Published online: 31/01/2016 Published print: 02/2016

ORIGINAL PAPER

doi: 10.5455/medarh.2016.70.48-52
Med Arch. 2016 Feb; 70(1): 48-52
Received: November 25th 2015 | Accepted: January 05th 2016

Prognostic Significance of Ascites and Serum Sodium in Patients with Low Meld Scores

Dzanela Prohic, Rusmir Mesihovic, Nenad Vanis, Amra Puhalovic

Department of Gastroenterohepatology, University Clinical Center Sarajevo, Bosnia and Herzegovina

Corresponding author: Dzanela Prohic, MD. Department of Gastroenterology, University Clinical Center Sarajevo Bosnia and Herzegovina. Bolnicka 25, 71000 Sarajevo, Bosnia and Herzegovina. Tlf:+387 33 297 246, Fax:+387 33 297 246. ORCID ID: http://orcid.org/0000-0002-8922-9041. E mail: dzanelaprohic@hotmail.com

ABSTRACT

Objective: to determine ascites and serum sodium significance in short term mortality prediction in patients with advanced liver cirrhosis. **Methods:** a cohort of 115 cirrhotic patients referred to our Department were followed up for 6 months in non-transplant settings. The c index equivalent to the area under the receiver operating curve (ROC) was calculated and compared to estimate the short-term prognostic accuracy of the following parameters: ascites, serum sodium and MELD score. **Results:** in patients with a MELD score less than 21, ascites and low serum sodium (c index 0,687, p<0 0,001 and 0,748, p<0,001 respectively) showed better prognostic accuracy and were independent predictors of mortality. For MELD scores above 21, only MELD was an independent mortality prognostic factor (c index 0,710, p<0,001). **Conclusion:** in our study, sample ascites and low serum sodium help identify patients with advanced liver disease who are at high risk of mortality despite low MELD scores. These parameters should be considered as additional prognostic parameters that could improve available treatment options and outcomes in this group of patients.
Key words: cirrhosis, ascites, serum sodium MELD, mortality.

1. INTRODUCTION

Ascites is the most common complication of cirrhosis, which is the most common cause of ascites, accounting for approximately 85 percent of cases (1). Within 10 years after a diagnosis of compensated cirrhosis, approximately 58 percent of patients will have developed ascites (2).

It is associated with 50% mortality at 5 years if patients do not receive a liver transplant (3, 4). The occurrence of hyponatremia in these patients determines a 25% probability of survival at 1 year (5-7).

Despite the many advantages of the MELD score, there are approximately 15%-20% of patients whose survival cannot be accurately predicted by the MELD score (8).

Factors that have proven to be most reliable in predicting a poor prognosis include hyponatremia, low arterial pressure, low urine sodium and increased serum creatinine as an objective marker for development of hepatorenal syndrome (9-12). These parameters are not included in the CTP score and only serum creatinine is included in the MELD score. Given that in many countries allocation for liver transplantation is based on the MELD score, patients with ascites may not receive an adequate priority position on the transplant lists. This indicates a need for improved methods to assess prognosis in patients with ascites. Several groups have identified ascites and serum sodium (Na) as an important and independent predictor of short term mortality. Despite adjustment for MELD, this indicator provides additional information about the risk of poor outcomes, particularly in patients with low MELD scores (13-15).

In the course of our research study, we performed a retrospective analysis of data collected from patients referred to our Department with liver cirrhosis and signs of decompensation and ascites. The aim was to determine whether ascites and serum sodium can provide ad-

ditional information about the mortality risk in patients with cirrhosis in non-transplant settings. Our hypothesis was that the MELD score, ascites and serum sodium have different prognostic significance in patients with low MELD scores of below 21 compared to patients with MELD scores above 21.

2. PATIENTS AND METHODS

1.1. Study population

One hundred and fifteen patients were evaluated in our Department for liver cirrhosis between 2009 and 2011 and had follow-up for 6 months.

According to our routine clinical practice, a detailed medical history was taken, the patients underwent a complete physical examination and a range of laboratory tests were performed for all patients on the day of admission. The diagnosis of decompensated cirrhosis was confirmed by biopsy or was based on clinical, laboratory, and radiological findings of cirrhosis with at least one sign of decompensation such as ascites, varices, hepatic encephalopathy. Study subjects were excluded in cases of insufficient data, if a diagnosis of cirrhosis was suspect or absent, if the patients exhibited signs of severe sepsis or hepatocellular carcinoma.

The underlying etiology of cirrhosis was attributed to hepatitis B virus infection for patients that tested seropositive for the hepatitis B surface antigen (HbsAg) for more than six months, and it was attributed to hepatitis C virus (HCV) infection for patients that tested seropositive in both qualitative and quantitative tests. Alcohol abuse was identified as the underlying cause for patients with a history of alcoholism, and a combination of alcohol abuse and serological positivity for other causes of liver injury such as hepatitis B or C were also identified. Other factors included in the analysis were age, sex, clinical complications of liver disease (severity of ascites) assessed semiquantitatively using the standard ordinal scale of the CTP score and biochemical data (serum creatinine, serum sodium, bilirubin, INR, albumin). Refractory ascites was defined as ascites that required paracentesis for control despite diuretic therapy and sodium restriction, which is consistent with the consensus statement (1). The study outcome was aimed at predicting six-month mortality.

The study complies with the standards of the Helsinki Declaration and current ethical guidelines.

1.2. Statistical analysis

All data was analyzed using the statistical program SPSS 17 (Chicago Inc., IL). Results were expressed as mean values (SD) or as median values (range). The accuracy of the different parameters (MELD, ascites and serum sodium) as predictors of mortality in the follow-up period was evaluated through concordance c statistics (evaluated by measuring the area under the receiver operating characteristic (ROC) curve). These statistics may vary from 0-1, with 1 indicating perfect discrimination, and 0.5 indicating A $p< 0.05$ was considered statistically significant. The interrelation between relative differences of the observed parameters was cross-tabulated into different subgroups of patients according to their MELD scores in order to compare the prognostic accuracy of the parameters in the different subgroups of patients.

3. RESULTS

The main demographic, clinical quantitative parameters and biochemical features of the study cohort are shown in Table 1. Age at the time of referral averaged 57,93 + 11,46 (mean+SD, range 28-74). The majority of patients were male 73 (63,5%). Hepatitis B was present in 33%, alcohol abuse in 28,7% and Hepatitis C in 14,8% of patients. Other etiologies (autoimmune, cholestatic liver disease) were found for 20% of the patients.

Cirrhosis at the time of referral was relatively advanced, with the mean CTP score being 8,72+2,14 (mean+ SD, range 5-14). CTP class B accounted for 56% of the patients, 33% were categorized as CTP class C and 18,3 % with CTP class A. At the end of the six month follow-up period, 40 (34,8%) patients had died.

We performed calculations based on previously published formulas for the MELD score (6), MELD = 3,78 log (bilirubin (mg/dl) + 1,12log(INR) + 9,57 log (creatinine(mg/dl))+6,43. The MELD values ranged between 6-34, with mean MELD at 15,76 +5,46 (mean+SD).

Serum sodium values for patients from the study cohort ranged between 115-145 μmol/L, with the mean serum sodium value of 137 μmol/L + 4,88 (mean+ SD). Hyponatremia (S-Na< 130 μmol/L) was identified in 9 patients from the study sample, and 8 of them had refractory ascites.

The prognostic reliability of the MELD score, ascites and Na in relation to patient survival rate was analyzed for the observed sample, first for the entire sample and using ROC analysis and c-statistics (Table 2, Figure1 and Figure 2).

In a comparative analysis, the MELD, ascites and serum sodium parameters were found to be significantly associated with mortality within the six month period.

Sensitivity and specificity indicators for MELD, ascites i S-Na for the entire sample are shown by measuring area under the curve (ROC curve) and c statistics in Table 2.

Among patients with MELD scores below 21, the mortality rate at 6 months was 24,7%, while in the group with MELD scores above 21, the mortality rate at 6 months was 77,3%. Comparing the attained relative differences, we found that variability between subcategories is higher in the subgroup of patients with MELD scores above 21, which indicates a stronger predictive accuracy of the MELD score for that subgroup (Figure 1 and Figure 2).

The effects of persistent ascites and low serum sodium on six-month mortality are shown in Figure 3. Diuretic resistant ascites was present in 42,9% of lethal outcomes in the group of patients who died with MELD scores less than 21, and in 88,9% of lethal outcomes in the group of patients who died with MELD scores above 21. Comparing the attained relative differences, we concluded that variability between subcategories is higher in the subgroup of patients with MELD scores less than 21 (25,48% and 19,3% for respective groups) indicating a stronger prognostic accuracy of ascites for MELD <21 subgroup of patients.

Characteristics	n (% of patients)	Mean (standard deviation)
Age (years)		57.93 (11.46)
Sex		
male	73 (63.5%)	
female	42 (36.5%)	
Aetiology		
alcohol	33 (28.7%)	
hepatitis B	38 (33%)	
hepatitis C	17 (14,8%)	
alcohol and hepatitis B or C	4 (3,5%)	
other causes (autoimmune, cardial)	23 (20%)	
Ascites		
grade 1 none or mild ascites	44 (38.7%)	
grade 2 medically treated ascites,	34 (29.6%)	
grade 3 refractory ascites	37 (32.2%)	
Childe Pugh score		
A	21 (18.3%)	
B	56 (48.7%)	
C	38 (33%)	
Mortality rate		
survived	75 (65.2%)	
death	40 (34.8%)	
Quantitative characteristics		
S-creatinin (μmol/L)		113.11 (92.35)
S-Na (μmol/L)		137.44 (4.88)
S-bilirubin (μmol/L)		53.06 (47.14)
INR		1.475 (0.35)
S-albumin (g/L)		29.54 (6.08)
Child Pugh score		8.72 (2.14)
MELD score		15.76 (5.46)

Table 1. Baseline patients demographic and quantitiative characteristiscs

Normal serum sodium was present in 15,3% of patients with a MELD score less than 21 and who died after 6 months, while 57,1% of the patients in the same group who died had serum sodium <136. In the high MELD score group of patients, serum sodium levels below 136 μmol/L were associated with six-month mortality of 75% compared to 80% among patients without hyponatremia.

The mortality rate in the high MELD score group was 77,3%, while the relative deviation for patients in the subgroup with serum sodium below 135 μmol/L and without hyponatremia was 5,9%. Comparing the achieved relative differences, we can conclude that the variability or difference between subgroups is higher in the subgroup of patients with MELD scores less than 21(40,98% and 5.9% for respective groups), meaning that serum sodium had better prognostic accuracy in MELD <21 subgroup of patients.

The predictive value of ascites and serum sodium in the group of patients with MELD scores less than 21 showed better prognostic accuracy (ascites c index 0,687, p=0,002, serum sodium c index 0,748 p=0,000) as compared to the MELD score alone.

This was not the case for the high MELD score patients where the MELD score showed a significantly prognostic yield as compared with ascites and serum sodium (MELD c index 0,710, p= 0,003).

	Area under the reciver operating characteristic (ROC) curve c statistic	p-value
All		
MELD	0.792	0.000
ascites	0.705	0.000
S-Na	0.691	0.001
MELD <21		
MELD	0.488	0.938
ascites	0.687	0.002
S-Na	0.748	0.000
MELD ≥ 21		
MELD	0.710	0.003
ascites	0.605	0.076
S-Na	0.388	0.457

Table 2. Sensitivity and specificity of parameters MELD, ascites and S- Na as predictors of 6 months mortality, according to different MELD subgroup. MELD Model for end stage liver disease

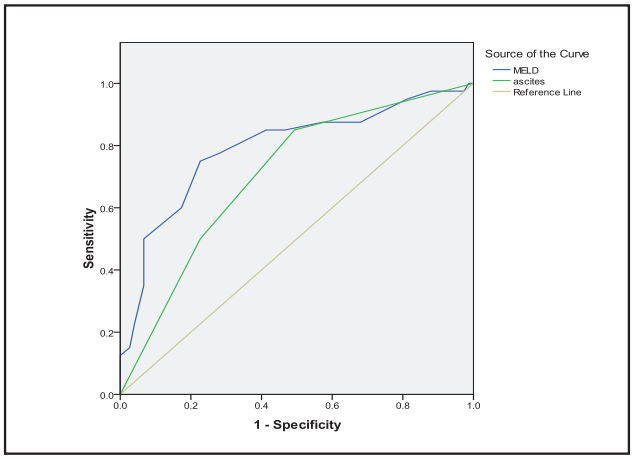

Figure 1. Reciver operating curve (ROC) for parameters MELD and ascites, as predictors of 6 months mortality

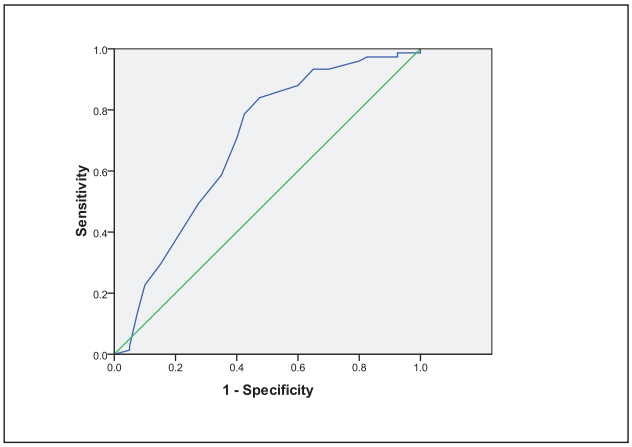

Figure 2. Reciver operating curve (ROC) for parameter S-Na as predictor of 6 months mortality

4. DISCUSSION

The course and outcome of chronic liver disease may be difficult to predict. Many factors need to be considered: the diagnosis, the stage, the disease activity and the occurrence of decompensation and complications. Hyponatremia is commonly associated with ascites, hepatorenal syndrome and a marker for increased mortality

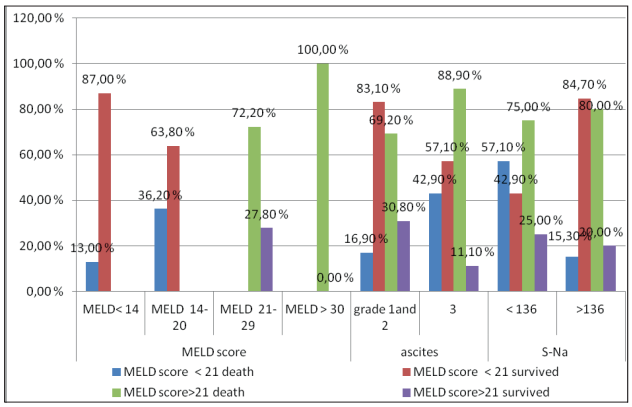

Figure 3. Cross tabulation figure of different subcategories of S-Na, MELD and ascites according to different MELD groups, MELD <21 and MELD>21

among candidates for LT (13, 14). Ascites has historically been incorporated into prognostic models for patients with advanced liver disease but its value in the MELD era is strongly debated (10). Although the mortality rate increases with higher MELD scores, studies have shown that early mortality often still happens in patients with an initial low MELD score (16, 17). We need better markers of mortality in patients with cirrhotic circulatory dysfunction and low MELD scores to identify patients who are at high risk of death (18, 19).

In our study population of patients with decompensated liver cirrhosis, we estimated the prognostic yield of ascites and low serum sodium among patients with MELD scores below 21 and MELD scores above 21.

Our patient sample was small, particularly in terms of analyzing the structure in relation to one or more aspects; inference based on chi-square was therefore not appropriate. This is the reason why conclusions were made based on descriptive indicators, with no intention to generalize. In other words, the results presented describe the situation at the level of the sample, and no generalization can be considered reliable.

The analysis we performed in our study population showed that low serum sodium and refractory ascites are good markers of early mortality, and especially important for patients with MELD scores less than 21. Comparing the attained relative differences for patients in mortality, subgroups MELD <21 and MELD ≥ 21 we concluded that variability among subgroups of patients higher in category MELD <21 (25,4% and 40,9% for ascites and S-Na respectively) comparing with subgroup MELD >21 (19,3 and 5,9% for ascites and S-Na respectively).

In this sample of patients with advanced liver disease, MELD scores above 21 had more significance for the prognosis estimation of mortality (c index =0,710, p=0,001), while ascites and serum sodium had significantly better prognostic relevance (c index =0,687 p=0,002 and c index =0,748 p=0,000 respectively) for patients with MELD scores less than 21.

There are several other studies that have supported the independent effect of ascites and water retention on disease severity and mortality (16, 20, 21). Heuman et al. determined that persistent ascites was an independent predictor of mortality, specifically, ascites and low serum sodium, and not MELD, were the important prognostic factors when the MELD score was less than 21 (22). Samosuk et al. showed in a study of 100 patients, that for cirrhotic patients, moderate ascites determined by CT scan, provides additional mortality risk prediction beyond MELD (16) and in other study that moderate ascites informs mortality risk prediction in cirrhotic patients beyond MELD and MELDNa (17).

Our findings as mentioned earlier, are subject to some limitations. The size of the study cohort is small and the number of outcomes within the six-month period limits closer validation of the impact ascites and hyponatremia have on early mortality.

The presence of ascites and serum sodium concentration are important variables associated with decreased patient survival and are manifestations of advanced hemodynamic derangement in patients with cirrhosis who have high risk of progressing to type I hepatorenal (23-25). However, they are relatively crude parameters of this underlying circulatory derangement. Concerns about the objectivity of quantifying ascites, as well as the influence of the caliber of diuretic treatment on the severity of both ascites and hyponatremia, coupled with interobserver variability, has excluded these parameters from being incorporated into models for organ allocation.

Secondly, the fact that most patients with ascites receive diuretics. The measured serum sodium concentration under these circumstances does not reflect the true status of liver function. Kim et al. showed in their study that serum sodium only <125 mEq/L statistically influence on short term mortality (19). In addition severe hyponatremia did not occur often. Clinically, the increased risk associated with moderate ascites can inform and influence clinical decisions in cases of patients with low MELD scores who are at risk of early death and can benefit from extended criteria for transplant list eligibility and more aggressive monitoring. Even though ascites is a subjective parameter its significance cannot be overlooked which was recognized and addressed in previous scores. Low serum sodium values are usually present in patients with advanced liver disease and refractory ascites given their increased risk of death when possibility of a liver transplantation is excluded this patients can benefit from extended criteria for transplantation.

5. CONCLUSION

Ascites and low serum sodium are important independent predictors of short-term morality in patients with advanced liver disease, especially in the groups of patients with low MELD scores. The results of our study suggest that ascites and serum sodium showed good predictability for 6 month mortality in patients with cirrhosis and low MELD scores. This suggests that incorporating ascites and serum sodium values gives us additional information about the mortality risk for these patients and should be used to inform clinical decisions to improve the selection process of patients for donor liver grafts, which would then also improve the available treatments options.

- **Author's contribution:** Dzanela Prohic, first author, worked on all the phases of production of this paper (concept, design, research, drafting etc.), including the final editing and proofreading. Rusmir Mesihovic contributed substantially to the concept and design of the study, including drafting and critical revision of the scientific content. Nenad Vanis provided a major contribution to the detailed design of the study, including research phases and data processing. Amra Puhalovic contributed to data collection and processing.
- **Conflict of interest: none declared.**
- **Funding:** No specific funding was received for this study.

REFERENCES

1. Runyon BA, AASLD. Introduction to the revised American Association for the Study of Liver Diseases Practice Guideline management of adult patients with ascites due to cirrhosis 2012. Hepatology. 2013; 57: 1651.
2. Asrani SK, Kamath PS, Natural history of cirrhosis. Curr Gastroenterol Rep. 2013 Feb; 15(2): 308.
3. Planas R, Montoliu S, Balleste B, Rivera M, Miquel M, Masnou H. et al. Natural history of patients hospitalized for management of cirrhotic ascites. Clin Gastroenterol Hepatol. 2006; 4: 1385-94.
4. Ginès P, Cárdenas A. The management of ascites and hyponatremia in cirrhosis. Semin Liver Dis. 2008; 28(1): 43-58.
5. Yu C, Sharma N, Saab S, Hyponatremia: clinical associations, prognosis, and treatment in cirrhosis. Exp Clin Transplant. 2013 Feb; 11(1): 3-11.
6. Kim WR, Biggins SW, Kremers WK, et al. Hyponatremia and mortality among patients on the liver-transplant waiting list. N Engl J Med. 2008; 359(10): 1018-26.
7. Moini M, Hoseini-Asl MK, Taghavi SA, et al. Hyponatremia a valuable predictor of early mortality in patients with cirrhosis listed for liver transplantation. Clin Transplant. 2011; 25(4): 638-45.
8. Kamath PS, Kim Wr,The model for end-stage liver disease (MELD). Hepatology. 2007 Mar; 45(3): 797-805.
9. Serste T, Gustot T, Rautou PE, Francoz C, Njimi H, Durand F, et al. Severe hyponatremia is a better predictor of mortality than MELDNa in patients with cirrhosis and refractory ascites. J Hepatol. 2012; 57: 274-80.
10. Pugliese R, Fonseca EA, Porta G, Danesi V, Guimaraes T, Porta A, Miura IK, Borges C, Candido H, Benavides M, Feier FH, Godoy A, Cardoso RA, Kondo M, Chapchap P, Neto JS. Ascites and serum sodium are markers of increased waiting list mortality in children with chronic liver failure. Hepatology. 2014 May; 59(5): 1964-71.
11. Cholongitas E, Burroughs AK, The evolution in the prioritization for liver transplantation. Ann Gastroenterol. 2012; 25(1): 6-13.
12. Guevara M, Cárdenas A, Uriz J, Ginès P. Prognosis in patients with cirrhosis and ascites. In: Ginès P, Arroyo V, Rodés J, Schrier RW, editors. Ascites and renal dysfunction in liver disease: pathogenesis, diagnosis and treatment. Malden: Blackwell; 2005: 260-70.
13. 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(1): 32-9.
14. Kim WR, Biggins SW, Kremers WK, Wiesner RH, Kamath PS, Benson JT, et al. Hyponatremia and mortality among patients on the liver-transplant waiting list. N Engl J Med. 2008; 359(10): 1018-26.
15. Biggins SW, Kim WR, Terrault NA, Saab S, Balan V, Schiano T, et al. Evidence-based incorporation of serum sodium concentration into MELD. Gastroenterology. 2006; 130(6): 1652-60.
16. Somsouk M, Guy J, Biggins SW, Vittinghoff E, Kohn MA, Indaomi JM, Ascites improves upon serum sodium and MELD for predicting mortality in patients with advanced liver disease, Aliment Pharmacol Ther. 2009 Oct; 30(7): 741-8.
17. Somsouk MA, Kornfield R, Vittinghoff E, Inadomi JM, Biggins SW, Moderate ascites identifies patients with low MELD awaiting liver transplantation with high mortality risk Liver Transpl. 2011 Feb; 17(2): 129-36.
18. Klein KB, Stafinski TD, Menon D., Predicting survival after liver transplantation based on pre-transplant MELD score: a systematic review of the literature. PLoS One. 2013 Dec; 12; 8(12).
19. Kim JJ, Kim JH, Koo JK, Choi YJ, Ko SY, Choe WH, Kwon SY. The refit model for end-stage liver disease-Na is not a better predictor of mortality than the refit model for end-stage liver disease in patients with cirrhosis and ascites. Clin Mol Hepatol. 2014 Mar; 20(1): 47-55.
20. Xirouchakis E, Marelli L, Cholongitas E, et al. Comparison of cystatin C and creatinine based glomerular filtration rate formulae with 51Cr-EDTA clearance in patients with cirrhosis. Clin J Am Soc Nephrol. 2010; 6: 84-92.
21. Cholongitas E, Germani G, Tsochatzis E, et al. Towards a better liver allocation system. J Hepatol. 2009; 51: 827-8.
22. Heuman DM, Abou-Assi SG, Habib A, Williams LM, Stravitz RT, Sanyal AJ, Fisher RA, Mihas AA. Persistent ascites and low serum sodium identify patients with cirrhosis and low MELD scores who are at high risk for early death. Hepatology. 2004; 40: 802-10.
23. Rössle M, Gerbes AL. TIPS for the treatment of refractory ascites, hepatorenal syndrome and hepatic hydrothorax: a critical update. Gut. 2010; 59: 988.
24. Alessandria C, Ozdogan O, Guevara M, et al. MELD score and clini¬cal type predict prognosis in hepatorenal syndrome: relevance to liver transplantation. Hepatology. 2005; 41: 1282.
25. Arroyo V, Fernandez J. Management of hepatorenal syndrome in patients with cirrhosis. Nat Rev Nephrol. 2011 Aug 9; 7(9): 517-26.