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PRECIPITANTS OF HEPATORENAL SYNDROME (HRS) AND THEIR IMPACT ON HOSPITAL STAY AND MORTALITY IN PATIENTS WITH LIVER CIRRHOSIS

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BACKGROUND & OBJECTIVES:
Hepatorenal syndrome (HRS) is a functional renal failure due to intense renal vasoconstriction that frequently develops in patients with cirrhosis. It is a unique form of functional renal failure due to diminished renal blood flow, which occurs typically in kidneys that are histologically normal. Past studies reported that in almost half of the cases of HRS, one or more precipitating factors can be identified. We conducted a study to determine the Precipitating factors and outcome of hepatorenal Syndrome in liver cirrhosis**.**

MATERIALS AND METHODS:
This cross-sectional analytical study was conducted in tertiary care centre. A total of 62 consecutive patients admitted with HRS were included in this study. All adult patients admitted with diagnosis chronic liver disease with hepatorenal syndrome after applying exclusion criteria. The precipitants of HRS were correlated with the type of HRS; length of hospital stay and mortality.

RESULTS:
Among the 62 patients, 52% were alcoholics who were predominantly male and they had alcoholic cirrhosis. 21% and 16% had hepatitis B related cirrhosis and hepatitis C related cirrhosis respectively. Remaining 11% of them had non-alcoholic fatty liver disease. In our study most of the patients were of type II HRS which was around 82.3%. We have found that precipitating causes of HRS in our patients were identified as bacterial infection in 20 patients (32.2%), large volume paracentesis in 16 patients (25.8%), GI bleeding in 12 patients (19.37%), Drugs like alpha blockers, Angiotensin converting enzyme inhibitors, NSAIDS in 9 patients (14.57%) and unknown factors in 5 patients (8.06%).

CONCLUSION:
From our study spontaneous bacterial infection was the most common precipitating factor at our centre. It was concluded that there are different factors, which play a key role in precipitating HRS. Patients presenting with two or more precipitating factors and advanced grade of HE had a prolonged hospital stay and increased mortality rate.
Keywords – HRS, cirrhosis of liver, spontaneous bacterial infection

INTRODUCTION:

Hepatorenal syndrome (HRS) is a life-threatening, functional renal failure associated with advanced liver disease. A prospective study in cirrhotic patients reported an incidence of HRS 18% in first year, 39% at five years[(1)]. Hepatorenal syndrome is of two types. Type 1 HRS is an acute form, in which renal failure occurs spontaneously in patients with severe liver disease and is rapidly progressive. It often follows a precipitating event usually an infection and is associated with extremely short survival. Type 2 is characterized by moderate

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and steady renal failure that develops insidiously. It usually occurs in patients with diuretic resistant ascites[2]. Past studies indicates that HRS is present in approximately 17% of patients admitted to hospital with ascites and in >50% of cirrhotic patients suffering from liver failure[3]. The frequency of HRS in fulminant hepatic failure and severe acute alcohol-related hepatitis has been reported to be as high as 55% and 30%, respectively[4]. The prevalence of un-precipitated HRS is only 1.8% therefore the major reason behind the incidence of HRS could be the precipitating factors[5]. HRS may occur spontaneously (typically in type 2 HRS) or may be triggered by a precipitating factor (in >70% of cases of type 1 HRS) [6]. Earlier studies have demonstrated that the most common precipitating factor of HRS is spontaneous bacterial peritonitis (SBP). SBP refers to infection of ascitic fluid (typically by enteric Gram-negative bacteria) in the absence of a specific intra-abdominal source for the sepsis [7]. Follo et al, found that SBP precipitated HRS in 28% of cases despite appropriate treatment and resolution of infection [8]. The second most common precipitating factor for HRS is large volume paracentesis (LVP) without plasma expansion [9]. Cardenas et al. found that renal impairment occurred in 11% of cirrhotic patients who experienced gastrointestinal bleeding [10].Understanding the prevalence and precipitating factors of HRS can help us to provide better treatment and prevent poor prognosis. So we intended to do this study to determine precipitants of hepatorenal Syndrome (HRS) and their impact on hospital stay and mortality in patients with cirrhosis.

MATERIALS AND METHODS

This was a cross-sectional analytical study conducted at Saveetha Medical collage and hospital, Thandalam, Tamilnadu. A total of 62 adult patients who consecutively got admitted with HRS were included in this study after applying exclusion criteria. All adult patients diagnosed to have chronic liver disease with hepato renal syndrome after applying exclusion criteria. Patients with fulminant hepatic failure, suspected Acute Kidney Injury, prior history of chronic kidney disease, age < 18 years and those not willing to participate in this study were excluded.

The precipitants of HRS were correlated with the type of HRS; length of hospital stay and mortality.

A detailed clinical history of each patient was taken, regarding the present complaints and the past illnesses. The history specifically included presence or absence of gastrointestinal bleeding, fever, constipation, high protein diet, recent trauma, surgery, or abdominal paracentesis. Patients were investigated about recent intake of alcohol, sedatives, tranquilizers, analgesics, or cough syrups. The statistical analysis was done using SPSS 21

The diagnosis of liver cirrhosis was based on clinical, biochemical, ultra-sonographic, or liver histological data obtained from the in-hospital patients' data records. All patients were carefully examined with special stress on the presence of jaundice, pedal oedema, spider naevi, parotid enlargement, anaemia, ascites, flapping tremors, lower limb oedema, and gynecomastia.

Following criteria was used to diagnose hepatorenal Syndrome[11]:

(i) Cirrhosis with ascites, (ii) Serum creatinine > 133 μmol/L (1.5 mg/dL), (iii) No improvement in serum creatinine (decrease to a level of ≤ 133 μmol/L) after ≥ 2 days with diuretic withdrawal and volume expansion with albumin; the recommended dose of albumin

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is 1 g/kg of body weight/day up to a maximum of 100 g/day, (iv) Absence of shock, (v) No current or recent treatment with nephrotoxic drugs and (vi) Absence of parenchymal kidney disease as indicated by proteinuria > 500 mg/day, microscopic haematuria (>50 red blood cells per high power field), and/or abnormal renal ultrasonography.

Routine labs were carried out for each patient including liver function tests, renal function tests, complete blood count, serum electrolytes, random blood glucose, urine analysis, and the coagulation profile.

Imaging in form abdominal ultrasonography, to assess liver, kidneys, splenic size and echogenicity, and portal vein diameter were performed.

Patients were also categorised using Child- Turcotte Pugh (CTP) scoring criteria:

Parameters	Numerical score			Total Numerical score	CTP score
	1	2	3		
Ascites	None	Slight	Moderate to severe		
Encephalopathy	None	Slight	Moderate to severe		
Sr. Bilirubin (mg/dl)	<2	2-3	>3	5-6	A
Sr. Albumin (g/dl)	>3.5	2.8 -3.5	<2.8	7-9	B
Prothrombin time (sec)	1-3	4-6	>6	10-15	C

RESULTS:

Among the 62 subjects, 52% were alcoholics who were predominantly male and they had alcoholic cirrhosis. 21% and 16% were affected by hepatitis B and C respectively (Table 1). Remaining 11% of them had non-alcoholic fatty liver disease. Table 2 and 3 describes the length of the stay and mortality,

Patients with spontaneous bacterial infection and large volume paracentesis had the longest duration of stay 16 ± 2 days. Patients with GI bleed was around 12 ± 1 days. Drug induced HRS had 8 ± 2 days and unknown factors were 5 ± 2 days. (Table 2)

TABLE 1: Etiology of cirrhosis

Etiology of cirrhosis	**Total patients**	**Males**	**Females**
Ethanol	32 (52%)	30 (93.7%)	2 (6.3%)
Hepatitis B	13 (21%)	8 (61%)	5 (39%)
Hepatitis C	10 (16%)	4 (40%)	6 (60%)
NAFLD	7 (11%)	2 (29%)	5 (71%)

TABLE 2: Association of precipitants and Length of stay

PRECIPITANTS	**LENGTH OF THE STAY**
Bacterial infection (n=20)	**16 ± 2 days**
Large volume paracentesis (n=16)	**16 ± 2 days**

GI bleeding	(n=12)	**12 ±1 days**
Drugs	(n=09)	**8 ±2 days**
Unknown factors	(n=05)	**5 ± 2 days**

In our study, we found that patients with bacterial infections (11.2%) had higher mortality followed by large volume paracentesis (8.06%) , GI bleed (6.4%) and drugs (3.2%).

TABLE 3: Association of precipitants and Mortality

PRECIPITANTS		**MORTALITY RATE**
Bacterial infection	(n=20)	**11.2% (n=7)**
Large volume paracentesis	(n=16)	**8.06% (n=5)**
GI bleeding	(n=12)	**6.4% (n=4)**
Drugs	(n=09)	**3.2% (n=2)**
Unknown factors	(n=05)	**_**

Patients were admitted with various symptoms and severities of chronic liver disease. We classified them based on Child- Turcotte Pugh (CTP) scoring criteria. Most of the patients were CTP class C (n=36) which was around 58%. (Table 4)

TABLE 4: Classification based on Child- Turcotte Pugh (CTP)

CTP Class	No. of patients	Percentage
A	06	10%
B	20	32%
C	36	58%

Patients were also classified into two types based on their progression. Most of the patients in our study were of type II HRS which was around 82.3%. (Table 5)

TABLE 5: Classification of patients with type I and II HRS

Type of HRS	No. of patients	Percentage
I	11	17.7%
II	51	82.3%

We have found that precipitating causes of HRS in our subjects were identified of which 32.2% were bacterial infection in which the most common organism found in culture is Escherichia Coli, 25.8% were large volume, GI bleeding (19.37%), drugs like alpha blockers, Angiotensin converting enzyme inhibitors, NSAIDS (14.57%) and unknown factors (8.06%). (Figure 1)

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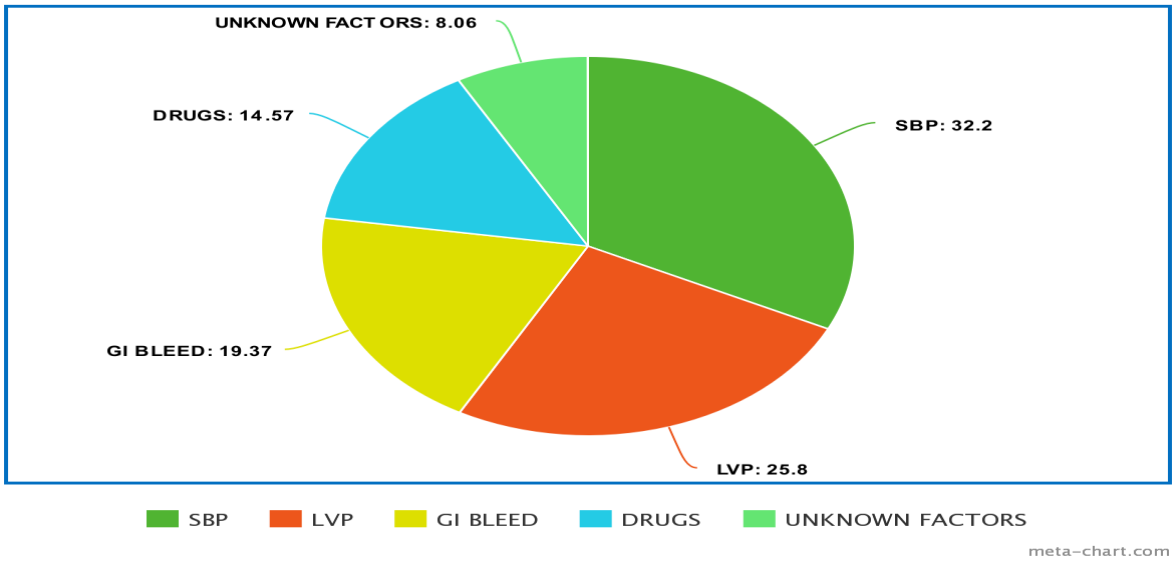
Figure 1 shows factors precipitating HRS



DISCUSSION:

HRS is a reversible functional renal impairment that occurs in patients with advanced liver cirrhosis or those with fulminant hepatic failure. It is a serious complication associated with poor prognosis.HRS is commonly noticed in patients with cirrhosis and its incidence increases with severity and duration of the cirrhotic disease. A prospective follow up study on cirrhotic subjects revealed that the incidence of HRS was 18% at 1 year and 39% at 5 years.

In our study we have found that 82.3% of our subjects had type II HRS. Garcia et.al, had reported that alcohol-related cirrhosis was the underlying etiology behind HRS which is around 57% [(12)]. Our results also support the previous findings and we have found that around 52% were suffering from alcoholic cirrhosis. 21% and 16% of our subjects were affected by hepatitis B and C respectively. Spontaneous bacterial peritonitis (SBP), large-volume paracentesis without albumin infusion, gastrointestinal bleeding, and acute alcoholic hepatitis are the identified precipitating factors so far by the past studies. We have also recognized such precipitating factor among 57 of our subjects. The patients with more than one precipitating factors had longer duration of stay in hospital than others. The length of the stay and mortality in Bacterial infection and Large volume paracentesis had the longest duration of stay 16 +/- 2 days and 12 deaths, GI bleed was around 12 +/- 1 days and 4 deaths, Drug induced HRS had 8 +/- 2 days and 2 deaths, unknown factors were 5 +/- 2 days. The total numbers of deaths were 18.

Renal failure in SBP is due to cytokine-induced augmentation of the circulatory dysfunction with further stimulation of the RAAS and SNS and worsening renal vasoconstriction. Renal vasoconstriction decreases the renal blood flow and thereby produces hepatorenal syndrome [(13)]. Gastrointestinal bleeding may induce a systemic inflammatory response associated with activation of pro inflammatory cytokines and also GI bleeding increases the susceptibility to infection. Likewise large-volume paracentesis without albumin expansion precipitates type 1 HRS in 15% of cases, and 25% of patients who present with acute alcoholic hepatitis eventually develop HRS.

Gines et.al, observed approximately 30% of patients with SBP develops HRS [14].We have found that precipitating causes of HRS in our subjects were identified as bacterial infection in 20 patients (32.2%), large volume paracentesis without albumin in 16 patients (25.8%), GI bleeding in 12 patients (19.37%), Drugs like alpha blockers, Angiotensin converting enzyme inhibitors, NSAIDS in 9 patients (14.57%) and unknown factors in 5 patients (8.06%).
Patients with type I HRS should be managed in an intensive care unit due to multi organ failure and rapid deterioration. Type 2 HRS patients can be managed on an outpatient basis or in a non–intensive care setting. There are more strategies developing in respect to prevention and postponing of HRS in cirrhotic subjects. The utmost aim of the clinician is to identify the precipitating factors and treating it. Since the most frequent precipitating factor is spontaneous bacterial peritonitis, prophylactic antibiotics should be given to prevent bacterial translocation. This helps in the suppression of pro-inflammatory cytokine formation implicated in the SBP pathogenesis and prevent HRS [15]. Albumin is the most abundant circulating protein produced by the liver. It has an excellent oncotic property. Patients with liver disease have decreased albumin level in their serum. So, large-volume paracentesis (more than 5 L) should be followed by 8 g of albumin infusion for each litre of ascitic fluid removed and diuretics should be stopped in those subjects. Care should be given to malnourished patients and salt restricted diet should be given to prevent the drastic changes. Understanding the pathophysiology and precipitating factors of HRS can help us to treat efficiently and prevent mortality.

CONCLUSION:

The results of this study highlight the importance of precipitating factors in HRS. Our results also describe a strong association between HRS and alcohol-induced liver disease, a finding that could provide insights into the pathogenesis of HRS. Spontaneous bacterial peritonitis present in almost 32% of our subjects as precipitating factor. The patients with more than one precipitating factors had longer duration of stay in hospital than others and higher mortality. So therapeutic interventions should be made to prevent or reverse hepatorenal syndrome in cirrhotic patients.

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