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Comparison of Prognostic Value of Predictors of Mortality in Patients with Cirrhosis and Refractory Ascites

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ABSTRACT

The Model for End-Stage Liver Disease-Sodium score (MELDNa) has been developed that has a better prognostic value to predict early mortality but has not been frequently used in cirrhotic and refractory ascites patients with recurrent incidences of severe hyponatremia. **Objective:** To compare the prognostic value of severe hyponatremia, Child-Pugh score, and the model for end-stage liver disease-sodium score in cirrhotic and refractory ascitic patients. **Methods:** A prospective, observational study was conducted at the Hepatology Department, Bakhtawar Amin Trust Hospital, Multan from March 2023 to March 2024. A total of 200 patients with cirrhosis and refractory ascites undergoing albumin paracentesis twice a month were selected for the study. The 135 patients (after exclusion of preexisting ascites patients) were administered diuretics symmetrically; 50 mg spironolactone and 40 mg furosemide in patients who did not have renal failure and severe hyponatremia. Prognostic scores were recorded and patients were followed up for minimum 3 months. **Results:** The area under the curve of the Child-Pugh score (0.90, 95% CI: 0.87-0.96) was significantly higher than the MELD score (0.60, 95 CI: 0.51-0.70) and MELDNa (0.75, 95% CI: 0.65-0.79) as a predictor of mortality (p<0.0001). With respect to the etiology of refractory ascites being an independent risk factor of mortality, the cumulative incidence function was highest in patients with hyponatremia (79%; 95% CI: 79-80%) followed by renal failure patients (55%; 95 CI: 54-56%) and patients receiving maximum dose of treatment (28%; 95% CI: 27-29%) (p<0.001). **Conclusions:** Severe hyponatremia, ineffective diuretic treatment, and Child-Pugh score were risk factors of death in cirrhotic and refractory ascitic patients.

INTRODUCTION

Cirrhotic patients often suffer serious complications including ascites. This condition is commonly managed by diuretics and sodium restriction [1]. Resistance to the diuretic medication or unchanged status after diuretic treatment can be regarded as refractory ascites. Refractory ascites can only be treated definitively by a liver transplant [2]. Several tools called predictors of mortality are used to predict the patient prognosis and outcomes of patients with liver diseases. Model for End-Stage Liver Disease (MELD) score is used to diagnose end-stage liver disease and predict its prognosis and 3-month survival. United Network for Organ Sharing had adopted it to test donor livers due to its objectivity and ability to predict risk of mortality. Child-Pugh score is also a prognostic tool for liver cirrhosis patients based upon ascites, hepatic encephalopathy, International Normalized Ratio, albumin and total bilirubin levels. Some studies have argued that MELD is a better predictor of mortality while some report comparable prognostic accuracy of both [3, 4]. Patients are referred for liver transplants by assessing them by end-stage liver disease score only. However, the MELD score cannot accurately assess the risk of mortality in cirrhotic and refractory ascitic patients [5]. Studies have shown that transplant patients with MELD scores less than 20

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were at high risk of mortality and were independently associated with the incidence of hyponatremia and refractory ascites [6, 7]. An improved version of the MELD score, the model for end-stage liver disease-sodium score has been developed that has a better prognostic value to predict early mortality [8]. The score assesses the severity of liver cirrhosis by using serum sodium values ranging from 125 mmol/L and 140 mmol/L. However, this score has not been frequently used in cirrhotic and refractory ascites patients with recurrent incidences of severe hyponatremia. It was conducted that the present study to evaluate the incidence and risk factors of low serum sodium in patients with cirrhosis and refractory ascites.

The aim of this study was to compare the prognostic value of severe hyponatremia, Child-Pugh score, and the model for end-stage liver disease-sodium score in cirrhotic and refractory ascitic patients.

METHODS

A prospective, observational study was conducted at the Medicine Department, Bakhtawar Amin Trust Hospital, Multan from March 2023 to March 2024. A total of 200 patients with cirrhosis and refractory ascites undergoing albumin paracentesis twice a month were selected for the study by consecutive sampling. The sample size was calculated by EpiInfo keeping 5% margin of error, 95% confidence interval and 50% population proportion. Patients who died during 1st month of the follow-up, who did not undergo a minimum of two large volume paracentesis, who had a transplant history, and patients with trans jugular intrahepatic portosystemic shunt were excluded. All patients provided their consent to become a part of the study. The ethical board of the hospital approved the study by Ref No.186/23.EC/BAM and DC. Refractory ascites patients were classified according to International Ascites Club, 30 patients had tense ascites and severe hyponatremia and 35 patients had renal failure without diuretics [9]. Patients were divided into classifications based on the etiology of refractory ascites; diuretic resistant ascites, diuretic intractable ascites caused by renal failure, and one caused by severe hyponatremia. These patients did not receive diuretic therapy. These patients were treated with 40 mg propranolol once a day. After excluding the refractory ascites patients, 135 patients were administered diuretics symmetrically; 50 mg spironolactone and 40 mg furosemide in patients who did not have renal failure and severe hyponatremia. These doses were increased per week by 50mg for spironolactone and 20mg for furosemide with a maximum dose administered of 400mg and 160 mg, respectively. A total of 62 patients were administered the maximum dosage of medication and were deemed to have diuretic-resistant ascites, 40 patients experienced severe hyponatremia when the dose was increased and were deemed to have diuretic intractable ascites by hyponatremia (cut-off sodium value during treatment: 125 mmol/L) and 33 patients had renal failure during treatment and were deemed to have diuretic intractable ascites by renal failure (cut-off serum creatinine: 1.5 mg/L). the effective dosage of medication in these patients was contraindicated so they were administered at low dosages while closely observing metabolic disturbances. A minimum 3-month follow-up was done (unless patients died before it) when the maximum dosage of medication started being ineffective or when limited diuretics were started. Transplant patients were followed up till transplant day and non-transplanted ones were follow up till last visit and survival data were noted. Sodium and creatinine values were measured by blood test when patients were divided into categories. Patients were divided into Group A (those with sodium level less than 130 mmol/L) and Group B (those with sodium levels more than 130 mmol/L). Patients' data including demographics, cause of cirrhosis (by lab tests, blood count, radiological assessment and hepatitis screening), prognostic scores (MELD, MELDNa, and Child-Pugh), physical exam were recorded at admission and information about biochemical test results, the incidence of diabetes, and treatment details (diuretics or betablockers) was extracted from patient records. MELD was measured by online Medscape calculator [10]. MELDNa was calculated by the formula used in Kim WR et al [11]. Child-Pugh score was calculated by MdCalc online calculator [12]. The frequency of large-volume paracenteses was recorded after satisfying the inclusion criteria. Patient outcomes i.e. transplant or mortality were recorded in 3-month follow-up. Cardiac output and cardiac index were measured by thermodilution and standard formula, respectively to check cardiac function. All the data were analyzed by SPSS version 24.0. Results of all patient groups were compared to assess predictors of low sodium by t-test or Wilcoxon Rank test in case of continuous data and by chi-squared or Fisher's test in case of categorical data. Binary logistic regression analysis was performed of these variables. The patients in whom the transplant was carried out and were discharged were at lower risk of mortality so transplantation defined the competing risk of death before discharge. The risk of mortality was defined by cumulative incidence competing risk estimate with transplant being the competing risk of the outcome. Gray's test was performed to assess cause-specific death (calculated by cumulative incidence function) differences. Univariate and multivariate analyses were performed to assess predictors of mortality by using the Fine-Gray hazards model. The area under the receiver operating characteristic curve was used to determine the prognostic value of predictors of mortality. A two-tailed p-value <5% was taken significant.

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RESULTS

Patients' characteristics were shown in table 1. With respect to the etiology of refractory ascites, 66 (33%) patients had renal failure, and 70 (35%) patients had severe hyponatremia. Seventy-six patients had low sodium levels. The average MELDNa score was 22 and 92 (46%) had a score below this median. Patients were followed up for a median duration of 9 months during which 135 (65%) patients died. 40 patients (20%) had a transplant with 54% (95% CI: 54-55%) cumulative incidence of death after one year and 66% (95% CI: 66-67%) after two years (Gray's test). Major causes of death were sepsis, hepatocellular carcinoma, and spontaneous bacterial peritonitis. Patients were categorized according to serum sodium levels which revealed that group B had a lower Child-Pugh score but higher albumin and protein levels. MELDNa scores were lower in high sodium patients with high creatinine levels (Table 1).

Table 1: Patient's Variables with Respect to Sodium Concentrations(n=200)

Variables	Group A Na <130 mmol / L N (%) / (Mean ± SD)	Group B Na >130 mmol / L N (%) / (Mean ± SD)	p-Value
Male	61 (80.3%)	98 (79.1%)	0.42
Age	61.8 ± 12.5	57.1 ± 12.4	0.27
Weight	79 (51-112)	75 (41-133)	0.89
Child-Pugh Class C	65 (85.6%)	69 (55.7%)	<0.001
MELD Score	18.8 ± 5.0	20.3 ± 5.3	0.070
MELDNa	26.9 ± 3.0	22 ± 4.5	<0.001
			0.30
Etiology of Cirrhosis			
Hepatitis C (by Hepatitis Screening)	40 (52.7%)	100 (80.7%)	-
Hepatitis B (by Hepatitis Screening)	36 (47.3%)	24 (19.3%)	-
Hepatocellular Carcionoma (Triphasic MSCT)	23 (30.3%)	36 (29.1%)	0.55
Hepatic Encephalopathy (Liver Function Test)	34 (44.8%)	41 (33.1%)	0.09
Diabetes (Patient Records)	19 (25%)	23 (18.6%)	0.25
INR (Blood Test)	2.0 (1.4-2.7)	1.9 (1.2-2.8)	0.09
Creatinine (Blood Test)	80 (50-250)	99 (43-319)	0.001
Sodium (Blood Test)	125 (115-130)	135 (129-147)	<0.001
Total Bilirubin (Blood Test)	65 (20-345)	49 (9-160)	0.28
Albumin (Blood Test)	27 (20-39)	30 (20-48)	0.020
HVPG	17.5 ± 8.0	18.0 ± 7.1	0.80
Cardiac Index	3.6 (2.8-9.0)	3.9 (2.6-6.8)	0.74
LVPs	2.0 (0.8-7.2)	2.0 (0.8-11.3)	0.56
Protein Concentration in Ascitic Fluid	11 (2-24)	13 (1-26)	0.001
Diuretics at Admission (Obtained from Patient Records)	44 (58%)	93 (75%)	0.015

According to multi-variable analysis a low sodium was independently related to low dosage diuretic treatment, high Child-Pugh score and low MELD score. The groups did not differ with respect to cause of mortality (86.6% vs 70%). The cumulative risk of mortality at one year was 80% and 39%, respectively (p<0.001). The difference between cumulative incidence at 125, 130, and 135 mmol/L of sodium was significant between both groups. The predictors were mortality were shown in table 2.

Table 2: Univariate Analysis of Predictors of Mortality in Entire Study Population

Variables	Crude Hazards Ratio (Before Adjustment of Variables)	Minimum	Maximum	p-Value
Male	1.05	0.72	1.56	0.910
Age	1.05	1.05	1.06	<0.001
Systolic Blood Pressure	1.03	1.01	1.03	0.051
Child-Pugh Class C	1.49	1.41	1.74	<0.001
MELD Score	1.06	1.03	1.12	0.072
MELD Na	1.15	1.11	1.22	<0.001
HCC	1.79	1.32	2.56	<0.001
Diabetes	1.11	0.76	1.59	0.67
Renal Failure	2.19	1.44	3.58	<0.001
Hepatic Encephalopathy	1.42	0.98	2.03	0.083
Esophageal Varices	1.42	1.15	1.71	0.001
Maximum Dose of Diuretics	**Reference**			
Severe Hyponatremia	4.36	2.76	6.85	<0.001
INR	2.07	1.35	3.42	0.002
Creatinine	0.97	1.01	0.98	0.36
Sodium	0.95	0.99	0.97	<0.001
Total Bilirubin	0.97	0.97	1.05	0.003
Albumin	1.00	0.92	0.96	0.092
HVPG	1.04	0.95	1.13	0.38
Cardiac Index	1.22	0.72	2.10	0.57
LVPs	1.45	1.27	1.58	<0.001
Protein Concentration in Ascitic Fluid	0.96	0.93	1.02	0.009
Beta-blockers at Admission	2.53	0.75	3.62	<0.001
Diuretics at Admission	0.66	0.47	0.96	0.019

The independent predictors of mortality were shown in table 3. No significant association between beta-blockers and LVPs was noted in relation to the risk of mortality in patients without beta blockers. (HR: 1.20, p=0.3). Hyponatremia, renal failure, and high Child-Pugh score were independent predictors of death in these patients.

Table 3: Multi-variate Analysis of Predictors of Death by Fine-Gray Model

Variables	Patients without HCC				Patients without Beta-Blocker Therapy at Admission			
	aHR	Minimum	Maximum	p-Value	aHR	Minimum	Maximum	p-Value
Etiology of Refractory Ascites								
Hyponatremia	2.19	1.20	4.16	0.01	4.38	1.92	10.10	<0.001
Renal Failure	1.8	0.88	2.90	0.2	2.45	1.18	4.91	0.02
Beta-Blockers	1.98	1.18	3.35	0.009	-	-	-	-
LVPs	1.68	1.29	2.08	<0.001	1.40	1.19	1.61	<0.001
Child-Pugh Score	1.51	1.29	1.68	<0.001	1.56	1.28	1.77	<0.001

The prognostic accuracy of predictors of mortality is shown in table 4. The area under the curve of the Child-

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Pugh score (0.90, 95% CI: 0.87-0.96) was significantly higher than the MELD score (0.60, 95 CI: 0.51-0.70) and MELDNa (0.75, 95% CI: 0.65-0.79) as a predictor of mortality (p<0.0001). With respect to the etiology of refractory ascites being an independent risk factor of mortality, the cumulative incidence function was highest in patients with hyponatremia (79%; 95% CI: 79-80%) followed by renal failure patients (55%; 95 CI: 54-56%) and patients receiving maximum dose of treatment (28%; 95% CI: 27-29%)(p<0.001).

Table 4: Prognostic Accuracy of Independent Predictors of Mortality Calculated the Area Under ROC Curve

Variables	Sensitivity	Specificity	PPV	NPV
Hyponatremia	50%	90%	90%	89%
Child-Pugh Class C	80%	65%	80%	66%
Beta-Blockers	60%	69%	78%	51%
LVPs	55%	49%	74%	40%

DISCUSSION

It was conducted that this study to compare the prognostic accuracy of predictors of mortality in cirrhotic and refractory ascites patients. The results demonstrated Child-Pugh score and severe hyponatremia as etiology of ascites were accurate predictors as compared to the MELDNa score. A low sodium level was frequent in these patients with a 38% incidence in the total population. Hyponatremia was diagnosed in 35% of patients due to which effective treatment course could not be followed. This incidence of severe hyponatremia was significantly higher than as recorded before [13, 14]. A poor prognosis was seen in patients with low sodium and refractory ascites as compared to patients with higher sodium levels [15, 16]. Literature has shown the association between hyponatremia and the degree of cirrhosis, the present study results also showed that low sodium levels were strongly related to the degree of cirrhosis evaluated by the Child-Pugh score [17, 18]. Hyponatremia was also an independent risk factor of mortality, as backed by other studies [19, 20]. This implies that hyponatremia and ascites play an important role in the disease outcome of cirrhotic patients besides adjustment of the MELD score. There were conflicting views regarding the reason for the association between hyponatremia and poor patient outcomes [21, 22]. Our study was unique as we selected patients consecutively and disregarded their position on the waiting list for transplants. Other studies conducted on the association between hyponatremia and cirrhosis followed distinctively different study designs [23]. In the current study, the prognostic accuracy of the MELDNa score in the prediction of mortality was not higher than the Child-Pugh score in refractory ascites and cirrhosis patients so it may not be an appropriate predictor of early mortality in this population. 38% of the population in the present study had low sodium levels <130 mmol/L as it was followed that the criteria of International Ascites Club to diagnose refractory ascites. Kim WR et al., reported that sodium levels in MELDNa were better predictors of prognosis when capped between levels <125 and >140mmol/L [11]. Zhang QK also supported these results [24]. However, some studies disagree with using sodium levels in these ranges when applying MELDNa scores although lower levels were common in refractory ascites patients [25]. Beta-blockers use was a strong riskfactor for mortality in ascitic patients. This was supported by other studies and may be due to the fact that beta-blockers alter survival in patients receiving frequent paracentesis by inducing circulatory dysfunctions [26]. In the current study, LVPs were an independent risk factor of mortality irrespective of treatment with beta-blockers.

CONCLUSIONS

Severe hyponatremia, ineffective diuretic treatment, and Child-Pugh score were risk factors of death in cirrhotic and refractory ascitic patients.

Authors Contribution

Conceptualization: MA, MM
Methodology: HA
Formal analysis: NU, MA
Writing, review and editing: MM, MA, SM, MAC

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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