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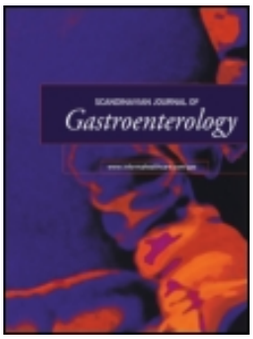

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ORIGINAL ARTICLE

Moderate hyperkalemia in hospitalized patients with cirrhotic ascites indicates a poor prognosis

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Abstract

Objective. Development of ascites in patients with liver cirrhosis is an ominous sign with a poor outcome. A liver transplantation must be considered, and it then becomes important to know if there are any factors indicating a worsened prognosis. ***Material and methods.*** We used official registers for a follow-up study of at least 5 years considering the prognosis of 155 prospectively recruited in-patients with cirrhotic ascites from medical units at nine Swedish university hospitals. All patients had undergone at least one diagnostic ascites tap, and had initially been questioned about background factors and physically examined according to a standardized case record form, followed by sampling of blood, urine, and ascites. ***Results.*** Death occurred within 1 year after inclusion in 53% of the cases, and was primarily liver-related in 70%. In a multivariable analysis, the two ordinary variables that showed the strongest correlation with risk of death were serum potassium and abdominal tenderness. All 22 patients with a serum potassium concentration of at least 4.8 mmol/L (maximum 5.8 mmol/L) died within 1 year after inclusion. Potassium concentration was related to renal function and potassium-saving drugs. ***Conclusion.*** This follow-up study of a prospectively recruited cohort of in-patients with cirrhotic ascites confirms their poor prognosis. Awareness of an elevated serum potassium value, which would reflect a threatened renal function, seems essential, because it may offer a simple way to identify cases with the worst prognosis. An area for further research should be to explore the significance of including serum potassium in prognostic models.

Key Words: *ascites, cirrhosis, potassium, prognosis, signs*

Introduction

The development of ascites in a patient with liver cirrhosis signals the end stage of liver disease, with an estimated 1-year survival of at most 80% [1]. Several therapeutic measures are available to relieve this symptom, but orthotopic liver transplantation (OLT) is the only way to eliminate the problem and to avoid the ultimate risk, development of hepatocellular carcinoma. Thus, it is important to identify those patients who have a high risk of deterioration and who are suitable for an OLT. Two scoring systems have been introduced and generally accepted for patients with end-stage liver disease, the CTP (Child-Turcotte-Pugh) score [2] and the MELD (model for end-stage liver disease) score [3]. It is not clear which of these is the best predictor of mortality. Although there are several reports claiming superiority

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for the MELD score, other reports indicate an equal [4] or even better [5] prognostic value of the CTP score. Another way to estimate the severity of liver disease is to use prognostic indices, a technique proposed by researchers such as the Barcelona group [6].

The applicability and the goodness of a prognostic score depend on the population studied. This study focuses on patients who have developed cirrhotic ascites. For this patient group, it would be of interest to explore the usefulness of ordinary data from case histories, physical examinations, and ordinary blood tests as predictors of death. We included not only laboratory tests primarily reflecting liver function but also other data, to explore whether signs of infection and renal impairment influenced the prognosis. For example, it is generally accepted that both spontaneous bacterial peritonitis (SBP) and hepatorenal syndrome worsen the prognosis in patients with cirrhotic ascites.

We recently published a report on symptoms and signs indicating SBP [7]. The study was based on data from a cohort of prospectively recruited in-patients with portal hypertension and ascites with no knowledge regarding possible SBP before inclusion. We judged that this cohort, which excluded those with ascites due to a cause other than cirrhosis with portal hypertension, would also suit the aim of studying whether initially registered symptoms, signs, and laboratory tests from an ascites episode could be related to the prognosis in any way.

Patients and methods

The study population comprised prospectively recruited in-patients with a diagnosis of cirrhotic ascites, treated at nine university hospitals in Sweden between June 1998 and October 2002. Most of these cases had been hospitalized because of this complication. Inclusion in the study was not restricted to cases with a formerly untreated ascites. Only data from the first ascites episode during the study period were registered. All patients recruited to our study were followed until the end of 2007, that is, for at least 5 years. In 155 cases (110 men, 45 women; mean age 59.8 years, range 36–89), it was possible to find all data about diagnoses during hospital care, including hepatocellular carcinoma and OLT, and date and cause of death from various official Swedish health registers at the National Board of Health and Welfare (the Swedish Cause of Death Register, the Swedish Cancer Registry, and the National Patient Register). The death certificates from the Register enclosed information about primary and contributing causes of death as well as underlying disease and thus generally made it possible to assess if the death cause was related to an underlying liver disease.

All patients were initially questioned by one of the authors at the hospital about background factors, alcohol habits, infections, and drugs. A regular daily intake of at least 20 g alcohol was chosen as possibly harmful and was classified as i) never (0 points), ii) before but not during the last week prior to inclusion (1 point), or iii) during the last week before inclusion (2 points).

Medical files were checked for information on earlier treatment for SBP, esophageal varices, and encephalopathy. All patients were initially physically examined by one of the authors at the hospital according to a standardized form regarding mental state, signs of infection, and abdominal state including presence of tenderness before the ascites tap. The ascites volume was determined as the fluid volume received by total paracentesis with a complete ascites mobilization as the goal (maximum 24 liters). Results from routine analyses of blood, serum, ascites, and urine were also recorded in accordance with a structured schedule, and the patients were then classified according to the CTP classification [2]. We used two different ranges for the INR middle group: CTP_I defined by converting the prothrombin time limits, given as % values, reported by Albers et al. [2] (i.e., INR 1.2–1.5), and CTP_{II} defined as the range recommended by authors such as Sherlock and Dooley [8] (i.e., INR 1.7–2.3). MELD score was calculated with the calculator presented by MD +Calc (http://www.mdcalc.com), using the formula 9.57 * ln(serum creatinine, mg/dL) + 3.78 * ln(serum bilirubin, mg/dL) + 11.20 * ln(INR) + 6.43.

Body mass index (BMI), calculated after ascites mobilization, was used to reflect malnutrition. SBP was diagnosed when there was a neutrocytic ascites with at least $0.250*10^9$ polymorphonuclear leukocytes per liter in the absence of an abdominal infectious focus [9].

Considering factors that could be closely related to the prognosis, we chose reasonable cut-off points to identify patients with the worst prognosis. Thus, the cohort was classified with regard to i) presence of abdominal tenderness; ii) serum potassium below, in the lower range of, in the upper range of, or above the current reference range used today (3.6–4.6 mmol/L); and iii) a MELD score of at least 10, 20, or 30 points as used by authors such as Wiesner et al. [10], and analyzed considering death or OLT within 1 year after inclusion.

We used standard methods for correlations between risk variables. The hazard function for death was estimated by use of a Poisson regression model, with the follow-up period for each individual divided into intervals of 0.05 years. First, a series of analyses were performed including current age and time since start of

Table I. Laboratory tests and MELD and CTP scores (see text) in patients with cirrhotic ascites; hazard ratio (HR) and confidence interval (CI). B = blood, S = serum, AST = aspartate amino transferase, ALT = alanine amino transferase, ALP = alkaline phosphatases, NS = not significant, * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$.

	N	Mean	HR	CI	*p*-value
B-Hemoglobin (g/L)	155	114.7	1.00	0.99–1.01	NS
B-Leukocytes (10^9/L)	153	10.3	1.02	0.99–1.05	NS
B-Platelets (10^9/L)	154	178.6	1.00	1.00–1.00	NS
S-AST (μkat/L)[1]	154	2.08	1.14	1.09–1.20	0.0000***
S-ALT (μkat/L)[1]	154	0.89	1.51	1.29–1.77	0.0000***
S-ALP (μkat/L)[1]	153	8.8	1.03	1.01–1.06	0.0172*
S-Bilirubin (mmol/L)	153	102	1.00	1.00–1.01	0.0004***
INR	153	1.49	0.82	0.45–1.50	0.5278NS
S-Sodium (mmol/L)	155	133.3	0.96	0.93–1.00	0.0700NS
S-K (mmol/L)	155	3.99	2.18	1.57–3.03	0.0000***
S-Creatinine (mmol/L)	154	131.6	1.00	1.00–1.00	0.0274*
S-Urea (mmol/L)	88	11.00	1.05	1.02–1.07	0.0001***
S-Albumin (g/L)	147	24.87	1.01	0.98–1.03	0.6145NS
CTP_I score	142	11.2	1.04	0.98–1.09	0.1705NS
CTP_{II} score	142	10.2	1.05	0.99–1.11	0.1061NS
MELD score	150	17.4	1.04	1.01–1.06	0.0039**

[1]Upper limits of normal were for AST 0.8, ALT 0.8, and ALP 5.0.

follow-up plus another covariate. The variables which turned out to be significant predictors were entered into a stepwise (forward) multivariable analysis. The follow-up of a patient was censored at OLT. We characterized the goodness of some predictors using the gradient of risk per 1 standard deviation [11], which is the hazard ratio obtained when comparing two individuals who differ by 1 standard deviation with respect to the risk variable. Although gradient of risk for death per standard deviation is reported to be a more adequate method than the area under the ROC curve, which is frequently used to show the discriminative ability of a test, we also calculated these curves at 1 month, at 1 year, and at 5 years after inclusion in the study. Based on the results of Poisson regression it was possible to construct a risk formula. A *p*-value < 0.05 was regarded as significant.

The Regional Ethical Review Board in Gothenburg approved the study at each center (T 717-08).

Results

All 155 patients were followed for more than 5 years or until death or OLT, the total follow-up period being 314.3 years. In the majority of cases ($n = 106$) the etiology of the liver cirrhosis was alcohol alone, and in further 13 patients alcohol was a contributing factor. A hepatitis C virus infection was present in 12 of these 13 cases, and in further 12 patients. Nine patients had primary biliary cirrhosis, and three primary sclerosing cholangitis. In 10 cases the cause of the liver disease was not specified. Esophageal varices were diagnosed in 57 of 97 examined patients (59%). In 25 of 153 cases (16%), an episode of hepatic encephalopathy had been reported prior to the inclusion, and this sign was present at inclusion in 29 of 153 cases (19%). The mean BMI, which could be calculated in 103 patients, was 23.7 (range 14.0–37.6).

The results of the routine laboratory analyses are presented in Table I. Serum urea was the only test with a significant number of missing values (43%). One patient had a CTP score of 7 points and the others had a CTP score of at least 8 points, using Albers limits, showing an absence of patients in CTP class A. The majority of the patients were in class C ($n = 108$) and the rest in class B ($n = 34$). The mean MELD score was 17.4 (range 6–45).

Forty-four patients (28%) reported a daily intake of at least 20 g ethanol during the week prior to admission, 54 were abstainers, and the rest ($n = 55$) constituted a middle group. The liver function as reflected by INR was poor in patients with a current drinking (mean 1.62), better in the middle group (mean 1.52), and best in the abstainers (mean 1.37) with a significant correlation ($r = 0.29$, $p = 0.0003$). Information on drug consumption prior to inclusion in the study was available for 142 of the 155 patients. Potassium-saving drugs had been given before inclusion in 83 cases, mainly spironolactone ($n = 79$) and the rest amiloride ($n = 4$). Another three patients had been given potassium chloride before inclusion. The use of these three drugs did not correlate with prognosis ($p = 0.2706$).

An OLT was performed in 11 patients within the first year after inclusion. Two of these died within the first year and another one within the next year, whereas the other eight patients survived for more

Table II. One-year survival in 155 patients according to abdominal tenderness, serum potassium value (ref. value 3.6–4.6 mmol/L), and MELD score at inclusion in the study.

	OLT and/or death <1 year				
	OLT		No OLT		
	Dead	Alive	Dead	Alive (%)	All
Abdominal tenderness					
No	2	8	46	46[1] (45)	102
Yes	0	1	33	16 (32)	50
All	2	9	79	62[1] (41)	152
Serum potassium					
< 3.6	0	4	15	24 (56)	43
3.6–4.1	1	2	24	27 (50)	54
4.2–4.6	1	3	19	12 (34)	35
> 4.6	0	0	22	1 (4)	23
All	2	9	80	64 (41)	155
MELD score					
6–9	0	2	10	15 (56)	27
10–19	1	6	34	29 (41)	70
20–29	1	0	27	16 (36)	44
≥ 30	0	1	6	2[2] (22)	9
All	2	9	77	62 (41)	150

[1]This figure includes two patients with OLT performed > 1 year after inclusion; [2]This figure includes one patient with score 32, and one patient with score 34.

than 5 years. Two further patients had an OLT performed more than 1 year after inclusion.

The risk of death was most striking during the first year after inclusion in the study. Within 1 year after inclusion in the study, 82 patients were dead, including two OLT cases (53%); 11 of these deaths were due to a non-liver-related diagnosis, such as lymphoma (n = 1), myocardial infarction (n = 1), and pneumonia (n = 1). In 14 cases, a liver disability contributed to the death, but in 57 patients (70%) the cause of death was registered as primarily liver-related: liver failure (n = 28), liver cirrhosis (n = 12), liver cancer (n = 6); hepatorenal syndrome (n = 6), esophageal varices (n = 4), and alcoholic hepatitis (n = 1).

Univariable analyses

Besides alcohol habits, we could not find any variable in the case histories, including former or present SBP, which could be related to the prognosis, although we did find a relation to bacterial growth in the ascites (p = 0.0202). Considering alcohol habits, we found a significant inverse correlation with risk of death; a recent intake was related to a better prognosis (HR 0.70, CI 0.56–0.89, p = 0.0028).

Among the physical signs, only abdominal tenderness was indicative of a poor outcome (p = 0.0040). This physical sign was correlated with present SBP (r = 0.293, CI 0.128–0.441, p = 0.0050) but not with the amount of ascites (p = 0.67). Sixteen of the 50 patients (32.0%) with abdominal tenderness were still alive and without an OLT 1 year after inclusion, compared to 46 of 102 patients (45.1%) without this sign (Table II). An OLT was performed in one patient with abdominal tenderness (2.0%) and in 10 patients without this sign (9.8%).

A strong relation was found between liver laboratory tests and risk of death, with the exception of the variable INR (Table I). A correlation with death was found for serum urea (p = 0.0001) and for serum creatinine (p = 0.0274). A positive correlation was also found for serum potassium (p < 0.0001); patients with hypokalemia showed the best prognosis (Table II). Potassium values were correlated with renal function as reflected by creatinine (r = 0.24, p = 0.0034) and urea (r = 0.34, p = 0.0015), and with reported use of potassium-saving drugs or potassium chloride (r = 0.25, p = 0.0027) (Table III).

Looking at the relation between risk of death and the scoring systems, we found a correlation with MELD score (p = 0.0039) but not with CTP score, regardless of the INR limits used (Table I). However, the MELD score was correlated with the two CTP scores (r = 0.6, CI 0.5–0.7, p < 0.001).

The area under the ROC curve was determined for some laboratory tests used as surrogate markers of the kidney function, and some scoring models at different time points after inclusion in the study (Table IV).

We found a substantial number of patients above the chosen upper cut-off levels for some factors (abdominal tenderness, serum potassium, and MELD score), which turned out to be closely related to a poor prognosis; hyperkalemia showed the best predictive power (Table II). All 22 patients with a

Table III. Use of potassium-saving drugs or potassium chloride in 155 patients according to serum potassium at inclusion in the study.

	Type of potassium-saving drug					
S-K	Spironolactone	Amiloride	Potassium chloride	None	No drug declared	All
<3.6	15	0	2	22	4	43
3.6–4.1	23	3	1	20	7	54
4.2–4.6	26	0	0	8	1	35
>4.6	15	1	0	6	1	23
All	79	4	3	56	13	155

Table IV. Area under the ROC curve (95% CI) for death at 1 month, at one year, and at five years after inclusion in the present study for routine laboratory tests reflecting kidney function, some scoring models, and the risk formula, which is described in the Multivariable analysis section and constructed according to the results of the study. The abbreviations CTP_I, CTP_{II}, and MELD are explained in the Methods section.

	1 month	1 year	5 years
S-K	0.744 (0.641–0.847)	0.710 (0.629–0.790)	0.662 (0.563–0.761)
S-Urea	0.839 (0.727–0.952)	0.717 (0.610–0.824)	0.637 (0.509–0.765)
S-Creatinine	0.729 (0.623–0.834)	0.693 (0.610–0.776)	0.663 (0.564–0.762)
CTP_I score	0.656 (0.538–0.773)	0.538 (0.443–0.633)	0.470 (0.359–0.581)
CTP_{II} score	0.672 (0.557–0.788)	0.568 (0.474–0.663)	0.495 (0.383–0.606)
MELD score	0.772 (0.674–0.870)	0.643 (0.555–0.731)	0.560 (0.455–0.666)
Our risk formula	0.761 (0.661–0.861)	0.742 (0.664–0.821)	0.698 (0.602–0.795)

serum potassium concentration of at least 4.8 mmol/L died within 1 year after inclusion.

Multivariable analysis

The multivariable analysis was performed in a stepwise manner (forward). Variables were entered if they were significant when age and follow-up period were included, provided that the number of missing values was less than 20. Serum potassium (Table V) was the variable with the highest gradient of risk per 1 standard deviation (1.68). The corresponding gradients of risk for AST and MELD were 1.51 and 1.32, respectively.

The multivariable model resulted in the construction of a linear risk variable: 0.7717*(serum potassium) + 0.5356 *(abdominal tenderness) + 0.0961*(serum AST) – 0.3449*(alcohol use). The multivariable hazard function can be used for calculation of the probability of surviving, for example, for 1, 2, and 5 years. The gradient of risk for the linear combination of these four variables was 2.30. The effects of changes in age and in the four variables are exemplified in Table VI. Even if the prognosis of most patients is poor, we can see from this table that some patients have a less poor prognosis.

Discussion

The Swedish official population and patient registers offer an excellent tool in follow-up studies. We therefore think that our results should be representative and reliable.

The reason for the unexpectedly high 1-year mortality in our study, compared with most other studies [1], is probably that our patients had an advanced liver disease, which was apparent according to the baseline data. Furthermore, they were included irrespective of the time point when ascites first appeared. It must also be pointed out that our study was not restricted to patients awaiting OLT.

Our finding of a better prognosis in patients with current alcohol consumption could be explained by the fact that this is an external factor that could be, and therefore often is, eliminated or reduced, resulting in an improved outcome [12]. This interpretation does not contradict our finding of the poorest liver function in the group of current drinking patients, and alcohol should thus not be regarded as a preventive factor. Alcohol as underlying cause of the liver disease, on the other hand, is reported to have no influence on the prognosis for patients awaiting OLT, probably because a ceased alcohol intake is already a prerequisite for OLT [3]. As a consequence, cause of liver disease was omitted in the revision of the original MELD score calculation [13].

The role of abdominal tenderness for a shortened survival is not easily understood, especially regarding the probable changeability of this physical sign, and we cannot explain why OLT was more commonly performed in patients without this sign. One reason for a worsened prognosis in patients with this sign could be a fast developing liver disease with a concomitant fast ascites formation and an associated abdominal tenderness, but this hypothesis could

Table V. Variables from the multivariable analyses; hazard ratio (HR) and confidence interval (CI). * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$.

	Beta value	HR	CI	*p*-value
S-K	0.7717	2.16	1.56–2.99	0.0000***
Abdominal tenderness	0.5356	1.71	1.16–2.52	0.0071**
Alcohol use	–0.3449	0.71	0.56–0.89	0.0037**
S-AST	0.0961	1.10	1.05–1.16	0.0001***

Besides the variables above, the hazard function includes a constant and four variables, which are functions of updated time since start of follow-up and of age.

Table VI. The hazard function mentioned in the text could be used for the calculation of the 1-, 2-, and 5-year survival; see examples below. Thus it is possible to apply the results to present a risk engine in this area.

					Probability of surviving		
Age	Abdominal tenderness	S-K	S-AST	Alcohol use (see text)	1 year	2 years	5 years
73.62	0	3.7	1.3	1	0.496	0.382	0.218
70.70	0	4.1	0.98	1	0.384	0.269	0.125
61.80	0	4.0	4.1	1	0.326	0.209	0.073
56.92	1	4.5	1.56	0	0.084	0.031	0.003
59.27	0	2.9	1.78	2	0.785	0.714	0.566
51.69	0	4.5	1.72	1	0.442	0.320	0.147
44.42	0	3.3	5.1	2	0.799	0.730	0.589
46.28	0	4.4	1.4	0	0.449	0.326	0.152
46.01	0	5.8	1.2	1	0.198	0.104	0.022
41.65	0	2.6	1.5	1	0.891	0.852	0.763

not be tested due to lack of relevant data. Because an ultrasound was not regularly performed it was not possible to exclude a possible portal thrombosis as cause of the tenderness. We have previously shown an association between abdominal tenderness and SBP [7], which is known to have a poor outcome, but in this prolonged study former or present SBP was not related to the long-term prognosis. Thus, the reason for a shortened survival in patients with abdominal tenderness seems obscure. However, in this study this sign did not discriminate well enough as a predictor. We therefore think that the finding of abdominal tenderness, although important, should not be used alone as a prognostic tool.

In the surveillance of patients with liver cirrhosis, especially when an OLT must be considered, it is important to have reliable prognostic tools. Child and Turcotte introduced a scoring system for patients with esophageal varices [14]. One of the five components, nutritional state, was later changed to the prothrombin value by Pugh et al. in 1973 [15]. Since then the CTP score has been used in several studies and is still considered useful. For more than one decade prothrombin has been measured as a ratio, "international normalized ratio" (INR), but without any clear declaration how the limits used correspond to the limits used by Pugh et al. This could at least partly explain the lack of correlation in the present study. Furthermore, because the presence of ascites is one of the components in the CTP score it may be inappropriate to use this sign in a study of patients where this finding is obligatory for inclusion. Another problem connected with the use of the CTP score is its instability. Elimination of ascites due to diuretics as well as successful treatment of hepatic encephalopathy could reduce the CTP score with at least one point [8]. A reduced INR due to therapeutic efforts against the cause of the liver disease, for example alcohol abstention, may also lead to a reduced CTP score.

An attempt to find a better prognostic instrument for patients on the transplantation list resulted in the development of the MELD score, in which the prothrombin value also plays an important role. However, the widespread use of the INR for describing liver function could be questioned, because the INR correction factor "international sensitivity index" (ISI) is generally developed for warfarin-treated patients and not for patients with liver diseases [16,17]. Thus, when using INR it is important to know if it is consistent for liver patients. The problems connected with INR calculation and limits may at least partly explain the lack of a correlation between INR and prognosis, found in our study.

Because progress to hepatorenal syndrome is associated with a high mortality and kidney function is important in the development of ascites, it seems reasonable to study the relation between kidney function and prognosis. However, the CTP scoring model does not include variables indicating a disturbed renal function. Giannini et al. found that the inclusion of serum creatinine in the CTP score did not improve the scoring efficacy [18], but conversely Papatheodoridis et al. reported that a creatinine-modified Child-Pugh score was better than CTP and comparable to MELD score and therefore useful in daily clinical practice [19]. MELD score, on the other hand, includes renal function measured as serum creatinine, which was also found to be an essential component in calculating the prognostic index, as described by the Barcelona group [6]. However, this laboratory test has several disadvantages as a measure of kidney function. Although values within the reference range are generally considered normal, this reference range may not be valid for patients with liver cirrhosis, and hence these disadvantages may also apply to its use as a measure in cirrhotic patients with values within the reference range [20]. This can explain our finding that the prognosis did not show

the same good correlation with serum creatinine as with serum urea, which in some ways better reflects renal function. However, it must be pointed out that serum urea may be as good as serum potassium as a prognostic predictor or even better, but this analysis was unexpectedly not used as a routine laboratory test. It must also be mentioned that serum creatinine and serum urea, as well as serum potassium, are surrogate markers of the renal function.

Due to ADH-linked water retention patients with ascites generally have a dilutional hyponatremia, although they also have sodium retention. This has led to the hypothesis that hyponatremia is another sign of poor prognosis; evidence for this was demonstrated by Biggins et al., who investigated patients with serum sodium < 126 mmol/L [21], but our study showed no significant correlation between low serum sodium and a poor prognosis. Recent studies, however, indicate that serum sodium should be included in the MELD score among patients awaiting OLT [22,23].

The main reason for our finding of a strong relation between serum potassium and prognosis, which to our knowledge has not been described earlier, is probably related to the severity of the disease and the need for therapeutic drugs, which in cases with a threatened renal function may result in hyperkalemia. This is in line with our finding of a relation between serum potassium and creatinine as well as urea values, but it seems unlikely that the poor outcome was a treatment effect, because use of drugs with risk of hyperkalemia did not relate to the prognosis. Thus, we propose that the appearance of hyperkalemia indicates a worsened prognosis in cirrhotic patients with ascites reflecting an endangered renal function. Furthermore, serum potassium seems to be the routine test that would suit as a proper surrogate marker of a renal dysfunction in cirrhotic patients with an acute ascites episode, because this test showed a stronger relation to prognosis than serum creatinine.

In conclusion, our study indicates that appearance of hyperkalemia in a cirrhotic patient with ascites is a finding that must be considered seriously and would be a useful factor to include in prognostic models. To further interpret the unexpectedly strong relation between S-K values and prognosis, it would be of interest to analyze data in patient groups separated according to S-K values before, and at various time points after start of diuretic therapy, indicating need for additional studies.

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References

[1] D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. J Hepatol 2006;44:217–31.

[2] Albers I, Hartmann H, Bircher J, Creutzfeldt W. Superiority of the Child-Pugh classification to quantitative liver function tests for assessing prognosis of liver cirrhosis. Scand J Gastroenterol 1989;24:269–76.

[3] Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Thernau TM, Kosberg CL, et al. A model to predict survival in patients with end-stage liver disease. Hepatology 2001;33: 464–70.

[4] Attia KA, Ackoundou-N´guessan KC, N'dri-yoman AT, Mahassadi AK, Messou E, Bathaix YF, et al. Child-Pugh-Turcotte versus Meld score for predicting survival in a retrospective cohort of black African cirrhotic patients. World J Gastroenterol 2008;14:286–91.

[5] Gotthardt D, Weiss KH, Baumgärtner M, Bruckner T, Sauer P. Limitations of the MELD score in predicting mortality or need for removal from waiting list in patients awaiting liver transplantation. BMC Gastroenterol 2009;9:72.

[6] Fernández-Esparrach G, Sánchez-Fueyo A, Ginès P, Uriz J, Quintó L, Ventura PJ, et al. A prognostic model for predicting survival in cirrhosis with ascites. J Hepatol 2001;34: 46–52.

[7] Wallerstedt S, Olsson R, Simrén M, Broomé U, Wahlin S, Lööf L, et al. Abdominal tenderness in ascites patients indicates spontaneous bacterial peritonitis. Eur J Intern Med 2007;18:44–7.

[8] Sherlock S, Dooley J. Diseases of the liver and biliary system. 11th ed. Oxford, UK: Blackwell Science; 2002. p 658.

[9] Rimola A, Garcia-Tsao G, Navasa M, Piddock LJV, Planas R, Bernard B, et al. Diagnosis, treatment and prophylaxis of spontaneous bacterial peritonitis: a consensus document. J Hepatol 2000;32:142–53.

[10] Wiesner R, Edwards E, Freeman R, Harper A, Kim R, Kamath P, et al. Model for end-stage liver disease (MELD) and allocation of donor livers. Gastroenterology 2003;124:91–6.

[11] Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. BMJ 1996;312:1254–9.

[12] D'Amico G, Morabito A, Pagliaro L, Marubini E. Survival and prognostic indicators in compensated and decompensated cirrhosis. Dig Dis Sci 1986;31:468–75.

[13] Cholongitas E, Marelli L, Shusang V, Senzolo M, Rolles K, Patch D, et al. A systematic review of the performance of the model for end-stage liver disease (MELD) in the setting of liver transplantation. Liver Transpl 2006;12:1049–61.

[14] Child CG, Turcotte JG. Surgery and portal hypertension. In Child CG, editor. The liver and portal hypertension. Philadelphia: WB Saunders Co; 1964. pp 50–8.

[15] Pugh RNH, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973;60:646–9.

[16] Tripodi A, Chantarangkul V, Primignani M, Fabris F, DellEra A, Sei C, et al. The international normalized ratio calibrated for cirrhosis (INR(liver)) normalizes prothrombin time results for model for end-stage liver disease calculation. Hepatology 2007;46:520–7.

[17] Bellest L, Eschwège V, Poupon R, Chazouillières O, Robert A. A modified international normalized ratio as an effective way of prothrombin time standardization in hepatology. Hepatology 2007;46:528–34.

[18] Giannini E, Botta E, Fumagalli A, Malfatti F, Testa E, Chiarbonello B, et al. Can inclusion of serum creatinine values improve the Child-Turcotte-Pugh score and challenge the prognostic yield of the model for end-stage liver disease score in the short-term prognostic assessment of cirrhotic patients? Liver Int 2004;24:465–70.

[19] Papatheodoridis GV, Cholongitas E, Dimitriadou E, Touloumi G, Sevastianos V, Archimandritris AJ. MELD vs Child-Pugh and creatinine-modified Child Pugh score for predicting survival in patients with decompensated cirrhosis. World J Gastroenterol 2005;11:3099–104.

[20] Francoz C, Glotz D, Moreau R, Durand F. The evaluation of renal function and disease in patients with cirrhois. J Hepatol 2010;52:605–13.

[21] Biggins SW, Rodriguez HJ, Bacchetti P, Bass NM, Roberts JP, Terrault NA. Serum sodium predicts mortality in patients listed for liver transplantation. Hepatology 2005; 41:32–9.

[22] Londoño MC, Cárdenas A, Guevara M, Quintó L, de Las Heras D, Navasa M, et al. MELD score and serum sodium in the prediction of survival of patients with cirrhosis awaiting liver transplantation. Gut 2007;56:1283–90.

[23] Leise MD, Kim WR, Kremers WK, Larsson JJ, Benson JT, Thernau TM. A revised model for end-stage liver disease optimizes prediction of mortality among patients awaiting liver transplantation. Gastroenterology 2011;140: 1952–60.