholic liver cirrhosis

Martin Janicko, Eduard Veseliny, Gabriela Senajova, Peter Jarcuska

Background. Alcoholic liver disease is a major cause of liver cirrhosis and the hepatorenal syndrome is a serious complication. Risk factors for hepatorenal syndrome (HRS) in alcoholic liver cirrhosis are not entirely explored.
Aim. To assess the risk factors for hepatorenal syndrome in alcoholic liver cirrhosis.
Patients and Methods. Consecutive patients with alcoholic liver disease were followed for two months, development of renal failure, classified either as HRS or renal failure not fulfilling criteria of HRS, was the main outcome.
Results. Of 171 patients, 14 (8.2%) developed HRS and 13 (7.6%), renal failure not fulfilling the HRS criteria. A significant difference was found between patients with and without HRS in serum sodium (131.1±3.8 vs. 135.7±5.2; $P = 0.003$), creatinine, (94.1±26.8 vs. 80.3±20.2; $P < 0.001$), albumin (23.5±4.9 vs. 29.9±5.8; $P < 0.001$), INR (1.76±0.45 vs. 1.44±0.41; $P < 0.001$), bilirubin (252.3±179.4 vs. 91.2±101.0; $P < 0.001$), MELD (23±6 vs 15±5; $P < 0.001$) and MELD-Na score (27±5 vs. 18±6; $P < 0.001$). Multivariate analysis adjusted for sex and age showed that sodium together with creatinine are the strongest HRS predictors, followed by bilirubin with respective odds´ ratios (95% CI) of 1.041 (1.012-1.072) for creatinine, 0.870 (0.766-0.988) for serum sodium and 1.005 (1.001-1.010) for serum bilirubin.
Conclusion. Serum levels of sodium, creatinine and bilirubin are important predictors of the hepatorenal syndrome.

Key words: alcohol, liver cirrhosis, hepatorenal syndrome, predictors

Received: August 20, 2014; Accepted with revision: February 18, 2015; Available online: March 26, 2015
http://dx.doi.org/10.5507/bp.2015.010

1st Department of Internal Medicine, University Hospital, P.J. Safarik University in Kosice, Slovak Republic
Corresponding author: Peter Jarcuska, e-mail: petjarc@yahoo.com

INTRODUCTION

Hepatorenal syndrome occurs in roughly 25% of patients with acute alcoholic hepatitis[1], 20-30% of patients with spontaneous bacterial peritonitis[2] and in 15% of patients undergoing large volume paracentesis (over 5 liters of evacuated fluid) without adequate plasma expansion[3].

The actual risk factors for HRS are much less studied. There are several papers documenting that patients with HRS have lower mean values of serum sodium[4-6] but this association does not necessarily mean that serum sodium also has any predictive value.

The diagnosis of HRS is based on exclusion of other types of renal failure. Currently most accepted, are the diagnostic criteria proposed by the International Ascites club[7].

There are at least five papers which report data on the predictive value of hyponatremia in HRS, but the results are controversial. Two studies found serum sodium was not a significant, independent HRS predictor[5,8] and two did[3,9]. The fifth paper was only a case-control design[10]. The foregoing formed the rationale for confirming the predictive value of hyponatremia in HRS development and quantifying its risk level relative to parameters of liver and kidney function in a methodically robust cohort design study which included a sufficient number of participants.

PATIENTS AND METHODS

Consecutive patients admitted to the 1st department of internal medicine, university hospital, Košice, Slovakia in 2002 to 2007 with decompensated alcoholic liver cirrhosis (ICD-10 code K70.3) were retrospectively analyzed. Diagnostic criteria for liver cirrhosis were: 1) morphologic – typical appearance of the liver on ultrasound or computed tomography, 2) laboratory parameters of impaired liver function, 3) clinical signs of liver cirrhosis and portal hypertension. Decompensation was defined as the presence of ascites, variceal bleeding, encephalopathy or icterus[11]. Alcoholic etiology was based on reported alcohol use on average more than 60 g daily for men and 40 g daily for women for at least five years, and on negative serology screening for viral hepatitis B or C. Patients with serum creatinine over 133 micromoles/L at the time of presentation were excluded. Other exclusion criteria were coronary heart disease, dilatation cardiomyopathy, acute coronary syndrome, acute surgical abdomen, chronic obstructive pulmonary disease with respiratory failure, prior hepatorenal syndrome.

Relevant data, which included age, sex, etiology of liver cirrhosis, comorbidities, reason for admission, duration of hospitalization and follow-up, serum creatinine, INR, bilirubin, serum and urine sodium and measured glomerular filtration (mGF) were extracted from patients' charts. All results were determined in Košice University hospital laboratories; glomerular filtration was measured by creatinine clearance.

The MELD score was calculated from the obtained parameters according to the formula (0.378 x ln (serum bilirubin [μmol/L]) + 1.12 x ln (INR) + 0.957x ln(serum creatinine[μmol/L]), The MELD Na score according to (MELD + 1.0*(140-Na) − 0.025*MELD*(140-Na), where Na was between 125-140 mmol/L), and Child-Pugh score and class were determined[12].

All patients were followed up for two months, which is the maximum time between scheduled check-ups for patients with advanced liver cirrhosis in our institution. Development of renal failure was the main outcome. Hepatorenal syndrome was diagnosed according to International Ascites Club guidelines from 2007 (ref.[12]), but we also accepted plasma expansion with 1.5 litres of normal saline with diuretic treatment stopped for 24 h (ref.[13]). Elevation of creatinine over 133 μmol/L without fullfilling other criteria for HRS was regarded as "non-HRS renal failure".

The study was approved by institutional ethics committee and performed according to the Declaration of Helsinki. Informed consent was obtained from all patients at the time of admission.

Data are presented as means ± standard deviation, if not stated otherwise. Statistically significant difference among continuous variables was analyzed by ANOVA or Kruskall-Wallis test, respecting these tests' data assumptions. Differences in categorical variables were assessed by the Chi-square test. Univariate and multivariate regression analysis was performed by logistic regression analysis. Second multivariate regression was performed with the standardized variables (Z-scores), so that the relative effect of the variables on the outcome would be easily comparable. Probability of development of HRS was assessed by the Kaplan-Meier method with log-rank test comparison of the curves. Statistical analyses were performed in SPSS statistical software package, version 17, IBM Corporation, New York.

RESULTS

The cohort consisted of 171 patients, 65% males. Eighty three patients were taking furosemide (mean dosage 21.3 ± 26.8 mg), 125 patients were taking spironolactone (mean dosage 56.5 ± 44.9). Baseline parameters of the study cohort are summarized in Table 1. Acute alcoholic hepatitis superimposed on liver cirrhosis was present in 24 cases (14%), hepatic encephalopathy in 35 cases (20.5%) and variceal bleeding in 19 cases (11.1%). Of 24 patients with acute alcoholic hepatitis at the time of admission, 4 (16.7%) developed renal failure. Two of these patients had HRS and two had renal failure which did not fulfill the criteria of HRS. In total, 120 (70.2%) patients had ascites and 66 (38.6%) patients had at least one infectious complication.

Patients were hospitalized for a median of 12 days (range 1 to 54); all patients were censored at day 60. Overall, the 60-day mortality in the cohort was 19.3% (33 patients out of 171), group-specific mortality is presented in Table 2.

Table 1. Basic characterization of the study cohort.

Parameter	Value
MELD	16.3 ± 6.0
MELD-Na	19.2 ± 6.5
Child Pugh	A: 11 (6.4%); B: 85 (49.7%); C: 75 (43.9%)
Serum creatinine	81.7 ± 21.6 μmol/L
Serum Na	135.1 ± 5.4 mmol/L
INR	1.5 ± 0.47
Total bilirubin	110.4 ± 124.8 μmol/L
Albumin	29.0 ± 5.1 g/L
Urine Na	74.8 ± 60.6 mmol/L

INR – international normalization ratio

Table 2. Mean values of parameters of interest in three outcome groups in the beginning of follow-up.

	N	Without renal failure Mean ±SD	Other renal failure Mean ±SD	Hepatorenal syndrome Mean ±SD	*P*
Creatinine (μmol/L)	171	80.3±20.2	83.3±28.6	94.1±26.8	<0.001
Serum Na (mmol/L)	171	135.7±5.2	133.0±7.1	131.1±3.8	0.003
Urine Na* (mmol/L)	113	81.4±62.8	62.8±42.2	31.7±23.4	0.02
MELD	171	15±5	21±6	23±6	<0.001
MELD-Na	171	18±6	24±6	27±5	<0.001
Bilirubin (μmol/L)	171	91.2±101.0	170.3±180.1	252.3±179.4	<0.001
INR	171	1.44±0.41	1.9±0.76	1.76±0.45	<0.001
Age* (years)	171	52.8±9.7	57.2±9.2	46.3±11.5	0.021
Body weight (kg)	171	77.7±14.7	82.3±12.7	80.2±21.0	0.583
Furosemide* (mg)	83	20.7±27.8	26.2±18.9	22.9±23.3	0.307
Spironolactone (mg)	126	55.8±44.7	63.5±39.0	57.1±54.1	0.563
Albumin (g/L)	171	29.9±5.8	25.0±5.4	23.5±4.9	<0.001
Mortality rate (%)	171	11.1	64.3	61.8	<0.001
Male sex (%)	171	66.7	71.4	76.9	0.717

mGF – measured glomerular filtration, eGF – estimated glomerular filtration. *P* calculated by ANOVA, * - *P* calculated by Kruskall-Wallis

Hepatorenal syndrome occurred in 14 (8.2%) patients. Type I hepatorenal syndrome occurred in 11 (6.4%), type II in 3 (1.8%) patients. Renal failure not fulfilling the criteria for hepatorenal syndrome occurred in 13 (7.6%) patients. Eight out of these patients had preexisting renal disease, 5 patients were taking nephrotoxic drugs (non-steroidal antiinflammatory drugs).

All patients received treatment with albumin and terlipressin. Albumin dosage was 20 g per day, terlipressin 2 mg per day divided to 4 doses. One patient required catecholamine treatment for hypotension and two patients underwent renal replacement therapy. We observed complete response to the therapy in 5 (35.7%) and partial response in 4 (28.6%) patients.

Mean values of selected parameters in the patients without renal failure, in patients who developed other renal failure and in patients who developed hepatorenal syndrome are summarized in Table 2. We found significant differences in serum creatinine, serum sodium, urine sodium, serum bilirubin, INR, MELD score and MELD-Na score. Patients who developed hepatorenal syndrome were younger than patients without renal failure or non-HRS renal falure. There were no significant differences in body weight or diuretic dosing.

Logistic regression adjusted for age and sex, confirmed serum sodium, urine sodium, MELD, MELD-Na, total bilirubin, albumin, INR, and serum creatinine as significant predictors of HRS development (Table 3.)

Multivariate logistic regression analysis was performed to assess the predictive value of an individual variable in combination with other variables in a mathematical model. Because of presumed high inter-correlation among similar parameters (bilirubin, albumin, MELD score, urine sodium and serum sodium) which could have inflated the variance and reduced the validity of the model, we only selected age, creatinine, serum sodium and bilirubin for the multivariate regression. All of the selected parameters analyzed together were found to be significant and independent predictors of hepatorenal syndrome. Odds ratios (95% CI) were 0.929 (0.862-1.000) for age, 1.041 (1.012-1.072) for creatinine, 0.870 (0.766-0.988) for serum sodium and 1.005 (1.001-1.010) for serum bilirubin. Comparison of the relative effect of variables shows that in this predictive model serum creatinine explains 28.1%, serum sodium 24.7%, age 24.6% and bilirubin 23.1% of the model performance. Optimal cut-off value had 100% sensitivity and 70.1% specificity with positive predictive value of 23.0% and negative predictive value of 100%. Model-generated probabilities were used to sort patients to high and low HRS probability group. The incidence of HRS between these groups was compared by Kaplan-Meier analysis (Fig. 1). The difference of survival between low and high risk groups was 23%, $P < 0.001$.

Table 3. Logistic regression analysis of predictors of hepatorenal syndrome. Parameters are adjusted for age and sex.

	Significance	OR	95% confidence interval for OR
Creatinine	0.011	1.035	1.008-1.062
Serum Na	0.004	0.848	0.759-0.948
Urine Na	0.024	0.977	0.958-0.997
Bilirubin	0.001	1.006	1.003-1.01
INR	0.049	2.635	1.004-6.919
Albumin	0.001	0.829	0.741-0.927
MELD	0.001	1.195	1.081-1.321
MELD-Na	<0.001	1.225	1.099-1.365

DISCUSSION

Hepatorenal syndrome is a potentially preventable, but serious complication of advanced liver cirrhosis[14].

Although several complex predictive tools exist for mortality of liver cirrhosis and its complications, no such tool is available for hepatorenal syndrome. For mortality of liver cirrhosis the most widely used scoring systems are MELD and Child-Pugh, out of which MELD score is slowly becoming the gold standard in liver transplantation[15]. Occasionally, data for unconventional mortality predictors in liver cirrhosis are published[16]. The predictors of some liver cirrhosis complications, such as variceal bleeding have also been described[17].

The predictors of hepatorenal syndrome are much less studied. That is very unfortunate, because there are several strategies for decreasing the probability of HRS in high risk patients. It is well-known that intravenous albumin infusion in high risk patients with spontaneous bacterial peritonitis, decreases the risk of renal impairment[18]. Another classic paper by Akriviadis reported that in high risk patients with acute alcoholic hepatitis pentoxifylline decreases the probability of hepatorenal syndrome[1]. This aside, new data are emerging that show that prophylaxis with rifaximin also decreases the risk of hepatorenal syndrome in decompensated cirrhotics. The authors suggest that the probable mechanism is reduction of endotoxin

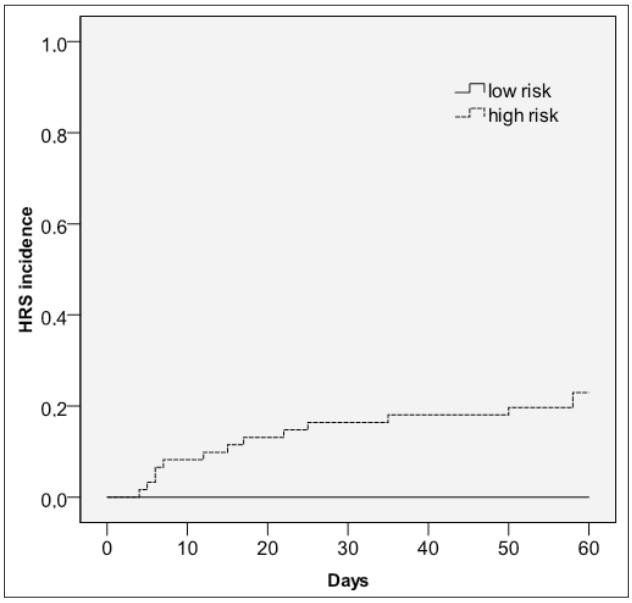

Fig. 1. Comparison of HRS development rate between patients with and without hyponatremia.

production with subsequent decrease in tumor necrosis alpha levels, which have positive effect on portal hypertension[19].

Unfortunately, the tools for identifying this group of high risk patients are inadequate. The most widely cited paper was published almost 20 years ago by Gines et al. In the cohort of 234 patients, with a one year HRS incidence of 18%, the authors determined the individual prognostic value of 16 variables. In the multivariate analysis, only hyponatremia, high plasma renin activity and lack of hepatomegaly were found to be independent significant predictors of HRS. Surprisingly, no variable reflecting liver function was found to be a significant predictor in this paper[3]. Liver function parameters (MELD, Child-Pugh, INR, bilirubin, albumin) were not found to be different in patients with and without subsequent development of HRS in a study published by Seo et al. There was also no difference in serum sodium between these two groups of patients[7]. These results are opposed to a large body of evidence showing that liver function parameters are the main mortality predictors in hepatorenal syndrome. A study by Yang et al. showed that serum bilirubin, albumin, creatinin and MELD score were significantly associated with prognosis of patients with hepatorenal syndrome[20].

In our study, in contrast to the above papers, the results of univariate regression analysis suggest that parameters of liver function (total bilirubin, albumin, INR, MELD and MELD-Na score) as well as age, serum and urine sodium and creatinine are significant predictors of hepatorenal syndrome. To assess the independent prognostic value of these variables we selected four for the multivariate analysis. The predictive model constructed from these four variables was very good at predicting HRS and furthermore each variable was an independent predictor. Serum creatinine contributed the most to the overall performance of the model followed by serum sodium, age and bilirubin, but the differences were small.

Deranged intravascular volume distribution with effective arterial hypovolemia on the one hand and volume overload in splanchnic vasculature on the other, with activation of compensatory mechanisms take place at the outsetof HRS development. For this reason, dilution hyponatremia and low sodium output in the urine are expected to be very common in patients with HRS. This association has been confirmed by published data[4-6]. It is however necessary to rule out, pseudohyponatremia in acute on chronic liver failure[21].

Data on the actual prognostic value of serum sodium are relatively controversial. Porcel et al. reported a case-control study which included 44 patients with cirrhosis and hyponatremia in the study group, and 20 controls with cirrhosis without hyponatremia. Reported odds ratio for developing HRS in hyponatremic group was 45.125 (95% CI 5.56-366.307) vs. eunatremic group. Unfortunately, as this was a case-control study, it carried inherent selection bias, manifested as a very high HRS incidence rate (52% in roughly 5 months), which is approximately 5 times higher than the generally reported HRS incidence[10].

It is necessary to rule out pseudohypoanatremia in this setting, which could by caused hypercholesterolemia. Other published papers, what include data for hyponatremia, concentrated mostly on novel parameters of renal failure, such as cystatin C. Ahn et al. studied 112 patients with a 21% 1-year HRS incidence and reported that serum sodium, along with MELD score and cystatin C, were significant predictors of HRS in univariate (OR 0.894, 95% CI 0.841-0.851) and multivariate (HR 0.93, 95% CI 0.87-0.99) analysis[9].

Younger age was also significantly associated with risk of HRS in our data. This association has never been published to the best of our knowledge. In fact, in some papers higher age was associated with higher risk of HRS (ref.[5]). We believe that this discrepancy was caused by the fact that we had a priori ruled out patients with elevated serum creatinine and who were generally older.

Our results reported here indicate that the baseline risk of HRS development is dependent on liver and kidney function (in our data represented by serum creatinine and bilirubin) and on systemic/splanchnic circulation derangement represented by hyponatremia.

CONCLUSION

A predictive model based on serum sodium, bilirubin and creatinine, could be helpful in HRS risk assessment in cirrhotic patients. It allows clinicians to identify patients with higher HRS risk, who require closer follow-up, intensive management of precipitating factors (such as variceal bleeding or spontaneous bacterial peritonitis) and caution when performing invasive procedures, such as paracentesis.

Acknowledgement: The funding was provided by P.J. Safarik University in Kosice, Slovakia.

Author contributions: All authors contributed equally to the manuscript.

Conflict of interest statement: The authors state that there are no conflicts of interest regarding the publication of this article.

REFERENCES

1. Akriviadis E, Botla R, Briggs W, Han S, Reynolds T, Shakil O. Pentoxifylline improves short-term survival in severe acute alcoholic hepatitis: a double-blind, placebo-controlled trial. Gastroenterology 2000;119(6):1637-48.
2. Follo A, Llovet JM, Navasa M, Planas R, Forns X, Francitorra A, Rimola A, Gassull MA, Arroyo V, Rodes J. Renal impairment after spontaneous bacterial peritonitis in cirrhosis: incidence, clinical course, predictive factors and prognosis. Hepatology 1994;20(6):1495-501.
3. Gines A, Escorsell A, Gines P, Salo J, Jimenez W, Inglada L, Navasa M, Claria J, Rimola A, Arroyo V. Incidence, predictive factors, and prognosis of the hepatorenal syndrome in cirrhosis with ascites. Gastroenterology 1993;105(1):229-36.
4. Angeli P, Wong F, Watson H, Gines P and the CAPPS Investigators. Hyponatremia in Cirrhosis: Results of a Patient Population survey. Hepatology 2006;44(6):1535-42.
5. Sharawey MA, Shawky EM, Ali LH, Mohammed AA, Hassan HA, Fouad YM. Cystatin C: a predictor of hepatorenal syndrome in patients with liver cirrhosis. Hepatol Int 2011;5(4):927-33.
6. Tyagi P, Sharma P, Sharma BC, Puri AS, Kumar A, Sarin SK. Prevention of hepatorenal syndrome in patients with cirrhosis and ascites: a pi-

lot randomized control trial between pentoxifylline and placebo. Eur J Gastroenterol Hepatol 2011;23(3):210-7.
7. Angeli P, Gadano A, Krag A, Sanyal A, Kim WR, Sarin S, Singh V, International Club of Ascites. Criteria for the diagnosis of Hepatorenal Syndrome. [cited 2015 Feb 24]; Available from: http://www.icascites.org/about/guidelines/
8. Seo YS, Jung ES, An H, Kim JH, Jung YK, Kim JH, Yim HJ, Yeon JE, Byun KS, Kim CD, Ryu HS, Um SH. Serum cystatin C level is a good prognostic marker in patients with cirrhotic ascites and normal serum creatinine levels. Liver Int 2009;29(10):1521-7.
9. Ahn HS, Kim YS, Kim SG, Kim HK, Min SK, Jeong SW, Jang JY, Lee SH, Kim HS, Kim BS, Park JM. Cystatin C is a Good Predictor of Hepatorenal Syndrome and Survival in Patients with Cirrhosis who have Normal Serum Creatinine Levels. Hepatogastroenterology 2011;59:115-6.
10. Porcel A, Diaz F, Rendon P, Macias M, Martin-Herrera L, Giron-Gonzalez JA. Dilutional hyponatremia in patients with cirrhosis and ascites. Arch Intern Med 2002;162(3):323-8.
11. Garcia-Tsao G, D'Amico G, Abraldes JG, Schepis F, Merli M, Kim WR, Christensen E. Predictive models in portal hypertension. In: De Franchis R, editor. Portal Hypertension IV Proceedings of the Fourth Baveno International Consensus Workshop. Oxford: Blackwell Publishing ltd.; 2006. p. 47-101.
12. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973;60(8):646-9.
13. Arroyo V, Gines P, Gerbes AL, Dudley FJ, Gentilini P, Laffi G, Reynolds TB, Ring-Larsen H, Scholmerich J. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. International Ascites Club. Hepatology 1996;23(1):164-76.
14. Lata J. Hepatorenal syndrome. World J Gastroenterol 2012;18(36):4978-84.
15. Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, D'Amico G, Dickson ER, Kim WR. model to predict survival in patients with end-stage liver disease. Hepatology 2001;33(2):464-70.
16. Tas A, Koklu S, Beyazit Y, Kurt M, Sayilir A, Yesil Y, Celik H. Thyroid hormone levels predict mortality in intensive care patients with cirrhosis. Am J Med Sci 2012;344(3):175-9.
17. Abraldes JG, Villanueva C, Banares R, Aracil C, Catalina MV, Garcia-Pagan JC, Bosch J. Hepatic venous pressure gradient and prognosis in patients with acute variceal bleeding treated with pharmacologic and endoscopic therapy. J Hepatol 2008;48(2):229-36.
18. Sort P, Navasa M, Arroyo V, Aldeguer X, Planas R, Ruiz-del-Arbol L, Castells L, Vargas V, Soriano G, Guevara M, Gines P, Rodes J. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. N Engl J Med 1999;341(6):403-9.
19. Vlachogiannakos J, Viazis N, Vasianopoulou P, Vafiadis I, Karamanolis DG, Ladas SD. Long-term administration of rifaximin improves the prognosis of patients with decompensated alcoholic cirrhosis. J Gastroenterol Hepatol 2013;28(3):450-5.
20. Yang YW, Wu CH, Hu RH, Ho MC, Tsai MK, Wu YM, Lee PH. Longitudinal assessment of prognostic factors for patients with hepatorenal syndrome in a tertiary center. Hepatol Int 2010;4(2):507-10.
21. Vo H, Gosmanov AR, Garcia-Rosell M, Wall BM. Pseudohyponatremia in acute liver disease. Am J Med Sci 2013;345(1):62-4.