Refractory Ascites in Cirrhosis: Prevalence and Predictive Factors

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Abstract

Introduction: Ascitic decompensation is a common major complication of cirrhosis and is associated with a poor outcome. In 5-10% of patients, ascites become resistant to treatment (either do not respond to a high dose of diuretics or because these drugs induce complications), which is called Refractory Ascites (RA). RA is associated with poor survival: 20-50% at 1 year. Different treatments have been proposed, however, only liver transplantation can improve survival.

The aims of this study were to determine prevalence and predictors of RA development in patients with cirrhosis.

Methods: Retrospective study including consecutive cirrhotic patients admitted for controlling ascites between January 2010 and April 2013. Patients and cirrhosis characteristics were studied. Development of RA during follow-up was investigated. Predictive factors for RA development were evaluated.

Results: We included 124 cirrhotic patients: 59 females (47.6%) and 65 males (52.4%) with a mean age of 58 years. Ascites was grade 3 in 38.5% and was the first episode in 45.1% of patients. Etiology of cirrhosis was mainly viral (57.3%). Child-Pugh score was B in 39.5% and C in 28.2%. Mean MELD score was 16 (6-40). During follow-up, 27 patients developed RA, meaning a prevalence of 21.8%. RA type was diuretic intractable in all cases. Predictive factors of RA development in univariate analysis were: ascites grade 3 (OR=4.17; p=0.004), Child-Pugh score C (OR=3.9; p=0.02), MELD score ≥ 15 (OR=4.99; p=<0.001), MELD/Na score>16 (OR=4.13; p=0.005), spontaneous bacterial peritonitis at the first admission (OR= 8,14; p=0.002), prothrombin time ≤ 64.5% (OR=3.36; p=0.013) and sodium urinary output ≤ 42 mmol/24 h (OR=5.13; p=0.03). In multivariate analysis, only urine sodium output was an independent predictive factor of RA development (OR= 4.74; p=0.015).

Conclusion: In this present study**,** prevalence of RA was 21.8%. Urinary sodium output at the first admission for controlling ascite could allow early identification of patients who will develop RA.

Keywords: Cirrhosis; Ascites; Predictive factors

Introduction

Refractory ascites (RA) is observed in 5%-10% of advanced cirrhosis cases and has a one-year mortality rate of 20%-50% [1-3]. Liver transplantation is the only definitive treatment for these patients, but the procedure is limited by donor liver resources and high cost. Repeated large-volume or total-volume paracentesis with intravenous albumin infusion is currently recommended as the first-line treatment for patients with refractory ascites [4,5]. To date, large volume paracentesis, peritoneo-venous shunt, and Transjugular Intra-Hepatic Portosystemic Shunt (TIPS), combined with diuretics, have widely been used to control ascites, so as to improve their quality of life and help ease the waiting time for liver transplantation. However, these interventions have failed to significantly improve survival, and the prognosis of RA has been demonstrated to be related more to the severity of underlying liver disease, regardless of treatment modalities. Thus, liver transplantation has been strongly recommended for patients with RA to improve survival [6]. Consequently, it is meaningful to investigate predictors of RA development in cirrhotic patients with ascitic decompensation, because these patients will benefit from prompt liver transplantation. However, there have been few investigations identifying predictors of RA development in cirrhotic patients and to our knowledge no Tunisian study has been conducted on that subject.

The aims of this study were to determine prevalence and predictors of RA development in patients with cirrhosis.

Methods

Patient characteristics

This retrospective study included 124 consecutive cirrhotic patients who were admitted to our department for the first time for controlling ascitic decompensation between January 2010 and April 2013. Demographic data, comorbid disorders, etiology and complications of cirrhosis, physical examination, biochemical values, Child-Pugh score, MELD score, MELD Na, and treatment were collected at entry. MELD Na score was calculated using the following formula: MELDNa=MELD+1*(140-Na)-0.025*MELD*(140-Na). For patients who developed RA during the follow-up period, we specified also the type of RA and treatment modalities for RA.

Exclusion criteria: We excluded patients aged<18 years, those with a diagnosis of RA previously established, hepato-renal syndrome, porto-caval shunt, TIPS, liver transplantation, ascites caused by another cause (nephrogenic, tuberculosis, malignancy, heart failure), organic renal failure and ascites grade 1 only detected by ultrasound).

Diagnosis of ascites and RA

The diagnosis of ascites was made based on physical examination and ultrasonography. Occurrence of RA during follow-up was

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diagnosed according to the International Ascites Club (IAC) diagnostic criteria as follows: ascites that cannot be mobilized, or early recurrence of ascites which cannot be satisfactorily prevented by medical therapy [7]. Accordingly, there were two types of RA: "Diuretic-intractable ascites" which could not be mobilized or its early recurrence could not be prevented because the development of diuretic-induced complications such as: hyper/ hypokalemia, (defined as a change in serum potassium to <3 mmol/L or >6 mmol/L despite appropriate measures), hyponatremia (defined as a decrease of serum sodium by >10 mmol/L to a serum sodium of <125 mmol/L), hepatic encephalopathy in the absence of any other precipitating factor, renal failure (defined by an increase of serum creatinine by >100% to a value >2 mg/dl=177 µmol/ L). However, in our clinical practice, the value of serum creatinine leading to the withdrawal of diuretics was below 177 mmol/L and about 125 mmol/L which corresponds to the upper limit defined by the laboratory. "Diuretic-resistant ascites", which is an ascites that cannot be mobilized or the early recurrence of which cannot be prevented because of a lack of response to sodium restriction and diuretic treatment (spironolactone 400 mg/day and furosemide 160 mg/day) and sodium restriction [7,8].

Treatment strategies: Patients with grade 2 or moderate ascites were treated with salt restriction (Na+80 mmol/day) and a progressive dose of spironolactone alone or with furosemide (starting dose: furosemide 40 mg/day, spironolactone 100 mg/day). Patients with grade 3 or tense ascites were treated with initially with therapeutic paracentesis and additional albumin replacement. After therapeutic paracentesis, patients receive the minimum dose of diuretics necessary to prevent the re-accumulation of ascites.

Statistical analysis

The data was summarized by descriptive statistics (means and frequencies) and analysed with SPSS version 19. Data are shown as percentage, mean and standard deviation (SD). Student test and Chi squared test (or Fisher) were used to compare quantitative and qualitative variable for univariate analysis. To identify independent predictors of RA development, variables that achieved a p-value <0.15 in univariate analyses were included in a multivariate analysis, based on a proportional hazards Cox regression model. Odds Ratio (OR) and corresponding 95% Confidence Intervals (CI) were calculated. P value less than 0.05 was accepted as statistically significant.

Results

Baseline characteristics

Of 124 patients hospitalized to control ascitic decompensation, 65 (52.4%) patients were males, and the mean age of all patients was 58 ± 13 years (18-90). Etiology of cirrhosis was mainly viral (57.3%): C in 37.1% and B in 20.2%. Child-Pugh score was B in 39.5% and C in 28.2%. Mean MELD score was 16+/- 8 (6-40) and mean MELD/Na was 18 +/- 8 (6-40). Ascites was grade 3 in 38.5%, grade 2 in 61.5% and was the first episode in 45.1% of patients. No patient had chylous ascites. Two patients had hydrothorax. At entry, 42 patients had diuretic treatment (33.9%): 17 patients (13.7%) received spironolactone alone, 4 patients (3.2%) receive furosemide alone and 15 patients (12.1%) receive both spironalactone and furosemide. The mean dose of spironolactone was 126.8 ± 46.6 mg (extremes 75- 225). The mean dose of furosemide was 42.9 ± 10.7 mg (40-80). Biochemical characteristics of cirrhotic patients at the first admission were shown in the Table 1. Complications of cirrhosis before and at the first admission were precised in Table 2.

RA occurrence during follow-up

The median follow-up period of 9.95 ± 9.74 months [extremes: 1-51] after the first admission for controlling ascitic decompensation. During follow-up, 27 patients developed RA, meaning a prevalence of 21.8% in a median of 2.3 ± 2.5 months (range: 1-9) after admission. Of these patients, 8 (14.2%) had presented RA after the first episode of ascites. RA type was diuretic intractable in all cases. The mean reason for intractable ascites was: decreased serum sodium in 9 patients, renal impairment in 10 patients; decreased serum potassium in 4 patients; increased serum potassium in 1 patient and hepatic encephalopathy in 3 patients. In the 10 cases of renal impairment, serum creatinine ranged from 125 to 414 µmol/L, among them, 5 had a value >177 µmol/L. Thus, according to the IAC criteria, prevalence of RA was 17.7%. For managing patients with RA, large-volume paracentesis was repeatedly performed for all patients every 2 ± 0.8 weeks [extremes: 1-4]. Thirteen patients (48%) also received furosemide.

Predictors factors of RA development

Predictive factors of RA development in univariate analysis were: ascites grade 3 (OR=4.17; p=0.004) and recidivant ascites at the first admission (p=0.06), Child-Pugh score C (OR=3.9; p=0.02), MELD score ≥ 15 (OR=4.99; p=<0.001), MELD/Na score> 16 (OR=4.13; p=0.005), spontaneous bacterial peritonitis at the first admission (OR= 8.14; p=0.002), prothrombin time ≤ 64,5% (OR=3.36; p=0.013) and sodium urinary output ≤ 42 mmol/24 h (OR=5.13; p=0.03). In multivariate analysis, only urine sodium output was an independent predictive factor of RA development (OR= 4.74; p=0.015). The output of 42 mmol/24 h had a sensitivity of 74% and specificity 63%. This result was not related to any use of diuretics (44.4 % vs 30.9%; p=019). Table 3 shows the univariate analyse that were performed to identify predictors of RA development.

Discussion

In our cohort, the prevalence of RA was 21.8%. RA type was diuretic intractable in all cases. Predictive factors of RA development in univariate analysis were: ascites grade 3 and recidivant ascites at the first admission, Child-Pugh score C, MELD score ≥ 15, MELD/

	Mean, SD, extrems
Serum sodium, mmol/L	135.8 ± 5.1 [120-146]
Serum potassium, mmol/L	4.3 ± 0.7 [3-5.5]
Serum creatinine, µmol/L	86.53 ± 87 [35-189]
Serum bilirubin, µmol/L	61 ± 79 [8-462]
TP, %	62 ± 22 [19-100]
INR	1.7 ± 0,8 [1-5.1]
Serum albumin, g/L	29.5 ± 5.9 [15-43]
sodium urinary, mmol/24h	48.5 ± 43.5 [1-172]

TP: Prothrombine Time, INR: International Normalized Ratio

Table 1: Biochemical characteristics of cirrhotic patients at admission.

Complication	Number	Pourcentage
SBP	11	8.9%
Bacterial infections	32	25.8%
Variceal hemorrhage	41	33.1%
EH	42	33.9%
Hydrothorax	8	6.5%
CHC	37	29.8%

SBP: Spontaneous Bacterial Peritonitis, EH: Hepatic Encephalopathy CHC: Hepatocellular Carcinoma

Table 2: Complications of cirrhosis.

	RA (+) N=27	RA (-) N=97	P	OR(IC 95%)
Mean age (Years)	56	59	0.29	
Male	14 (51.9%)	51 (52.6%)	0.947	
Diabetes mellitus	6 (22.2%)	34 (35.1%)	0.2	
Ascites Grade 3	15 (55.6%)	16 (16.5%)	0.004	4.17[1.52-11.43]
Diuretic treatment	12 (44.4%)	30 (30.9%)	0.19	
VHC	9 (40.9%)	37 (50%)	0.47	
VHB and VHC	16 (72.7%)	54 (73%)	0.98	
Score of Child-Pugh C	14 (51.9%)	21 (21.6%)	0.02	3.9[1.59-9.55]
Score of MELD ≥ 15	21 (77.8%)	40 (41.2%)	<0.001	4.99[1.8-13.5]
Score of MELD/Na>16	22(81.5%)	50 (51.7%)	0.005	4.13[1.5-11.8]
VO grade 2-3	8 (29.6%)	33 (34%)	0,67	
Bbloquants	17 (63%)	60 (61.9%)	0.92	
Spontaneous bacterial peritonitis	7 (25.9%)	4 (4.1%)	0.002	8.14[2.2-30.5]
Bacterial infections	6 (22.2%)	26 (26.8%)	0.7	
Variceal bleeding	10 (37%)	31 (32%)	0.53	
Hepatic encephalopathy	12 (44.4%)	30 (30.9%)	0.19	
Hydrothorax	2 (7.4%)	6 (6.2%)	0.54	
Hepatocellular carcinoma	5 (18.5%)	32 (33%)	0.15	
Prothrombin time ≤ 64.5%	6 (22.2%)	21 (21.6%)	0.013	3.36[1.24-9.05]
INR>1.28	22 (81.5%)	50 (51.5%)	0.005	4.13[1.49-11.81]
Natriuresis ≤ 42 mmol/24h	17 (63%)	16 (16.5%)	0.03	5.13[1.69-15.63]
Soduim (mmol/l)	135.1	136	0.41	
Creatine (µmol/l)	118	96	0.32	

RA: Refractory Ascites, OD: Odds Ratio; HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; VO: Variceal Oesophagus

Table 3: Predictors of refractory ascites Development in Patients with Cirrhosis Who Were Hospitalized to Control Ascitic Decompensation.

	Number of patients	Prevalence of RA	Diuretic-intractable ascites	Diuretic-resistant ascites
Moreau et al. [6]	75		93%	7%
Planas et al. [9]	263	11.4%	93.3%	6.7%
Sersté et al. [13]	174		68.4%	31.6%
Seo et al. [14]	199	8%	31.3%	68.7%
Our study	124	21.8%	100%	0

RA: Refractory Ascites

Table 4: Prevalence of refractory ascites.

Na score>16, spontaneous bacterial peritonitis at the first admission, prothrombin time ≤ 64.5% and sodium urinary output ≤ 42 mmol/24 h. In multivariate analysis, only urine sodium output was an independent predictive factor of RA development.

Five to 10% of ascitic patients per year become refractory to standard medical treatment, because of either an insufficient natriuretic effect of diuretic medications, or more often, to the development of diuretic-related severe side effects, which compel the patient to discontinue the diuretic treatment [7,8]. However, these figures are derived from observational studies performed in hospitalized patients or from controlled clinical studies in highly selected populations and the true incidence of refractory ascites in everyday clinical practice remain unsettled [9-12]. It is likely that it varies considerably in relation to the stage of cirrhosis, being far greater in patients with impaired renal function. Therefore, unresponsiveness to pharmacological treatment may be more often observed in patients with cirrhosis and ascites admitted to tertiary referral centers or to liver transplant centers. In our cohort the prevalence of RA was higher than reported in the literature and this can be explained by many reasons: firstly, about 75% of our patients had a severe cirrhosis (Child Pugh B or C), secondary the compliance of our patients to diuretic treatment and salt-restricted diet could not be checked due to the retrospective character of our study, and finally the value of serum creatinine motivating the withdrawal of diuretics, in our study, was below than 177 mmol/L in 5 patients. Using the criteria of the IAC, prevalence was lower: 17.7%, yet, remaining higher than previously reported. Concerning the type of RA, the diuretic intractable is the more frequent type such reported in the literature. The prevalence of different types of RA was illustrated in Table 4 [6,9,13,14].

Recent studies reported a poor prognosis after RA development, and the 1- and 2-year survival probabilities of patients with RA were only 50 and 30%, respectively, without liver transplantation [6,12]. Thus, the identification of predic¬tors that can select a subgroup of patients with liver cirrhosis who will experience RA, carries important meaning in establishing the priority of prompt liver transplantation. In the literature, we identified only two studies which principal aim was to determine the predictor's factors of RA development in patients with cirrhosis: the Spanish study of Planas et al. [9], and a Korean study of Seo et al. [14]. The liver failure was probably sufficient for RA development in patients with Child-Pugh C liver function [6,8]. In the prospective study of Planas et al. [9], the score Child-Pugh > 8 at inclusion was an independent predictor factor of RA with an OR of 1.47. In our study, Child-Pugh class, MELD score and MELD/Na score were found to be a significant predictor of RA development in the univariate analysis but not in multivariate analysis. This suggests the independent role that may have liver failure in occurrence of RA.

In our series, the occurrence of AR was significantly associated with

tender ascites with an OR=4.17. This parameter has not been sought in other studies of RA predictive factors. But it is interesting to consider, in order to strictly following these patients according to the high risk of developing RA. Sodium urinary output ≤ 42 mmol/24 h was identified as the only independent predictor of RA development in our study. This result is not related to any use of diuretics, and natriuresis is an easy parameter which can be useful in our clinical practice in early differentiation of the response to diuretics treatment. Our result was similar to the results of two others studies which found that natriuresis lower than 50 mEq/8 hours measured 8 hours after a bolus of 80 mg furosemide was an independent predictor of RA development [15,16]. These studies shown that patients with RA can be identified quickly and accurately by using this simple furosemide-induced natriuresis test, which could be very useful to select patients for liver transplantation. Studies that have investigated the predictors of the occurrence of AR did not identified natriuresis as predictor factors: Planas et al. [9], and Seo et al. [14], B showed a relationship between serum electrolyte levels and responsiveness of ascites to diuretic therapy. Our study has several limitations: Firstly, being a retrospective study, there was a selection bias of patients: in fact the diagnosis of AR does not fully respond the criteria of the IAC for the definition of acute renal failure induced by diuretics. Secondly, even if natriuresis was not statistically different between patients with or without diuretics, it would be preferable to measure the natriuresis to all patients in the same conditions: without diuretics or in the same dose of diuretics.

In conclusion, we found in the present study that the prevalence of RA in cirrhotic patients is not insignificant, and that sodium urinary output was an independent predictor of RA development in cirrhotic patients admitted to control ascitic decompensation. However, future prospective studies should assess whether natriuresis can be used to establish the priority of liver transplantation in these patients.

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