ORIGINAL RESEARCH

Hepatorenal syndrome in cirrhotic patients in Madagascar: epidemiology, clinical profile and in-hospital outcomes

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ABSTRACT

Background: Hepatorenal syndrome (HRS) is a frequent and serious complication in decompensated cirrhosis. The objective of this study was to describe the epidemiology, clinical profiles and outcomes of hepatorenal syndrome (HRS).

Methods: This was a retrospective and descriptive study over a period of 75 months, from January 2011 to March 2017, carried out at the Gastroenterology Unit, University Hospital Joseph Raseta Befelatanana, Antananarivo, Madagascar.

Results: The hospital prevalence of decompensated cirrhosis with HRS was 7.9% (41/519). The mean age of the patients was 49.8 ± 11.33 years (range 25–70 years). Male gender predominated at 83% (n = 34). History of alcohol (46.3%) and viral hepatitis B (34.1%) were the main aetiologies of cirrhotic disease. Most of our patients (88%) had a Child-Pugh C score. HRS occurred during the first decompensation (63.4%) and the first years of cirrhosis (81%). Spontaneous bacterial peritonitis (46%) and gastrointestinal bleeding (32%) were the main risk factors. HRS type-1 predominated at 66% (n = 27). The prognosis was poor with a mortality rate of 81% (100% in HRS type 1 and 42.9% in type 2). Most patients (n = 22; 67%) died within 14 days.

Conclusion: The prevalence of HRS was 7.9%. It affects young people with advanced cirrhosis. The prognosis is grim with a mortality rate of 81%.

Keywords: Acute kidney injury, liver cirrhosis, hepatorenal syndrome, Madagascar.

BACKGROUND

Hepatorenal syndrome (HRS) is functional renal failure complicating decompensated hepatic cirrhosis with portal hypertension and ascites, in the absence of other causes of renal failure [1-3]. It is a frequent complication of cirrhosis with an incidence of 18% at one year and 39% at 5 years; its prevalence in hospitalized patients with ascites can reach 20% [4-7]. HRS is a turning point in the course of cirrhosis because its prognosis is poor and spontaneous reversibility is rare [8]. However, the two types of HRS offer different evolutionary profiles. Type 1 is severe acute kidney injury that is rapidly progressive over days or weeks, most often triggered by a risk factor. Type 2 HRS is moderate, stable or slowly progressive renal failure, usually in the setting of refractory ascites [1-3]. In the absence of treatment or in the event

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of delayed treatment, HRS type 1 has a poor prognosis with a median survival of around 15 days and survival at one month is estimated at 20% [4,9]. As for HRS type 2, the median survival is 6 months [7]. In Madagascar, cirrhosis was described in 2012 as the most frequent digestive disease (33.5%) and the deadliest [10]. However, no data are available on HRS, which is a formidable complication of this disease. Despite specific treatments being available in high-resource regions, none was available in Madagascar at the time of this study due to their high cost. The objective of this study was to describe the epidemiological and clinical profiles and outcomes of HRS observed at the Gastroenterology Unit at University Hospital Befelatanana, Antananarivo, Madagascar.

METHODS

This was a retrospective and descriptive study on HRS, carried out within the Gastroenterology Unit at the University Hospital Joseph Raseta Befelatanana in Antananarivo over a period of 75 months from January 2011 to March 2017.

We had recruited all patients with decompensated cirrhosis who were hospitalized during the study period. Included were all cirrhotic patients in whom HRS was diagnosed. Each patient had serum creatinine measured at admission and at each acute complication; and serum creatinine was monitored 48 hours after the introduction or increase in dose of diuretics. One incomplete file was excluded as the admission serum creatinine result was unavailable. Socio-demographic data (age, gender), clinical data (factors favouring HRS, aetiology, duration of development, number of decompensations and complications, cirrhosis, urine output (mL/24 h), biochemical variables (serum creatinine value (µmol/L), glomerular filtration rates (mL/min/1.73 m^2) at the time of admission and diagnostic confirmation, type of HRS) and hospital outcomes (favourable or death, causes of death and length of hospitalization) were collected.

HRS was diagnosed according to International Ascites Club (IAC) criteria of 2015 [11-13]: (1) diagnosis of cirrhosis and ascites, (2) diagnosis of acute kidney injury according to IAC criteria [13] defined as the increase of serum creatinine of 26.5 µmol/L within 48 hours or an increase in serum creatinine of 50% or more from baseline observed in the previous 7 days, (3) no response for 2 consecutive days after diuretic withdrawal and plasma volume expansion with albumin (1 g per kg of body weight), (4) absence of shock, (5) no current or recent use of nephrotoxic drugs (non-steroidal anti-inflammatory drugs, aminoglycosides, iodinated contrast media, etc.), (6) no signs of kidney injury defined as absence of proteinuria (>500 mg/day), absence of haematuria (>50 red blood cells per high-power field), and normal findings on renal ultrasonography. Data collection was carried out by consulting the medical files of hospitalized patients, respecting the anonymity of the patients. The data were collected on Microsoft Excel and analysed with Epi Info version 7.2. Continuous variables with normal distributions are expressed as means ± standard deviation. Categorical variables are presented as counts and percentages.

This study was approved by the Ethics Committee of Biomedical Research of the Ministry of Public Health of Madagascar (certificate no. IORG0000851MSANP/CERBM).

RESULTS

Epidemiological and clinical characteristics

Of the 519 patients with decompensated cirrhosis hospitalized in the Department of Gastroenterology during the study period, 41 patients had HRS, giving a hospital prevalence of 7.9%. Of the 41 patients with HRS, 34 (83%) were males, giving a sex ratio of 4.9. The average age of our patients was 49.8 ± 11.3 years with a range of 25–70 years. The aetiology of cirrhosis was dominated by alcohol (46%) and viral hepatitis B (34%). HRS occurred during the first decompensation (63%) and the first years of cirrhosis (81%). Thirty-six patients (88%) had a Child-Pugh C score and 22 (54%) a urine output less than 500 mL/24 h. A risk factor for hepatic decompensation was found in 36 cases (88%); spontaneous bacterial peritonitis (46%) and gastrointestinal bleeding (32%) were the main risk factors. Twenty-seven patients (66%) had HRS type 1 and 14 (34%) had HRS type 2. The median serum creatinine at diagnosis was 282 (211; 409) µmol/L and the median glomerular filtration rate was 8 (20; 24) mL/min. The demographics, risk factors, types of HRS and clinical characteristics of our patients with HRS are reported in Tables 1 and 2.

Management and in-hospital progress

All patients with viral hepatitis B were treated with lamivudine, whereas patients with viral hepatitis C did not have access to specific antiviral treatment. All of our patients (100%) had received rehydration and management of risk factors. No patient had received specific treatment for the HRS. Thirty-three patients (81%) died during hospitalization. All 27 patients with HRS type 1 died; 6 of 14 patients (43%) with HRS type 2 died. Metabolic complications (hyperkalaemia, metabolic acidosis, azotaemia) and complications of cirrhosis (hepatic encephalopathy, haemorrhagic shock, spontaneous bacterial peritonitis, hepatocellular carcinoma, acute pulmonary oedema, septic shock) were the causes of death of patients with respective

Table 1. Epidemiological and clinical characteristics.

Parameters	N (%)
Male	34 (82.9)
Age (years; mean±SD)	49.8 ± 11.3
Age groups (years),	
<40	7 (17.1)
40–50	15 (36.6)
≥50	19 (46.3)
Aetiology of cirrhosis	
Alcohol	19 (46.3)
Hepatitis B virus	14 (34.1)
Hepatitis C virus	3 (7.3)
Auto-immune hepatitis	1 (2.4)
Haemochromatosis	1 (2.4)
Alcohol + hepatitis B virus	2 (4.9)
Alcohol + hepatitis C virus	1 (2.4)
Duration of cirrhosis (years), <1/[1–5]/≥5	33 (80.5)/7 (17.1)/1 (2.4)
Number of decompensations, 1/2/≥3	26 (63.4)/11 (26.8)/4 (9.8)
Child-Pugh scores	
Child-Pugh A	1 (2.4)
Child-Pugh B	4 (9.8)
Child-Pugh C	36 (87.8)
Complications	
Ascites (41/41), moderate/large volume	19 (46.3)/22 (53.7)
Hepatic encephalopathy (23/41), stage 2/3	9 (22)/14 (34.1)
Spontaneous bacterial peritonitis	19 (46.3)
Gastrointestinal bleeding	15 (36.6)
Urine output (mL/24 h)	
<500	22 (53.7)
500–1000	17 (41.5)
≥1000	2 (4.9)

Abbreviations: SD, standard deviation.

Table 2. Risk factors, types of HRS and clinical characteristics.

Parameters	N (%)
Risk factors	34 (82.9)
Spontaneous bacterial peritonitis	19 (46.3)
Gastrointestinal bleeding	13 (31.7)
Repeated paracentesis	3 (7.3)
Acute alcoholic hepatitis	1 (2.4)
None	5 (12.2)
Types of HRS	
HRS type 1	27 (65.9)
HRS type 2	14 (34.1)
Serum creatinine when diagnosis HRS, mean (µmol/L)	383.3±322.4
<170/[170-200]/≥200	4 (9.8)/6 (14.6)/31 (75.6)
GFR when diagnosis HRS, mean (mL/min)	22.2±15
< 40/[21-40]/[10-20]/<10	7 (17.1)/17 (41.5)/12 (29.3)/5 (12.2)

Abbreviations: HRS, hepatorenal syndrome; GFR, glomerular filtration rate according to MDRD (mL/min/1.73m^2); serum creatinine (µmol/L); serum creatinine (µmol/L); SD, standard deviation.

rates of 46% and 55%. Death occurred within 14 days in 67% of cases. The management and hospital course of patients with HRS are listed in Table 3.

DISCUSSION

To our knowledge, this is the first study on HRS conducted in Madagascar. The study found that the in-hospital prevalence of HRS in decompensated cirrhosis was 7.9%. Men were the most affected (83%). HRS occurred at a younger age than in other international cohorts. The prognosis of HRS was poor, especially in type 1.

Because this was an observational study, it has limitations. Although the size of our sample is not representative of the prevalence of HRS in Madagascar, it allowed us to obtain epidemiological and clinical descriptions and in-hospital outcomes of HRS in cirrhotic patients in the country.

The prevalence of HRS varies between 7% and 45%, according to the literature [14]. Its prevalence in hospitalized patients with ascites is 20% [4-7]. In our study the hospital prevalence of HRS was 7.9% (66% HRS type 1; 34% HRS type 2). Sehounou et al. (Cotonou, 2010) reported a prevalence of 5.4% [15]. Seetlani et al. (Pakistan, 2016) found a prevalence of 15% in 265 cirrhotic patients [16]. A higher prevalence has been reported in other studies. Rey et al (Colombia, 2020) reported a prevalence of 23.9% (67% HRS type1; 33% HRS type 2) [14]. Salerno et al. (Italy, 2011) recorded a prevalence of 45.8% (30% HRS type 1; 15.8% HRS type 2) [17]. The majority of publications demonstrated that the prevalence of HRS type 1 was higher; our results are in keeping with this. HRS type 1 is reported to occur due to risk factors in 75% of cases [1,17]. A risk factor for HRS was found in 88% of this cohort. This may account for the high prevalence of HRS type 1.

The participants' mean age was 49.8 ± 11.3 years in our study, with extremes of 25 and 70 years. Our findings are similar to those reported by Seetlani et al. (Pakistan) [16]. The patients were older in European countries, with a mean age of 56 ± 3 years and 56 ± 10 years, respectively,

Table 3. Management and in-hospital outcomes.

Parameters	Overall (n = 41)	Type 1 HRS (n = 27)	Type 2 HRS (n = 14)
Treatments received			
Rehydration and others*	41 (100)	27 (100)	14 (100)
Specific treatments**	0 (0)	0 (0)	0 (0)
In-hospital outcomes			
Favourable	8 (19.5)	0 (0)	8 (57.1)
Death	33 (80.5)	27 (100)	6 (42.9)
Causes of death			
Metabolic complications of HRS***	15 (45.5)	15 (55.6)	0 (0)
Complications related to advanced liver disease****	18 (54.6)	12 (44.4)	6 (100)
In-hospital survival	11±5.5		
<14 days	22 (66.7)	22 (81.5)	0 (0)
>14 days	11 (33.3)	5 (18.5)	6 (100)

*Transfusion or laxatives or antibiotics or correction of fluid and electrolyte disturbances; **albumin and/or vasoconstrictors or TIPS or liver transplantation; ***hyperkalaemia, metabolic acidosis, azotaemia; ****hepatic encephalopathy, haemorrhagic shock, spontaneous bacterial peritonitis, hepatocellular carcinoma, acute pulmonary oedema, septic shock.

in Italy and France [17,18]. This is due to the ageing of the European population, on the one hand. Alternatively, the causes of cirrhosis can have an important role, because in Madagascar infection with hepatitis virus B is prevalent at birth. Thus, among Madagascans, the cirrhotic population is relatively young [10].

Also in Madagascar, several authors have reported a male predominance in cirrhotics, explaining the male predominance of HRS in this study [10,20,21]. As expected, a clear male predominance (83%) was demonstrated in this series, with a sex ratio of 4.9. Martin-Llahi et al. reported that HRS mainly affected men (70%) [19].

Alcohol (46.3%) and hepatitis B virus (HBV) (34.1%) were the main aetiologies of cirrhosis with HRS in our study. According to the literature, alcoholic cirrhosis was one of the most common causes of HRS [17,22]. In an Italian study, alcohol and HBV accounted for 55% and 40%, respectively, of cirrhosis with HRS [17]. Watt et al. reported that HRS affected 89% of alcoholic cirrhosis [23].

The incidence of HRS increases with progression of cirrhotic disease, ranging from 18% to 20% at one year, and 39% after 5 years of diagnosis [8,24,25]. However, we found that it occurs earlier in this study. At one year, 80.5% of cirrhosis cases were complicated by HRS. In addition, it occurred early, from the first decompensation of cirrhosis (in 63%). The discovery of advanced-stage cirrhosis in this study and the poor out-of-hospital management of the disease by taking hepatotoxic and nephrotoxic drugs, misuse of diuretics, paracentesis of over 5L without compensation, may be contributing factors [21].

Ascites is one of the most common complications of cirrhosis. It was observed in all patients, regardless of the duration or the number of decompensations of the condition. It constitutes a fundamental element in the mechanism of occurrence of HRS.

Cirrhosis with Child-Pugh C scores was the most vulnerable to HRS in this study (88%). According to the literature, HRS is more common in the more advanced stages of cirrhosis. Moreau et al. reported that 90.7% of cirrhosis complicated by HRS had Child-Pugh C scores [18]. Risk factors were present in 88% of our patients. Spontaneous bacterial peritonitis was the main risk factor (46%). Numerous studies (for example, EASL, Colle et al., and Fernandez et al.) had observed that spontaneous bacterial peritonitis was the most frequent risk factor for HRS [2,26,27]. Paracentesis of more than 5 litres was identified in the series of Rey et al. [14]. The ideal treatment for HRS, regardless of type, is liver transplantation. However, specific treatment of risk factors is mandatory for HRS type 1 associated with vasoconstrictor therapy (that is, terlipressin) and volume expansion with albumin pending liver transplantation. For HRS type 2, large-volume paracentesis, serial therapeutic paracentesis and transjugular intrahepatic porto-systemic shunts (TIPSs) are the treatments pending liver transplantation [2,12]. Our patients had received treatment for only risk factors and rehydration. No patient had received specific treatment for HRS, regardless of type. This is essentially linked to problems in accessing these treatments in Madagascar, because of the lack of availability and especially the high cost of these drugs. Other alterna-

tives, such as liver transplantation and transjugular intrahepatic portosystemic shunt (TIPSs) are not as available.

HRS has a poor prognosis [4,14,17]. In the absence of treatment, the mortality rate is high over 2 weeks, with survival of 10% at 3 months [14,24]. In our series, the overall hospital mortality rate was 81%. Chris-Olaiya et al. (2020) reported an in-hospital mortality rate of 36.9%, significantly lower than those reported in our series [28]. The lack of specific treatment for HRS received by our patients explains the high mortality rate in our cases. In addition, terlipressin, currently used in the management of HRS, has been associated with a 9% reduction in HRS-related mortality, explaining the decrease over recent years [29]. All of our patients with HRS type 1 had died, but only 6 out of 14 of our subjects with HRS type 2 (43%) died. This large difference is explained by the fact that HRS type 1 has a poor prognosis compared to HRS type 2. Numerous studies have reported that in the absence of specific treatment, the average survival is only 2 to 4 weeks for HRS type 1 compared to 6 months for HRS type 2 [4,7,9].

Most of our patients died within 14 days, with a mean duration of 11 ± 5 days. This confirms the severity of HRS, especially type 1. We note that death occurred earlier than previously described [23], probably due to the absence of specific treatments that promoted the rapid progression of the disease.

This study has some limitations, notably the retrospective nature of the data. First, we used the old IAC definition of hepatorenal syndrome. Second, the lack of availability of specific therapies, such as terlipressin, in Madagascar makes our findings less generalizable to countries where these treatments are available.

CONCLUSION

This study on HRS in cirrhotic patients in Madagascar is important in demonstrating the young age of people with advanced cirrhosis and an overall high in-hospital mortality, especially in cases of HRS type 1. The lack of accessibility to vasoconstrictor therapy poses a challenge to all health stakeholders and it is essential to have these treatments available. Meanwhile, prevention remains the best way to deal with the morbidity and mortality of HRS as well as focusing on the early diagnosis of liver cirrhosis and the effective management of risk factors.

Conflict of interest

None declared.

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