ORIGINAL ARTICLE

HEPATORENAL SYNDROME IN PATIENTS WITH CIRRHOSIS OF LIVER ACCORDING TO 2007 INTERNATIONAL ASCITES CLUB CRITERIA

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Background: Heptorenal syndrome is a complication of cirrhosis of liver and is characterized by progressive renal failure. This study was done to determine the frequency of hepatorenal syndrome according to 2007 international ascites club criteria among patients of cirrhosis attending Medical Units of Civil hospital Karachi. **Methods:** This is a cross-sectional study conducted on the hospitalized patients in the Department of Medicine-Civil Hospital Karachi from 01-04-2014 to 30-09-2014 where total 265 patients of either gender, age >18 years & <60 years & diagnosed case of CLD were included. Patients with shock, SIRS, sepsis, known cases of intrinsic renal diseases, or history of diabetes mellitus, Hypertension or connective tissue diseases were excluded. Mean±SD were expressed for continuous variable like, age, duration of CLD. Frequency & percentages of other categorical variables, i.e., gender, residence were expressed. Effect modification was tested through Chi-square with *p*-value <0.05 significant. **Results:** The mean±SD age of patient was 48.23±7.87 years with range 18–60 years. Mean±SD duration of chronic liver disease was 5.60±1.92 years with a range of 3–12 years. More than 155 (58%) participants in this study were male and females were 110 (41.51%). More than 36 (13%) were of age less than and equal to 40 years; 121 (45.67%) were from 41–50 years, while 108 (40.75%) were from age 51–60 years. More than 176 (66.41%) belonged to rural areas while only 89 (33.58%) belonged to urban areas. The study observed that according to IAC 2007 criteria of diagnosis of hepatorenal syndrome 15.09% of patients with cirrhosis were found to have HRS. **Conclusion:** Hepatorenal syndrome represents the end stage of a sequence of reduction of renal perfusion induced by advanced liver failure. Almost every seventh patient of Cirrhosis can develop hepatorenal Syndrome. This should be looked up at an early stage so that it can be prevented.

Keywords: Hepatorenal Syndrome; renal failure; Cirrhosis.
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INTRODUCTION

Progressive Hepatic fibrosis, resulting from various etiological factors, results in liver cirrhosis, which is characterized by distorted parenchymal architecture and impaired liver functions. These patients are prone to various complications, which can decrease life expectancy.[1] Hepatorenal Syndrome (HRS) is a serious complication of end stage liver disease, occurring mainly in patients with advanced cirrhosis with portal hypertension.[2] Abnormal hemodynamics resulting in splanchnic and systemic vasodilation and renal vasoconstriction causes renal functions impairment, in the absence of histological or tubular functions abnormalities.[3,4]

Hepatorenal Syndrome is mostly triggered by some precipitating events, usually by bacterial infections, which result in arterial circulation disruption. In some instances it has been found to occur spontaneously.[4]

Previously two types of HRS were identified. Type 1 is characterized by rapid deterioration of renal function, while type 2 has comparatively slower progression, with less severe renal dysfunction and longer survival.[4] Recently HRS type 3, advanced liver disease with co-existing intrinsic renal dysfunction and type 4 HRS in acute liver failure, have also been defined.[5]

Impaired Heart Functions, Hyponatremia with serum creatinine and bilirubin levels are identified to be strongest predictive factors for development of HRS.[6,7] Factors which may affect the prognosis of patients with HRS include older age group, degree of hepatic encephalopathy, gastrointestinal bleed, blood neutrophilic count, low urinary sodium excretion and serum creatinine levels.[8,9]

In 1978 a consensus conference defined and proposed diagnostic criteria for hepatorenal syndrome. In 1996 International Ascites Club (IAC) proposed another criterion for HRS diagnosis, in which HRS was defined as renal impairment in hepatic failure with portal hypertension, in the absence of any other possible cause of renal failure like shock, volume loss, ongoing bacterial infection, use of nephrotoxic medications or any evidence of renal parenchymal injury.[10] In 2007 IAC further updated the definition, diagnostic criteria and types of HRS.[5]

The prevalence of HRS in patients affected by cirrhosis and ascites was 18% after 1 year which

increases to 39% at 5 years[11] but it has declined over the last two decades owing to better management of cirrhotic patients. In a recent study by Planas R *et al*[12] included 263 cirrhotic patients followed for 41±3 months from their first episode of ascites showed much lower risk of HRS development with the cumulative 5-year probability of HRS development of only 11.4%. In Pakistan, Data from local hospital showed prevalence of HRS in cirrhotics to be 15% among 240 patients, according to the proposed criteria of 1996.[13]

The prevalence of HRS according to 2007 IAC criteria has been studied by Salerno F *et al*[14] and they found that prevalence of HRS was 45.8%. (116 out of total 253 patients) In 36% of cases HRS was presumed because not all diagnostic criteria could be fulfilled which means only 64% met all diagnostic criteria as outlined by the IAC.

The identification of HRS in cirrhotic patients is an open clinical problem. There has been growing interest in assessing the 2007 IAC criteria of diagnosis of HRS. Till date and to the best of my knowledge, there has no study in Pakistan on the actual prevalence according to 2007 IAC criteria. With high prevalence of cirrhosis in our population, early identification of patients with HRS is vital to plan management and is helpful in determining prognosis.[15] So this study was done to determine the frequency of HRS in patients of cirrhosis which would be helpful in elucidating the current magnitude of such patients according to 2007 IAC criteria which can lead to adequate planning by health care providers in emphasizing means to prevent HRS and its contribution to morbidity in cirrhosis.

MATERIAL AND METHODS

The study was sought from College of Physicians and Surgeons of Pakistan at Karachi. Permission for the study was taken from ethical review committee of Dow University of Health Sciences and Civil Hospital Karachi. The respondents were assured of confidentiality of their information. Written informed consent was obtained from each patient. Sample size was calculated using WHO sample size calculator keeping confidence level (1-α) of 95%. Anticipated population proportion (P) of 45.8%[14] and absolute precision (d) of 6%, the sample size is calculated as 262.

$$Z^2 \times (P) \times (1-P) / d^2$$

Where Z = Z value (e.g, 1.96 for 95% confidence interval level), P=prevalence of disease, d=absolute precision of 6% (0.06) and non-probability consecutive sampling technique was applied to collect data. Males and Females aged above 18–60 years and previously diagnosed patients of cirrhosis for more than 6 months admitted in the medical wards of Civil Hospital, Karachi were included in this study. Therefore, previously diagnosed patients of cirrhosis for more than 6 months admitted in the medical wards of Civil Hospital Karachi, Overt Renal Failure (Serum Creatinine of >7 mg/dl), Shock (BP <90/60 mmHg with Pulse rate of >100/min), Systemic inflammatory response syndrome or Sepsis (marked by two or more of the following: temperature >38 °C or <36 °C; heart rate >100 beats/min; respiratory rate of >22 breaths/min; or white blood cell count >12,000/μL or <4000/μL) were excluded from the study.

The hepatorenal syndrome is characterized by the following features in a patient who has established or clinically evident acute or chronic liver disease:[10]

- A progressive rise in serum creatinine
- An often normal urine sediment
- No or minimal proteinuria (less than 500 mg per day)
- A very low rate of sodium excretion (ie, urine sodium concentration less than 10 meq/L)
- Oliguria

All the patients of cirrhosis of liver who fulfilled selection criteria as defined above were enrolled in the study. Informed consent obtained from all the patients after explanation of the study protocol. All relevant investigations including Blood CP, Serum creatinine and urine for urinalysis sent from all the included patients. Renal Ultra sound was performed by a radiologist of Medical Unit with experience of >10 years. Patients were labeled as having hepatorenal syndrome according to 2007 IAC criteria: if creatinine was more than 1.5 mg/dl and no improvement of serum creatinine (a decrease in serum <1.5 mg/dL) after 2 days off diuretics and volume expansion with albumin (1 g/kg body weight up to a maximum of 100 g/d), absence of shock (BP >90/60 mmHg with Pulse rate of <100/min), there was no current or recent treatment with nephrotoxic drugs and Absence of signs of parenchymal renal disease (in urinary analysis: proteinuria of <500 mg/day or <50 RBC s/hpf , and normal sized kidneys >10 cm on ultrasound. All values were catered in the pre-approved *pro forma*.

The Data was collected and analyzed on software SPSS version 17.0. Descriptive statistics include mean±standard deviation (SD) of continuous data, like age, duration of cirrhosis and Serum creatinine, Frequencies and percentages were calculated from the categorical data, like gender and patients with Hepatorenal Syndrome (Outcome Variable). Chi-square's / Fisher's exact test was applied, where appropriate to check the effectiveness of age, gender and duration of illness for Hepatorenal Syndrome in Patients with Cirrhosis and *p*-value <0.05 was considered as significant.

RESULTS

The mean±SD age of patient was 48.23±7.87 years with range 18–60 years. Mean±SD duration of chronic liver disease was 5.60±1.92 years with a range of 3–12 years.

More than 155 (58%) participants in this study were male and females were 110 (41.51%). More than 36 (13%) were of age less than and equal to 40 years; 121 (45.67%) were from 41–50 years, while 108 (40.75%) were from age 51–60 years.

More than 176 (66.41%) belonged to rural areas while only 89 (33.58%) belonged to urban areas. The study observed that according to IAC 2007 criteria of diagnosis of hepatorenal syndrome 15.09% of patients with cirrhosis were found to have HRS. Stratified analysis of age showed that frequency of hrs was slightly increased with increasing age of cirrhotic patients but result was not statistically significant. (*p*-value=0.237).

Other stratified variable was gender with which it was non-significantly found that female groups 17 (15.45%) of patients were more affected of HRS than males 23 (14.84%) (*p*-value=0.445) (Table-2)

And lastly the duration of chronic liver disease was also a non-modifier and it was found that with increasing duration of illness from 4–9 years there was initially decrease than increase in frequency of HRS but the result was not statistically significant. (*p*-value=0.419) (Table-3)

Table-1: Effect of age on frequency of Hepatorenal syndrome in patients with cirrhosis

Age of Patients	Hepatorenal Syndrome		Total	*p*-value
	Yes	No		
≤40 years	2 (5.56%)	34 (94.44%)	36 (13.58%)	0.237
41–50 years	20 (16.53%)	101 (83.47%)	121 (45.66%)	
51–60 years	18 (16.67%)	90 (83.33%)	108 (40.75%)	
Total	40 (15.09%)	225 (84.91%)	265 (100%)	

Table-2: Effect of gender on frequency of Hepatorenal syndrome in patients with cirrhosis

Gender of Patients	Hepatorenal Syndrome		Total	*p*-value
	Yes	No		
Males	23 (14.84%)	132 (85.16 %)	155 (58.49%)	0.445
Females	17 (15.45%)	93 (84.55%)	110 (41.51%)	
Total	40 (15.09%)	225 (84.91%)	265 (100%)	

Table-3: Effect of duration of illness on frequency of Hepatorenal syndrome in patients with cirrhosis

Duration of illness	Hepatorenal Syndrome		Total	*p*-Value
	Yes	No		
Upto 4 years	14 (16.67%)	70 (83.33%)	84 (31.68%)	0.419
5–8 years	22 (13.84%)	137 (86.16%)	159 (60.1%)	
≥9 years	4 (18.18%)	18 (81.82%)	22 (8.31%)	
Total	40 (15.09%)	225 (84.91%)	265 (100%)	

DISCUSSION

Hepatorenal syndrome is the development of renal failure in patients with advanced liver disease. This syndrome is diagnosis of exclusion and is associated with poor prognosis as renal failure is usually irreversible.

Main aim of this study was to identify the frequency of hepatorenal syndrome in patients with cirrhosis. This was small descriptive cross sectional study in which 265 patients of cirrhosis were enrolled. Other causes of renal failure were assessed and excluded to label the patient as a case of hepatorenal syndrome, according to operational definition as described by 2007 IAC criteria.

It was observed that the mean±SD age of patients enrolled in the study was 48.23±7.87 years with range 18–60 years. Mean±SD duration of chronic liver disease was 5.60±1.92 years with a range of 3–12 years. More than 58% participants in this study were male and females were 41.51%.

The frequency of hepatorenal syndrome as observed in this study was 15.09% as compared to recent study by Planas R *et al*[12] which showed lower risk of hepatorenal syndrome, i.e., 11.4%. Till now no study has been conducted in Pakistan which is based on 2007 IAC criteria. A data from a local hospital which was according to 1996 criteria, showed prevalence of HRS to be 15%, among 240 cases studied in 6 months period.[13]

Based on 2007 IAC criteria, the prevalence of HRS was found to be much higher, i.e., 45.8% in a study conducted by Salerno F *et al*[14], but this was probably because not all cases in that study met the diagnostic criteria and HRS was presumed to be present in 35% of the cases.

In this study stratified analysis of gender revealed that HRS was predominantly observed in female patients but the result was not statistically significant. This is in contradictory to the findings of Martin[14] and Llahi[15] who found that up to 70% of the affected patients with HRS are male. Males, besides at greater risk of developing Cirrhosis and consequently HRS, differ in etiology of disease for cirrhosis being alcohol related causes in their study whereas infectious causes in ours. When data was accounted for both genders comparing etiologies, we found a greater tendency towards female instead, although not statistically significant. This was also supported by literature review as frequency of HRS is equal in both genders.[15–20] As per literature, most of the patients with cirrhosis developed in Hepatorenal syndrome in forth to eighth decade of their life.[4,14,16] It was observed in this study that frequency of HRS was increased with increasing age of cirrhotic patients but result was not statistically significant with *p*-value of 0.237.

With increasing age, deterioration in renal function is seen which may be responsible for findings of greater number of HRS patients in the later decade as compared to younger age groups. Another difficulty lies in the fact that renal dysfunction may be far worse than what is apparent in HRS due to liver failure the urea and creatinine are decreased whereas creatinine from muscle breakdown increases masking the renal status by altering creatinine's interpretation parameters.[16,17]

The duration of chronic liver disease was also found to be a non modifier variable. Though it was observed that with increasing duration of illness from 4–9 years there was initially decrease and then increase in frequency of HRS but the result was not statistically significant. Literature suggests that hepatorenal syndrome is a complication of advanced liver injury, i.e., cirrhosis, but it has also been reported in patients with acute or fulminant liver failure with ascites and portal hypertension.[18,19] Thus the duration of illness does not increase the tendency of development of HRS.

This was a small, with limited time and resources descriptive study which had main aim of assessing the magnitude of burden of HRS in cirrhosis patients which was achieved. Yet, the study had certain limitations. The onset of renal failure in cirrhosis is typically insidious but it can be precipitated by an acute insult, like bacterial infections, SBP use of diuretics etc, prevalence and affects of these variables were not observed in our study.

CONCLUSION

Hepatorenal syndrome is a type of kidney failure that affects individuals with liver cirrhosis. It represents the end stage of a sequence of reduction of renal perfusion induced by advanced liver failure and almost every seventh patient with cirrhosis of liver can develop Hepatorenal Syndrome. This is important to diagnose the disease at an early stage so that prompt treatment can be started which can help to reduce the further progression of the disease and increase the survival chances in patient with cirrhosis of liver.

AUTHORS' CONTRIBUTION

FI generated the Idea and wrote the manuscript while all other authors contributed equally.

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