Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 7, Issue, 04, pp.15096-15110, April, 2015

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

ISSN: 0975-833X

RESEARCH ARTICLE

A STUDY OF ACUTE RENAL FAILURE IN PATIENTS WITH CIRRHOSIS OF LIVER FOR EVALUATION OF CAUSES,TREATMENT AND PROGNOSIS: A PROSPECTO-RETROSPECTIVE STUDY

***K.C. Das, Sumeet David, Pardeep Kumar, Rohit Ronald and Rohit Massy**

Department of Gastroenterology and Hepatology, Christian Medical College and Hospital, Ludhian-141008, Punjab, India

ARTICLE INFO

Article History:
Received 10th January, 2015
Received in revised form
14th February, 2015
Accepted 23rd March, 2015
Published online 30th April, 2015

Key words:

Advanced stage of liver disease,
ARF,
HRS,
Outcome.

ABSTRACT

Context: Patients with advanced cirrhosis commonly have reduced renal function. Renal failure is frequently related to cirrhosis and renal function is often compromised as a secondary consequence of heaptic failure, independent of etiology of cirrhosis, which is called the functional renal failure or hepatorenalsyndrome (HRS).

Aims: To evaluate the causes of ARF in patients with cirrhosis of liver of any etiology and to study the outcome of treatment and prognosis of ARF in patients with cirrhosis of liver of any etiology.

Setting and design: Hospital based prospecto-retrospective study, an evaluation of the causes (types) of acute renal failure in patients with cirrhosis, treatment of acute renal failure and its prognosis was done.

Materials and Methods: The patients were selected from the gastroenterology and Nephrology unit Christian Medical College & Hospital, Ludhiana. It included all patients admitted in wards who were diagnosed to have cirrhosis of any etiology complicated by renal insufficiency. A total of 131patients were included, 61 prospective and 70 retrospective.

Results: Out of 131 patients, 51 (38.93%) had pre-renal ARF, 20 in the prospective group, and 31 in the retrospective group. The average age of patients in the study was 49.87+/-10.10 years. The mortality rate was maximum in the age group of 40 to 49 years. HRS was diagnosed in 44 patients (33.54%),of whom, 30 had HRS type1 and 14 had HRS type 2. ATN was seen in 36 patients (27.48%). FENa was found to be a good predictor of pre-renal ARF and ATN, however, it was not found to be very useful as a predictor of HRS in this study. Haemodialysis was done on 36 patients. Only 38 of the 131 patients had an improvement in the renal function. Of these, 25 had pre-renal ARF, 11 had HRS type2, one had HRS type1 and another one had ATN. In 43 patients, ARF was associated with upper gastrointestinal haemorrhage, of which 29 (67.44%) died.

Conclusion: About 35% of these patients have HRS, 40% have prerenal ARF and 25% have acute tubular nercrosis. An intravascular volume expansion should be given to all patients of ARF with cirrhosis except to those with fluid overload. Reversal of HRS is seen in a high proporation of patients treated with Terliperssin. There is a high mortality associated with these patients, especially so with HRS type1 and ATN.

INTRODUCTION

Patients with advanced cirrhosis commonly have reduced renal function and in terminal stages of the disease, about 75% develop oligoanuric renal failure (Shear *et al*., 1965). Renal failure is frequently causally related to cirrhosis and renal function is often compromised as a secondary consequence of heaptic failure, independent of etiology of cirrhosis, which is called the functional renal failure or hepatorenalsyndrome (HRS). These patients can also have prerenal acute renal failure (ARF), especially those with gastrointestinal hemorrhage, or those on high doses of diuretics. HRS and prerenal ARF can involve into ATN if renal perfusion is compromised for a significant duration. Treatment of ARF in cirrhosis should primarily be aimed at reversing life-threatening conditions, like shock, hyperkalemia, severe metabolic acidosis and fluid overload. The only effective treatment of HRS is liver transplantation. Treatment options for prolonging life span of patients with HRS, awaiting liver transplantation or in patients, in whom liver transplant is not feasible, are selective splanchnic vasoconstrictors, like Terlipressin, combined with iv albumin and or transjugular intrahepatic portosystemic shunts (TIPSS), or MARS. Prognosis in patients of acute renal failure with cirrhosis is very high mortality for HRS type is apprcximately 95%,and median survival after diagnosis is less than two weeks.

****Corresponding author: K.C. Das,***
Department of Gastroenterology and Hepatology, Christian Medical College and Hospital, Ludhian-141008, Punjab, India.

REVIEW OF LITERATURE

Patients with advanced cirrhosis commonly have reduced renal function and in terminal stages of their disease, about 75% develop oilgoanuric renal failure This secondary compromise of renal function has a complex pathophysiological background with at least three different components

Table 1. Pathomechanism of secondary renal dysfunction in cirrhosis

1. Diminished renal perfusion Secondary to reduced effective circulating volume. Secondary to renal vasoconstriction.
2. Enhanced sodium re-absorption Secondary to diminished renal perfusion Independent of renal perfusion
3. Impairment of tubular function and structure Secondary to serve impairment of renal perfusion(ischemia) Secondary to nephrotoxic agents (e.g. aminoglycoside antibiotics, contrast media, non steroidal anti-inflammatory drugs), endotoxin or a systemic inflammatory response. Secondary to substances accumulating in cirrhosis (bile acids, bilirubin).

Depending upon which of these functional abnormalities predominate and serverity of the derangement, the clinical manifestations range from clinically in apparent renal hypo-perfusion to different forms of acute renal failure including pre-renal failure, acute tubular necrosis and hepatorenal syndrome (Eckardt KU,1999).

Types of acute renal failure in cirrhosis

Not many studies have been reported on classification of acute renal failure in cirrhosis. Shear *et al.* (1965) did a prospective study on 15 patients with cirrhosis and renal dysfunction. They found that the patients could be separated into three groups.

Group 1– This group included 8 patients and in these, renal failure was indistinguishable from acute tubular necrosis were noted in six of the eight patients and these were severe hypotention, convulsions and nepphrotoxic drugs.

Group 2 – This group included 2 patients in whom etiology of renal failure was other than ATN. These 2patients had normal urinary sediments, specific gravity>1.020, low urinary sodium concentrations and a high urine versus plasma creatinine ratio. Renal failure in one was followed by a episode of acute CCF and other was followed by dehydration as revealed by hypotension and increased serum osmolality and hypernatremia.

Group 3- This group included 5 patients, in whom, clinical and laboratory investigations permited exclusion of group 1 and group 2. Three of these five patients had renal failure following an acute illness or therapeutic manipulation, one following excessive gastrontestinal losses, and the other after two weeks of starting diuretics.

Pre-renal Failure

The transition from clinical in apparent renal hypo-perfusion to overt and frequently progressive impairment of kidney function can be triggered by a variety of clinical events and complications. Any cause of an incremental intra vascular hypovolemia such as gastrointestinal bleeding, diarrhoea, vomiting, increased ascites formation, or reduced sodium intake can aggravate renal hypoperfusion sufficiently to cause oliguria and renal failure. Iatrogenic events are also frequently responsible for volume contraction, such as, when intensive diuretic therapy induces a diuresis that exceeds the rate of ascites mobilization (*Sherlock et al,* 1966), when volume depletion develops secondary to lactulose therapy or when paracentesis is performed without intra vascular volume replacement. This results in an increased susceptibility of patients to the development of prerenal failure, a functional impairment of kidney function, which by definition is reversible after restoration of renal perfusion.

Table 2. Different diagnosis of renal failure in advance cirrhosis

	Pre renal failure	Acute tubular necrosis	Hepatorenal syndrome	Primary nephropathy
Urine sodium urine- to- plasma	<10mmol/l	>30mmol/l	< 10mmol/l	>30mmol/
Creatinine ratio	>30:1	<20:1	>30:1	<20:1
Proteinuria	-	(+)	(+)	+/+++
Urine sediment	Normal	Casts. Debris	Unremarkable	Variable
Ultrasound resitive index	Elevated resitive index	Elevated resitive index	Elevated resitive index	Elevated
History & coarse volume Contraction agents, septicemia	Precipating concentration, nephrotoxic ascities	Volume cirhosis usually tense	Advanced renal functional impairment	Longstanding
Effect of volume Expansion	Return of renal function	-	-	-

Different diagnosis of renal failure in advance cirrhosis

Hepatorenal Syndrome (HRS)

The term heapatorenal syndrome implies that the pathophysiology of this form of renal failure is different from other types of renal failure and is more specific for the association with advanced cirrhosis. Extreme renal

vasoconstriction is considered the most important characteristic of HRS (Kew *et al.,* 1971; Epstein, 1994). In cirrhosis portal hypertension with portosystemic shunts and splanchnic dilatation leads to development of hyperdynamic circulation (Groszman, 1994) with attendant systemic arterial vasodilation and effective arterial underfilling and hence renal hypoerfusion (Bataller *et al*.,1998).

Although spontaneous recovery occurs only rarely (Goldstein *et al.,* 1965), HRS is nevertheless a functional and also a principally reversible from of renal failure. As in pre-renal failure, intact tubular function is reflected by typically highly concentrated urine with low sodium concentration (<10mmol). Most investigators believe that HRS can evolve into ATN (Epstenin, 1994). The respective mediators of these systems, norepinephrine and angiotensin II, are potent renal vasoconstrictors. So, they contribute to renal hypoperfusion and the resulating glomerular hypofiltration. The finding that vasodilation in the splanchnic vascular bed leads to vasoconstriction in the renal circulation is the rationale for using a splanchnic vasoconstrictor in the treatment of renal failure in patients with HRS.

In patients with cirrhosis and ascites, serum concentrations of nitrite and nitrate [products that indicate nitric oxide (NO) oxidation] have been shown to be higher in those patients with HRS than in those without (Guarner *et al.,*1993). This suggests that the patients with HRS have a marked increase in the endogenous NO production. As NO is a potent endothelium-derived relaxing factor, (Sogni *et al.,* 1995) marked vasodilation in patients with HRS may be due to an overproduction of NO by the endothelium in splanchnic arterial walls.

In one study in patients with HRS, plasma endothelin-I concentrations were significantly higher in the renal vein than in the renal artery, suggesting an overproduction of endothenin-I (Moore *et al.,*1992) (or a decrease in the plasma clearance of endothelin-I) in the kidneys of these patients. In patients with ascites, the urinary excretion of vasodilator prostaglandins (PG). Such as PGE2 and 6-keto-PGE1a (a stable metabolite of the vasodilator PGI2) has been shown to be lower in patients with HRS than in without (Bataller *et al.,*1997). Interestingly the urinary excretion of vasoconstrictor PG, such as thromboxane B2 was lower in patients with HRS than in non-azotemic cirrhotic patients with ascites. Finally, the inhibition of PG synthesis following the administration of non-steroidal anti-inflammatory drugs is known to induce a marked decrease in GFR in non-azotemic cirrhotic patients with ascites (Bataller *et al.,* 1997).

The most recent definition of HRS proposed by the international Ascites Club in 1996, (Table 3) - (Arroyo *et al.,* 1996) as compared to a previous consensus statement that was formulated in Sassari in 1978 (Early *et al.,* 1979).

*Corresponding author *K.C. DAS, Associate professor and Head Department of Gastroenterology and Hepatology, Christian Medical College and Hospital, Ludhiana, Punjab,141008, India.*

AIMS AND OBJECTIVIES

To evaluate the causes of ARF in patients with cirrhosis of liver of any etiology and to study the outcome of treatment and prognosis of ARF in patients with cirrhosis of liver of any etiology.

MATERIALS AND METHODS

This study was conducted in the Department of Gastroenterology and Nephrology, Christian Medical College & Hospital, Ludhiana. It was a study of four and a half years duration (18 months) retrospective study from 1st November 2013- 31st May 2014, and 36 months retrospective study from 1st November 2009 – 31st May 2011. It included all patients admitted in wards who were diagnosed to have cirrhosis complicated by ARF. A total of 131patients were included, 61 prospective and 70 retrospective.

Inclusion criteria

All adult patients admitted with evidence of cirrhosis of liver of any etiology and acute renal insufficiency.

Exclusion criteria

1. Patients having pre-existing renal disease, either historical or in the form of biochemical derangement of renal function or sonographical evidence of chronic parenchymal renal disease.
2. Patients having evidence of obstructive uropathy / nephropathy.
3. Patients with acute or chronic liver disease other than liver cirrhosis.

The diagnosis of cirrhosis of liver was regarded as confirmed, if the findings were based on histology, diagnosis of oesophageal varices or ascites on combination with the characteristic findings on ultrasound (coarse nodular liver, splenomegaly, increased caliber of splenic and portal veins, increased velocity of portal blood flow and collaterals at the splenic hilum), after exclusion of portal or hepatic vein occlusion as a cause for the portal hypertension by Doppler ultrasonic examination. Grading of cirrhosis was done according to the child Pugh criteria. Liver biopsy was considered only in a select group of patients, where it was clinically indicated and feasible.

Table 3. Child Pugh classification of cirrhosis

Factor	1	2	
Serum bilirubin, mg/dl	<2.0	2.0 – 3.0	>3.0
Serum albumin g/dl	<3.5	3.0 – 3.5	<3.0
Ascites	None	Easy controlled	Poorly controlled
Neurological disorder	None	Minimal	Advanced coma
Prothrombrin time (second prolonged)	0 – 4	4 – 6	>6
INR	<1.7	1.7 – 2.3	>2.3

The child Pugh score was calculated by adding scores of these five factors to get a range, from 5 to 15. The grades were given

according to the range, Grade A- 5 to 6, Grade B- 7 to 9 and Grade C- 10 and above.

The diagnosis of acute renal failure was made as per the following criteria –

Baseline serum creatinine of >1.5 mg %, or a rise in the serum creatinine of more than 30% of baseline.

In order to distinguish between main causes of ARF in patients with cirrhosis, viz, hepatorenal syndrome, Pre-renal failure and acute tubular necrosis, clinical examination and the following urinary indices were looked at:

Table 4.

	Hepatorenal syndrome	Pre- renal ARF	Acute Tubular necrosis
1. Spot urine sodium concentration	<10meq/l or <20meq/l on diuretics	< 10meq/l	> 30meq/l
2. Urine to plasma creatinine ratio	> 30:1	> 30:1	<20:1
3. Fractional excretion of sodium	< 1	< 1	> 1

Criteria for diagnosing HRS (International ascites Club, 1996)

Major criteria

1. Chronic or acute liver disease with advanced hepatic failure and portal hypertension.
2. Low glomerular filtration rate, as indicated by serum creatinine > 1.5mg/ dl or creatinine clearance, 40ml/minute.
3. Absence of treatment with nephrotoxic drugs, shock, infection or significant fluid loss.
4. No sustained improvement in renal function after diuretic withdrawal and plasma volume expansion with 1.5 liters of isotonic saline.
5. Proteinuria, 500 mg / dl, no ultrasonic evidence of renal tract obstruction and renal disease.

Additional criteria

1.Urine volume<500 ml/ day
2.Urine sodium <10 meq /day
3.Urine osmolality greater than plasma osmolality
4.Urine red blood cells than 50 per high powered field.
5.Serum sodium concentration <130 meq / liter.

For the purpose of this study, HRS was diagnosed in patient if major criteria number 1 to 4, as well as either proteinuria and normal ultrasound or, if one of these tests were not performed, three of the five additional criteria were met. In the retrospective study, patient's records were assessed, ARF categorized, investigations done, and the treatment given and the outcome were noted. In the prospective study, patients were assessed according to the protocol and guidelines. The patient's work up included a detailed history with complete general, physical and systemic examination. The investigations included hemogram, liver function tests, renal function tests, urine routine examination, urine osmolality, urine (calculated), ultrasound abdomen, upper gastrointestinal endoscopy and ascitic fluid examination, wherever indicated. Once the diagnosis of ARF was confirmed, after noting the central venous pressure, plasma volume expansion was done if required; by giving the patients 1.5 liter of normal saline, and the effect on urine output and renal function tests was noted. If no improvement was seen and urine Na was less than 10meq/L, a diagnosis of HRS was presumed and the patients were given injection Terlipressin 0.5mg to 1mg 8 hourly, along with 20% salt free human albumin solution (100ml per day). The dose of terlipressin was increased in a stepwise fashion according to the response, as required. Renal support in the form of hemodialysis was provided when indicated. Treatment with portosystemic shunts was not considered. Patients were evaluated clinically everyday and renal function tests and liver function tests were done every alternate day and once a week respectively. Improvement in terms of liver functions and renal parameters was noted and the outcome of hospitalization was noted as improved/discharged or expired.

Data analysis

Statistical analysis of the collected data was done using Student's t-test and Z-test.

RESULTS AND DISCUSSION

In this study, an evaluation of the causes (types) of acute renal failure in patients with cirrhosis, treatment of acute renal failure and its prognosis was done.

The average age of patients in this study was 49.87+10.10 years (Table 5).

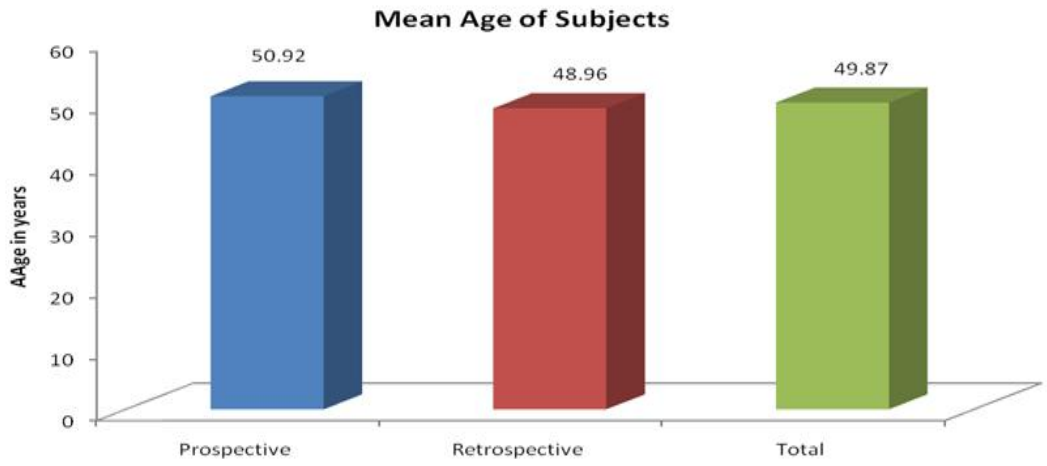
Table 5. Age Distribution

Age (in years)	Prospective (n 61)	Retrospective (n 70)	Total (n 131)
25 – 39	6 (9.84%)	14 (20.00)	20 (15.27)
40 – 49	8 (29.51%)	21 (30.00)	39 (29.77)
50 – 59	26 (42.62%)	24 (34.29)	50 (38.17)
60 – 69	9(14.75%)	6 (8.57)	15 (11.45)
70 – 79	2 (3.28%)	5 (7.14)	7 (5.34)
Mean + SD	50.92 + 8.76	48.96 + 11.11	49.87 + 10.10

The morality of patients in relation to age in cirrhosis complicated by acute renal failure is shown in Table – 6. This was worst in the age group 40 – 49 years.

Table 6. Age in Relation to Mortality

Age	Prospective			Retrospective			Total		
(in years)	n	M	M%	n	M	M%	n	M	M%
<40	5	6	83.3	9	14	53.57	14	20	70.00
40 – 49	16	19	3	1	20	75.00	31	39	79.48
50 – 59	13	23	84.2	5	27	66.66	31	50	62.00
< 60	8	13	1	1	10	70.00	15	23	65.21
			5.52	8					
			61.5	7					
P value	>0.10			>0.10			<0.05		



The commonest cause of cirrhosis in the present study was alcoholic liver disease, which was present in 87% patients, only 5.3% patients had HCV/HBV related etiology, and in 7.63% patients the etiology of cirrhosis remained indeterminate (Table 7).

Table 7. Cause of Cirrhosis

Cirrhosis	Prospective	Retrospective	Total
Alcoholic HCV/HBV related Unknown	51 5 5	63 2 5	114(87.02%) 7(5.34%) 10(7.63%)
P value	<.001	<.001	<.001

Alcoholic cirrhosis is predominantly a disease of males and is seen very infrequently in females (Table 8).

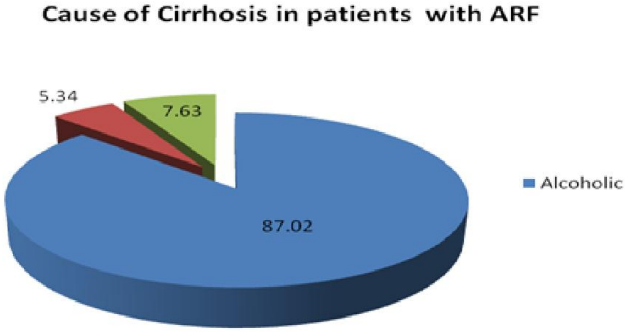


Table 8. Sex Distribution

Sex	Prospective	Retrospective	Total
Male Female	54 (88.52%) 6 (11.48%)	69 (98.57%) 1 (1.43)	123 (93.89%) 7 (6.11%)
P value	<.001	<.001	<.001

In the presents tudy, 71(54.19%) patients had hepatic encephalopathy and 60 (45.80%) patients had normal sensorium. In cirrhosis patients with ARF hepatic encephalopathy did not influence mortality (Table 9).

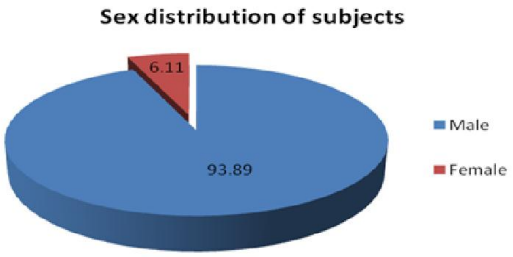
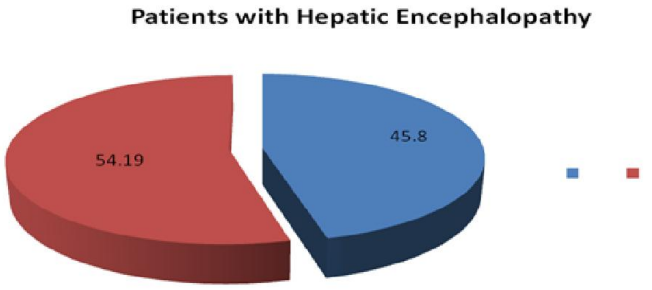


Table 9. Sensorium

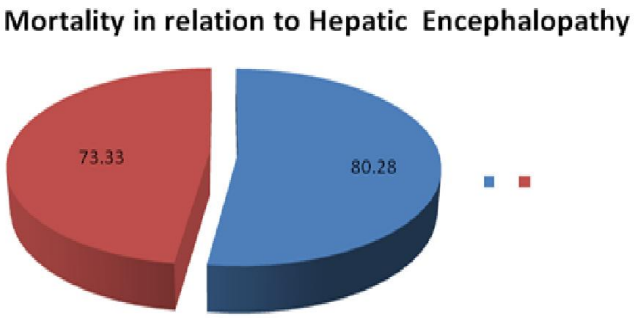
Sensorium	Prospective	Retrospective	Total
Conscious Oriented Hepatic Encephalopathy	26/61 (42.63%) 35/61(57.37%)	34/70(38.58%) 36/70(51.42%)	60/131(45.80%) 71/131(54.19%)
P value	>0.10	>0.10	>0.10



In patients with cirrhosis, complicated by ARF, hepatic encephalopathy did not independently influence the mortality, the difference inmortaility inthose with hepatic encephalopathy, compared to those without hepatic encephalopathy was not found to be statically significant (p value>0.10) (Table 10).

Table 10. Mortality in relation to Hepatic Encephalopathy

Hepatic Encephalopathy	Prospective			Retrospective			Total		
	n	M	M%	n	M	M%	n	M	M%
Present	35	28	80.00	36	29	80.55	71	57	80.28
Not Present	26	20	76.92	34	24	70.55	60	44	73.33
P value	> 0.10			> 0.10			> 0.10		



A large number of patients had hyponatreamia (54.96%). However, this did not alter the outcome in terms of mortality, which was nearly the same in those with or without hyponatraemia (Table 11, 12)

Table 11. Serum Sodium (Na)

Na	Prospective	Retrospective	Total
< 134	39 (63.93%)	34(48.57%)	72(54.96%)
134-140	18(29.51%)	28(40.00%)	46(35.11%)
>140	4 (6.56%)	8(11.43%)	12(9.16%)
Mean ± SD	131.08 ± 7.29	133.30± 6.44	132.20± 6.91
P value	<0.01	<0.05	<0.01

Table 12. Mortality in relation to Serum Sodium

Na	Prospective	Retrospective	Total
< 134	29/39 (74.36%)	20/34(58.82%)	49/73(67.12%)
134-140	11/18(61.11%)	26/28(92.86%)	37/46(80.43%)
>140	2/4 (50.00%)	7/8(87.50%)	9/12 (75.00%)
P value	>0.10 NS	<0.01	>0.10NS

Most of the patients had normal levels of serum potassium and hypokalemia or hyperkalemia did not significantly influence mortality (Table 13,14)

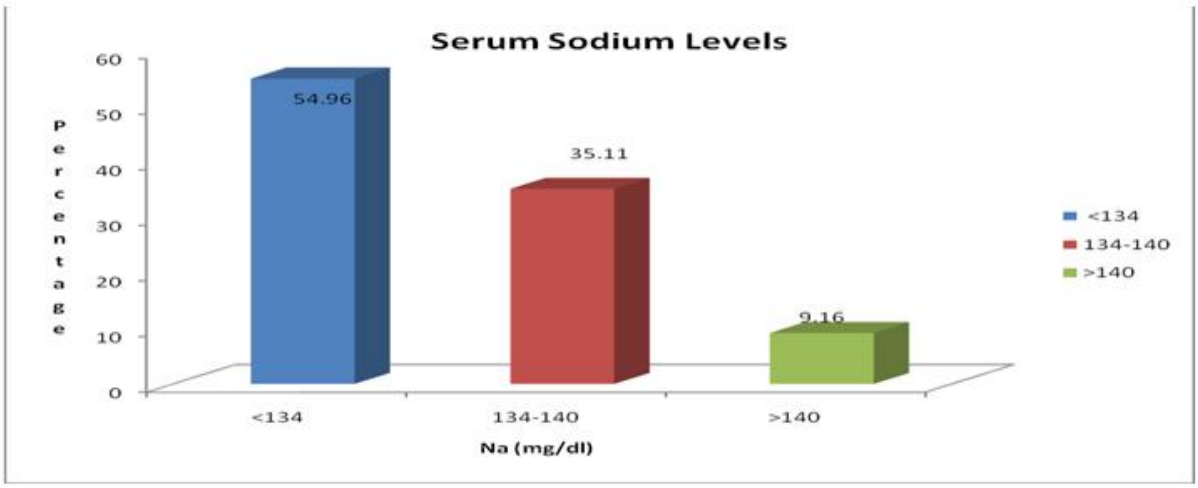
Table 13. Serum Potassium (K)

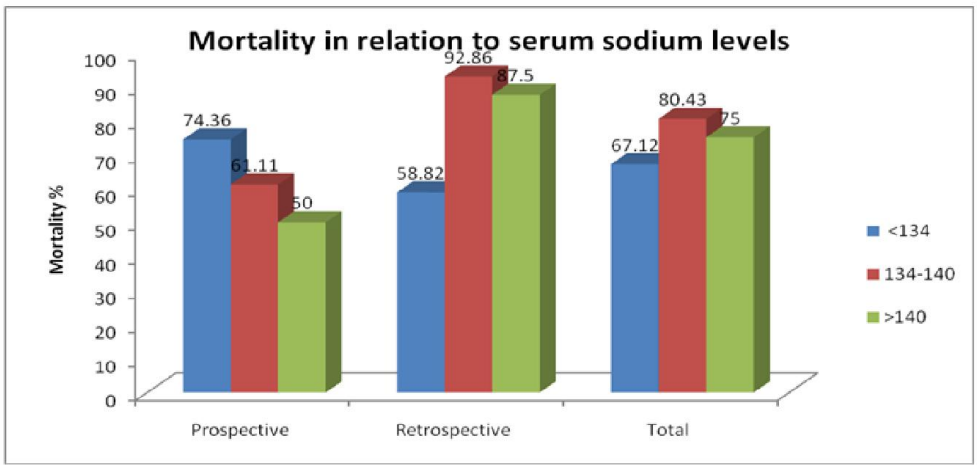
K	Prospective	Retrospective	Total
< 3.5	11 (18.03%)	12 (17.14%)	23 (17.56%)
3.5 -5.5	39 (63.94%)	51 (72.86%)	90 (68.70%)
> 5.5	11 (18.03%)	7 (10.00%)	18 (13.74%)
Mean ± SD	4.6 ± 1.2	4.3± 0.9	4.5± 1.1
P value	<0.01	<0.01	<0.01

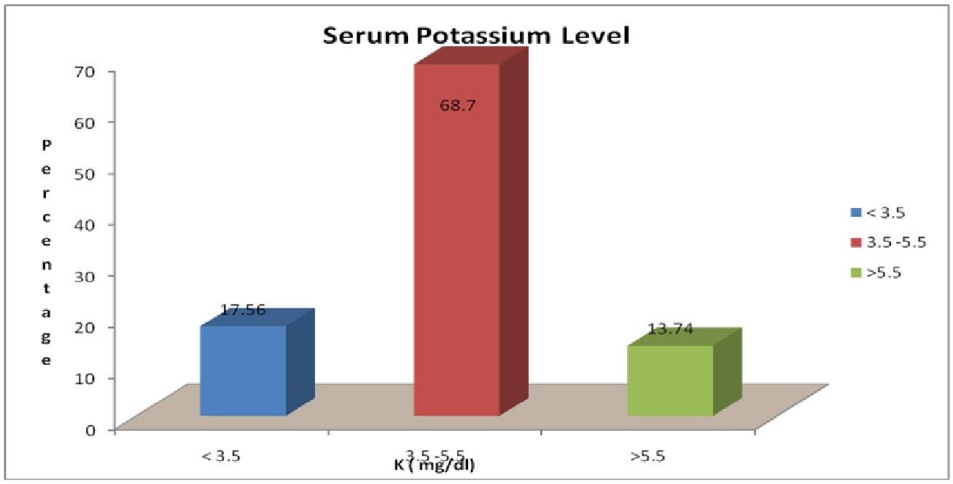
Table 14. Mortality in relation to Serum Potassium

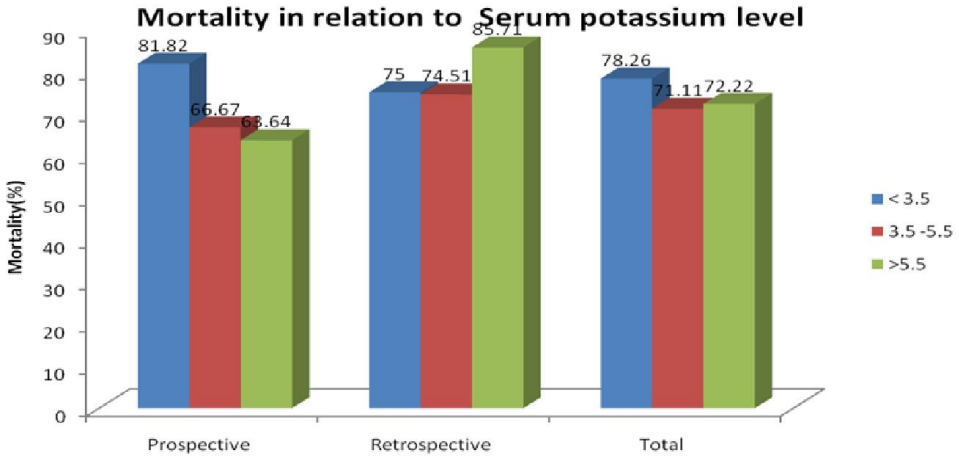
Serum potassium (mg/dl)	Prospective	Retrospective	Total
< 3.5	9/11 (81.82%)	9/12 (75.00%)	18/23 (78.26%)
3.5 -5.5	26/39 (66.67%)	38/51 (74.51%)	64/90 (71.11%)
> 5.5	7/11 (63.64%)	6/7 (85.71%)	13/18 (72.22%)
P value	>0.01	>0.10	>0.10

There were 16.7% patients with child's B cirrhosis and 83.2% patients with child's C cirrhosis in the study. The mortality was significantly higher in patients with child's C cirrhosis and this was found to be statistically significant (p <0.01) Table 15).




Mortality in relation to serum sodium levels
Mortality %
100
90
80
70
60
50
40
30
20
10
0
74.36
61.11
50
58.82
92.86
87.5
67.12
80.43
75
Prospective
Retrospective
Total
<134
134-140
>140


Serum Potassium Level
Percentage
70
60
50
40
30
20
10
0
17.56
68.7
13.74
< 3.5
3.5 -5.5
>5.5
K (mg/dl)
< 3.5
3.5 -5.5
>5.5


Mortality in relation to Serum potassium level
Mortality(%)
90
80
70
60
50
40
30
20
10
0
81.82
66.67
63.64
75
74.51
85.71
78.26
71.11
72.22
Prospective
Retrospective
Total
< 3.5
3.5 -5.5
>5.5

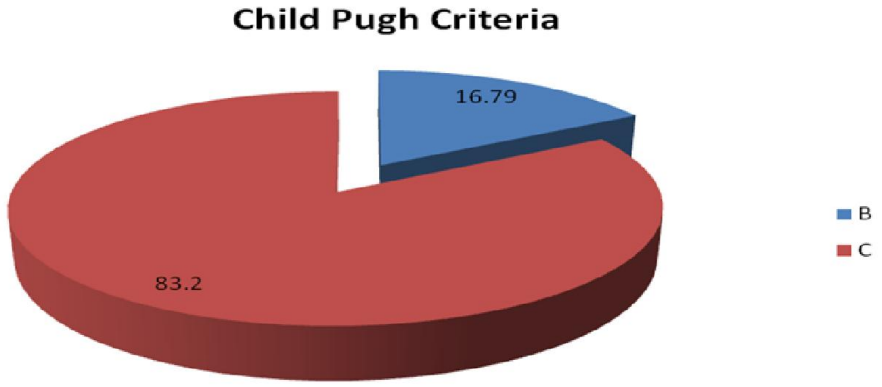

Child Pugh Criteria
16.79
83.2
B
C

Table 15. Child Pugh Criteria

Child Pugh Criteria	Prospective	Retrospective	Total
B C	13 (21.31%) 48 (78.68%)	9 (12.85%) 61 (88.57%)	22 (16.79%) 109 (83.20%)
P value	<0.01	<0.01	<0.01

Table 16. Mortality in relation to Child Pugh grade of Cirrhosis

Child Pugh grade	Prospective			Retrospective			Total		
	n	M	M%	n	M	M%	n	M	M%
B C	13 48	4 38	30.76 79.16	9 16	5 48	55.55 78.68	22 109	9 86	40.90 78.89
P value	< 0.01			<0.01			< 0.01		

Patients INR less than 1.7 had a mortality of 53.84% whereas INR in excess of 1.7 was associated with a mortality of 90.24%. INR in excess of 1.7 was found to significantly influence mortality in patients with ARF with cirrhosis (Table 17).

Table 17. Mortality in relation to INR

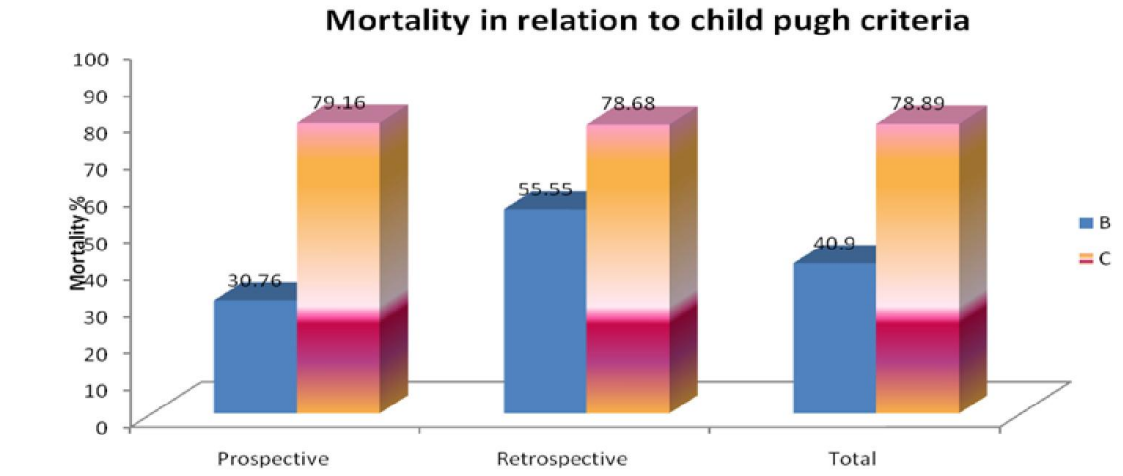
INR	Prospective	Retrospective	Total
< 1.7 >1.7	7/18 (38.89% 35/43 (81.40%)	14/21 (66.66%) 29/39 (74.35%)	21 /39 (53.84%) 74/82 (90.24%)
P value	<0.01	<0.05	<0.01

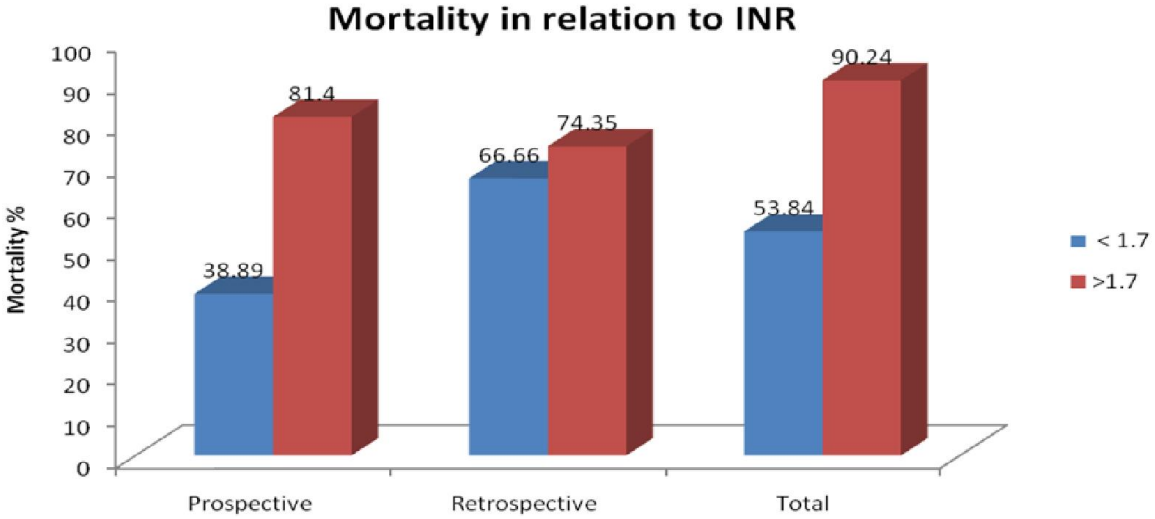
Severe jaundice was associated with higher mortality. Patients with total billirubin in excess of 17 mg/dl, had 98.04% mortality, while those with total billirubin less than 17mg/dl had a mortality of 56.25%. This difference was found to be statistically significant (p <0.01), (Table 18).

Table 18. Mortality in relation to Total Billirubin

INR	Prospective	Retrospective	Total
< 1.7 >1.7	7/18 (38.89% 35/43 (81.40%)	14/21 (66.66%) 29/39 (74.35%)	21 /39 (53.84%) 74/82 (90.24%)
P value	<0.01	<0.05	<0.01

In the present study, 67.44% patients who had ARF associated with gastrointestinal haemorrhage died and 62.50% patients who had ARF along with spontaneous bacterial peritonitis died (Table 19).





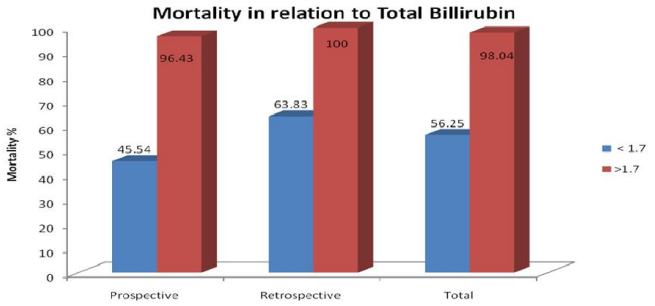
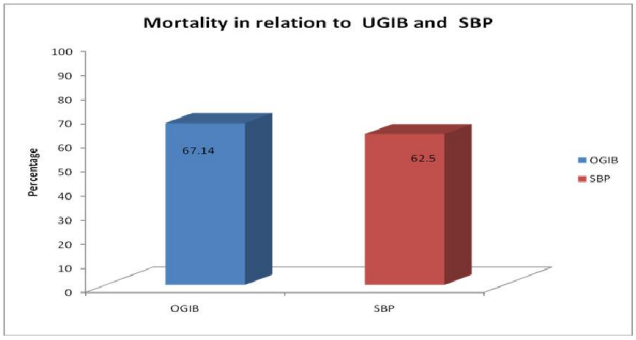


Table 19. Mortality in relation to Associated Features

Associated Features	Prospective			Retrospective			Total		
	n	M	M%	n	M	M%	n	M	M%
UGIB	21	14	66.67	22	15	68.18	43	29	67.44
SBP	13	8	61.54	11	7	63.67	24	15	62.50
P value	< 0.01			<0.01			< 0.01		



Fractional excretion of sodium of sodium (FENa) was performed in 70 patients. Of these, 26 patients were diagnosed to have HRS, 17 had ATN and 27 had prerenal ARF. Since the time of collection of urine samples was often not standardized, and the fact that urinary electrolytes can be confounded by the prior us of diuretics, in this study in patient with HRS, the use of urinary electrolytes as predictor of type of ARF was not found to be useful. However, in those with ATN and prerenal ARF, urinary electrolytes was a good indicator of the type of ARF, this being statistically significant (Table 20, 21).

Table 20. FENa

FENa	Prospective	Retrospective	Total
< 1	13	17	30
>1	21	19	40
P value	>0.10	>0.10	>0.10

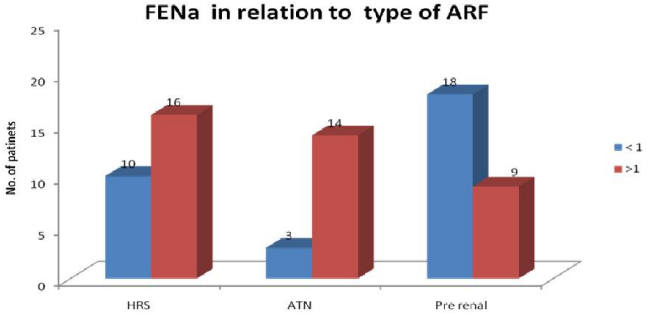


Table 21. Types of ARF in relation to FENa

FENa	HRS	ATN	Pre renal	Total
Prospective				
< 1	7	0	6	13
>1	12	3	5	21
P value	>0.10	>0.10	> 0.10	
Retrospective				
< 1	3	3	12	17
>1	4	11	4	19
P value	>0.10	<0.05	<0.01	
Total				
< 1	10	3	18	30
>1	16	14	9	40
P value	>0.10	<0.05	<0.01	

In this study, HRS 1 was seen in 18 patients in the prospective group and 12 patients in the retrospective group. HRS 2 was seen in 9 patients in the prospective group and 5 patients in the retrospective group. ATN was the cause of ARF in14 patients in the prospective group and in 22 patients in the retrospective group. Prerenal ARF was seen in 20 patients in the prospective group and 30 patients in the retrospective group (Table 22).

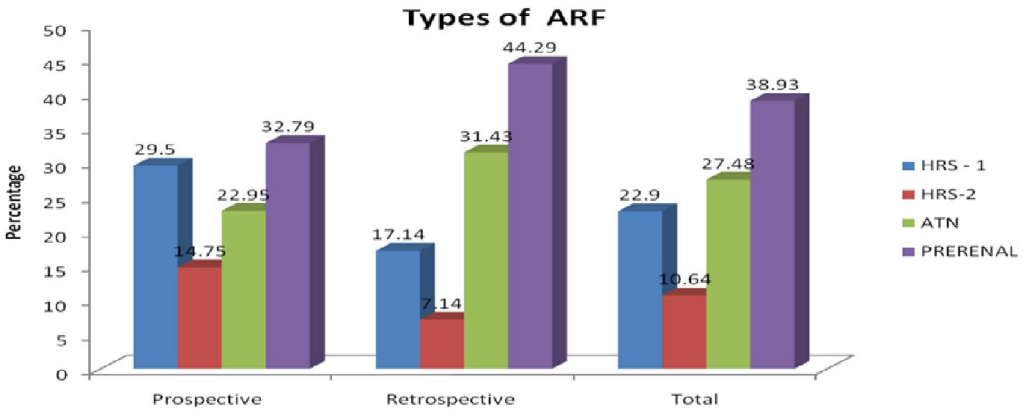
Table 22. Cause of ARF

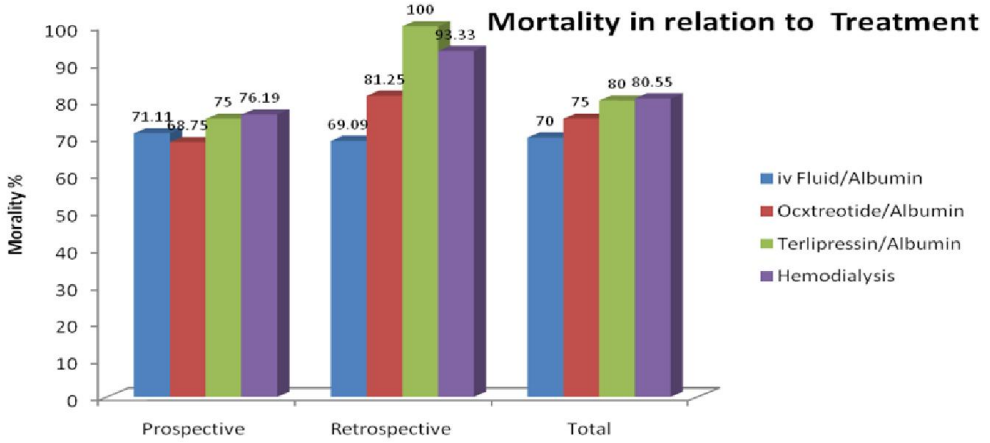
Cause of ARF	Prospective	Retrospective	Total
HRS – 1	18 (29.50%)	12 (17.14%)	30 (22.90%)
HRS - 2	9 (14.75%)	5 (7.14%)	14 (10.64%)
ATN	14 (22.95%)	22 (31.43%)	36 (27.48%)
Prerenal	20 (32.79%)	31 (44.29%)	51 (38.93%)
P value	<0.05	<0.05	< 0.05

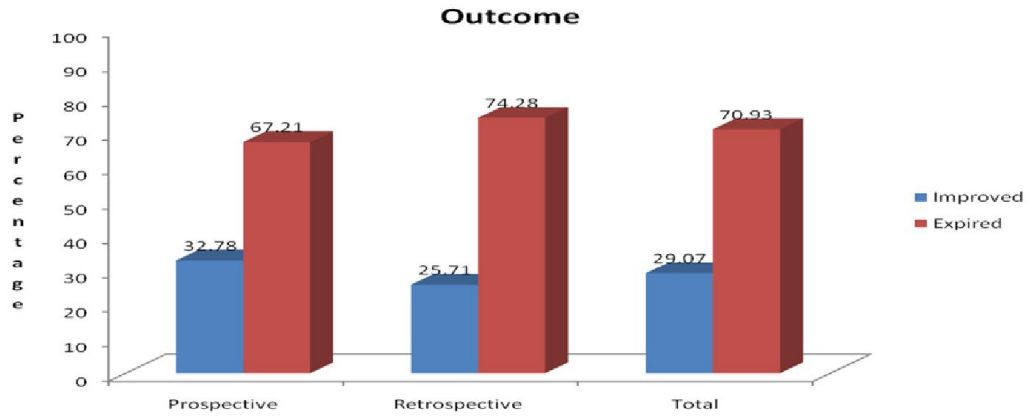
Plasma volume expansion was given to all patients except in those with clinical evidence of fluid overload. A total of 100 patients were given volume expansion, 45 in the prospective group and 55 in the retrospective group. An improvement was seen in renal functions in 30 patients. Octreotide with albumin was given to 16 patients in each group, most of these patients had upper gastrointestinal haemorrhage. In those who received octreotide a total mortality of 75% was noticed. The mortality was 68.75% in the prospective group and 81.25% in the retrospective group. Terlipressin with albumin was administered was administered to 8 patients in the prospective group, 7 has HRS1 and 1 had HRS 2. Two patients with HRS1 showed improvement in renal function but 1 of these again had deterioration in renal function. He was administered terlipressin again without any further improvement. The renal function in the only patient with HRS2 improved and he was discharged. High mortality of 80.55% was observed in patients who received haemodialysis, 15 of 21 patients (76.19%) died in the prospective group while 14 of 15 patients (93.33%) died in the retrospective group (Table 23).

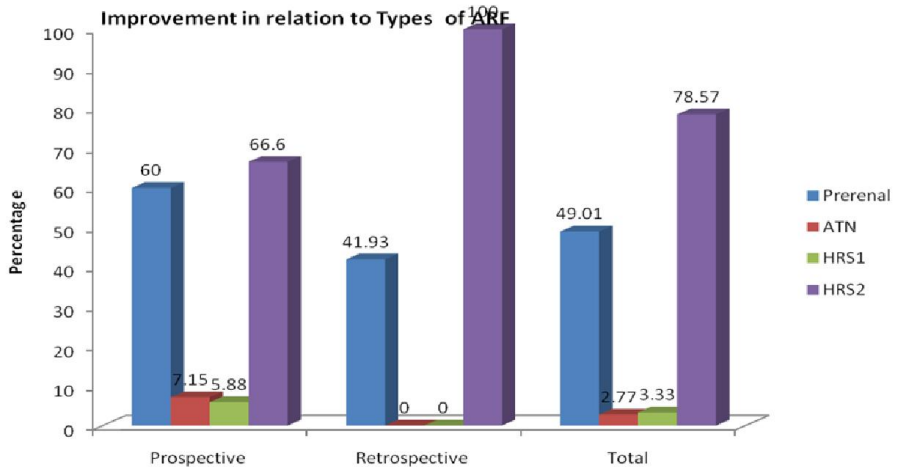
Table 23. Mortality in relation to Treatment

Treatment	Prospective			Retrospective			Total		
	n	M	M%	n	M	M%	n	M	M%
Plasma Vol. Exp. (IV fluid/Albumin)	45	31	71.11	55	38	69.09	100	70	70.00
Octreotide /Albumin	16	11	68.75	16	13	81.25	32	24	75.00
Terlipressin/Albumin	8	6	75.00	2	2	100.00	10	8	80.00
Hemodialysis	21	16	76.19	15	14	93.33	36	29	80.55
P value	>0.10			>0.10			> 0.10		


Types of ARF
Percentage
50
45
40
35
30
25
20
15
10
5
0
29.5
14.75
22.95
32.79
17.14
7.14
31.43
44.29
22.9
10.64
27.48
38.93
Prospective
Retrospective
Total
HRS - 1
HRS-2
ATN
PRERENAL


Mortality in relation to Treatment
Morality %
100
90
80
70
60
50
40
30
20
10
0
71.11
68.75
75
76.19
69.09
81.25
100
93.33
70
75
80
80.55
Prospective
Retrospective
Total
iv Fluid/Albumin
Ocxtreotide/Albumin
Terlipressin/Albumin
Hemodialysis


Outcome
Percentage
100
90
80
70
60
50
40
30
20
10
0
32.78
67.21
25.71
74.28
29.07
70.93
Prospective
Retrospective
Total
Improved
Expired


Improvement in relation to Types of ARF
Percentage
100
90
80
70
60
50
40
30
20
10
0
60
7.15
5.88
66.6
41.93
0
0
100
49.01
2.77
3.33
78.57
Prospective
Retrospective
Total
Prerenal
ATN
HRS1
HRS2

In 36 of the 131 patients in the study, an improvement in renal functions was observed. Of these, 25 had prerenal ARF, 11 had HRS type 2, 1 had ATN and 1 had HRS Type 1. The outcome of the patients with ARF was determined at the end of hospital stay. These patients were not followed up subsequently (table 24, 25).

Table 24. Outcome

Outcome	Prospective	Retrospective	Total
Improved Expired	20 (32.78%) 41 (67.21%)	18 (25.71%) 52 (74.28%)	38 (29.07%) 93 (70.93%)
P value	<0.01	<0.01	< .001

Table 25. Improvement in relation to type of ARF

Type of ARF	Prospective			Retrospective			Total		
	I/D	Exp.	I/D%	I/D	Exp.	I/D%	I/D	Exp.	I/D%
Prerenal	12	8	60	13	18	41.93	25	26	49.01
ATN	1	13	7.15	0	22	0	1	35	2.77
HRS 1	1	17	5.88	0	12	0	1	29	3.33
HRS 2	6	3	66.6	5	0	100.00	11	3	78.57

Table 26. Outcome inpatients who received intra vascular volume expansion alone

Type of ARF	Prospective			Retrospective			Total		
	n	Imp.	I/D%	n	Imp.	I/D%	n	Imp.	I/D%
Prerenal	15	9	60	19	10	52.63	34	19	55.88
ATN	4	0	0	8	0	0	12	0	0
HRS 1	2	0	0	4	0	0	6	0	0
HRS 2	6	3	50	4	4	100	10	7	70.00
							62	26	41.93

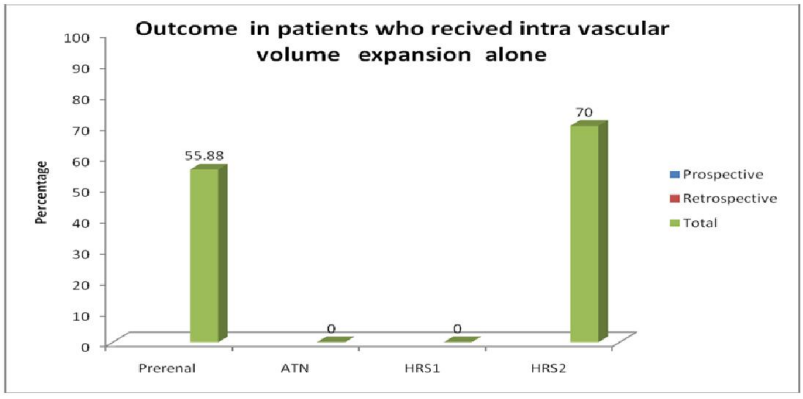
In this study 62 patients received intra vascular fluid expansion as the only treatment. An improvement was seen in 41.93% patients (26 out of 62 patients). An improvement in renal functions was seen in 55.88% patients (19 out of 34 patients) with prerenal ARF and 70% patients (7 out of 10 patients) with HRS type 2, Most of the patients in this treatment group who expired had died within the first 48 hrs of hospitalization.

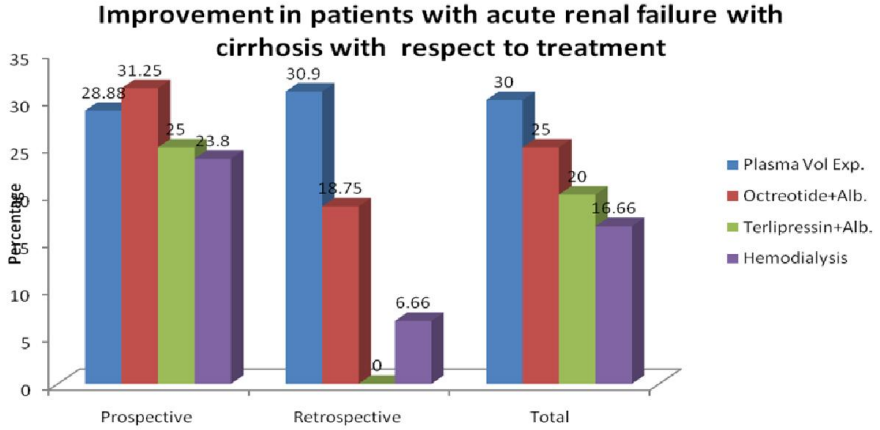
Table 27. Improvement in patients with acute renal failure with cirrhosis with respect to treatment

Treatment	Prospective			Retrospective			Total		
	n	Imp.	I/D%	n	Imp.	I/D%	n	Imp.	I/D%
Plasma Vol. Exp. (IV fluid/Albumin)	45	13	28.88	55	17	30.90	100	30	30.00
Octreotide /Albumin	16	5	31.25	16	3	18.75	32	8	25.00
Terlipressin/Albumin	8	2	25.00	2	0	0.00	10	2	20.00
Hemodialysis	21	5	23.80	15	1	6.66	36	6	16.66

Plasma volume expansion was given to 100 patients, alone or with octreotide, terlipressin or haemodialysis. An improvement was seen in renal functions in 30 patients (30%).

Octreotide was administered to 16 patients in the prospective group and 16 in the retrospective group. An improvement in renal parameters was seen in 5 patients (31.25%) in the prospective group and 3 patients (18.75) in the retrospective group. Terlipressin with albumin was administered to 8 patients in the prospective group, of these 7 had HRS type 1 and 1 had HRS type 2. Two patients with HRS type 1 showed improvement in renal function but 1 of these again had deterioration in renal function. He was administered terlipressin again without any further improvement. The reneal function in the only patient with HRS type 2, who was administered terlipressin, improved and he was discharged.





Haemodialysis was utilized as a mode of treatment of ARF in 21 patients in the prospective group of which 5 patients (23.80%) showed improvement. In the retrospective group 15 patients were haemodialysed, of which only 1 (6.66%) showed improvement.

DISCUSSION

In advanced cirrhosis more than 50% patients develop ARF including the heapatorenal syndrome, either spontaneously or following an acute insult like upper gastor intestinal bleeding or spontaneous bacterial peritonitis. Patients with cirrhosis may also develop prerenal ARF especially those with gastronitestinal bleeding and those receiving high doses of diurectics, Pre-renal ARF or HRS may later evolve into ATN if renal blood flow is compromised for a significant duration. ATN can also be seen with severe systemic infections or with use of nephrotoxic drugs (Shear *et al*., Eckardt KU). In the present study out of 131 patients, 44(33.5%) patients had HRS, 36 (27.4%) had ATN and 51(38.9%) had prerenal ARF. In the prospective group, 18 patients were diagnosied to have HRS type1, and 9 patients had HRS type2 while in the retrospective group, 12 and 5 patients were diagnosed to have HRS type1 andHRS type2 respectively. ATN was seen in 14 patients and prerenal ARF in 20 patients in the prospective group, while 22 patients had ATN and 31 patients had prerenal ARF in the retrosepctive group.

Not many studies have been done so far to classify types of ARF in cirrhosis. The few available studies have reported a different incidence of various types of ARF in cirrhosis. Shear *et al* (1965), did a prospective study on 15 cirrhotic patients with renal dysfunction and reported acute tubular necrosis in 8 patients, prerenal ARF in 2 and HRS in 5. The diagnosis was based on urine sediment examination and the clinical events precipating ARF. Ring Larsen *et al.* (1981), did a prospective study on 40 patients with terminal cirrhosis out of which 26 developed ARF during their hospital stay. He found that 15 of these patients had HRS, 3 patients had ATN, and in 8 patients, the cause of ARF was indeterminable. His classification was based primarily on urine sodium concentration and urine to plasma creatinine ratio. In the present study, 66.5%patients had prerenal ARF and ATN, which was due to the fact that a high proportion of patients presented with shock secondary to gastrontestinal hemorrhage or sepsis. The classification into various types of ARF is based mainly on clinical criteria and fractional excretion of sodium (FENa) considered simultaneously, because FENa can be confounded by prior use of diuretics and urinary indicase are not always consistent with the type of renal failure (Wilkinson 1982; Dudley *et al.,* 1986).

The predominant cause of cirrhosis in this study was alcoholic liver disease, which is seen infrequently in females. Most of the patients (83.20%) in the present study belonged to child Pugh grade C and the mortality was found to be significant higher (78.89%) in these patients. Among patients with child Pugh grade B, a mortality of 40.90% was noticed. Severe jaundice and INR in excess of 1.7 were also found to be related to a higher mortality rate. Hyponatremia, hyperkalemia, or high levels of liver enzymes were not found to be appreciably associated with mortality. A mortality of 66.6% (29 out of 43) was seen in patients who developed ARF along with gastrointestinal bleeding and a 61.5% mortality (15 out of 24 patients) was noticed in ARF associated with spontaneous bacterial peritonitis. This study confirms the poor outcome traditionally known in patients with acute renal failure in cirrhosis. In this study only 38 out of 131 survived. The prognosis was particularly poor in patients with HRS type1 or ATN. A favourable outcome was seen in 25 patients with pre-renal ARF and 11 patients with HRS type2, while only 1 patient with HRS type1, and 1 with ATN survived. *Gines A*, has reported a mortality of 100 % over an average of 1.7weeks in patients with HRS type1. A total of 100 patients received intravenous volume expansion alone or with octreodite, terlipressin or hemodialysis. Intravenous volume expansion alone was given to 62 of these patients, of which 34 patients had prerenal ARF, 10 patients had HRS type2, 6 patients had HRS type1, and 12 patients had ATN. An improvement was seen in 19 patients with prerenal ARF (55.88%) and 7 patients with HRS type 2 (70%), whereas a 100% mortality was seen among patients with HRS type1 and ATN.

Terlipressin was given to 10 patients with HRS of whom, 2 patients of HRS type1 and 1 patient of HRS type2 showed improvement in renal function. One of the patients with HRS type1who had improved, again showed deterioration and re-administration of Terlipressin did not bring further improvement in renal function. In our study, the cause of a relatively higher mortality in patients treated with Terlipressin was probably a shorter duration of Terlipressin administration, which was given on an average for 5 to 6 days due to cost effectiveness. Octreotide was given to 32 patients who had presented with gastrontestinal hemorrhage and an improvement in renal function was seen in 8 patients (25%). Octreotide is primarily used as a splanchnic vasocnstrictor and not used as a specific treatment of HRS. Six patients with prerenal ARF and 2 patients with HRS type2 improved with Octreotide. A very high mortality was seen in patients who needed dialysis. Hemodialysis was done on 36 patients, of whom 19 had ATN, 13 had HRS type1, 3 had prerenal ARF and 1 hsad HRS type2. Out of these 36 patients, 3 patients with prerenal ARF, 1 with ATN, 1 with HRS type1 and 1 with HRS type2 survived. In the present study, most of the patients who were hemodialysed had ATN and HRS type 1.

SUMMARY

The most common cause of ARF with cirrhosis in our study was found to be prerenal failure. Out of 131 patients, 51 (38.93%) had pre-renal ARF, 20 in the prospective group, and 31 in the retrospective group. The most frequent causes of pre-renal ARF were upper gastrointestional hemorrhage, high doses of diurectics and sepsis. HRS was diagnosed in 44 patients (33.54%), of whom, 30 had HRS type1 and 14 had HRS type 2. In the prospective group, 18 had HRS type 1, and 9 had HRS type 2. In the retrospective group, 12 were found to have HRS type 1, and 5 had HRS type 2. ATN was seen in 36 patients (27.48%), 14 patients in the prospective group, and 22 patients in the retrospective group. ATN was seen predominately in patients presenting with septic shock. The average age of patients in the study was 49.87+/-10.10 years. The mortality rate was maximum in the age group of 40 to 49 years. The

predominant cause of cirrhosis was alcoholic liver disease, seen in 114 patients. Hepatitis B and hepatitis C related cirrhosis was present in 7 patients. In 10 patients, the cause of cirrhosis remained inderterminate. Majority of patients (83.20%) had child's C cirrhosis, which was significantly higher in patients with total bilirubin in excess of 17mg/dl and INR in excess of 1.7.Patients were classified into various types of ARF on the basis of clinical features and FENa considered together. FENa was found to be a good predictor of pre-renal ARF and ATN, however, it was not found to be very useful as a predictor of HRS in this study.

Plasma volume expansion was given to 100 patients alone, or in combination with Octreotide, Terlipressin or hemodialysis. An improvement was seen in 30 of these patients. 62 patients received intravascular expansion alone, of these 34 had prerenal ARF, 12 had ATN, 6 had HRS type 1 and 7 had HRS type2. Of these, 26 patients improved, 19 with prerenal ARF and 7 with HRS type 2. Terlipressin was given to 10 patients, of whom, 2 patients with HRS type 1 and one patient with HRS type 2 had improvement in the renal function. One of the HRS type 1 patients who had improved, again showed deterioration of renal function, which did not improve with another course of Terliperssin. In the study, only 36 patients had haemodialysis, an improvement in renal function was seen in 6 patients, 3 of whom had pre-renal ARF and were dialysed for hyperkalemia and severe metabolic acidosis. Of the other 3 patients who showed improvement, one had HRS type 1, one had HRS type2, and the last one had ATN. Only 38 of the 131 patients had an improvement in the renal function. Of these, 25 had pre-renal ARF, 11 had HRS type2, one had HRS type1 and another one had ATN. In 43 patients, ARF was associated with upper gastrointestinal hemorrhage, of which 29 (67.44%) died. In 24 patients, ARF was associated with SBP and 15 (62.50%) of these patients died.

Conclusıon

Acute renal failure is commonly seen in patients with advanced cirrhosis. About 35% of these patients have Hepatorenal syndrome, 40% have prerenal ARF and 25% have acute tubular nercrosis. Prerenal ARF and HRS can evolve into ATN if renal blood flow is compromised for a significant duration of time. An intravascular volume expansion should be given to all patients of ARF with cirrhosis except to those with fluid overload. Reversal of HRS is seen in a high proporation of patients treated with Terliperssin. Therefore, treatment with Terlipressin must be considered in all patients with HRS. Hemodialysis should be readily used for life threatening complications of ARF. There is a high mortality associated with these patients, especially so with HRS type1 and ATN. Thus it is of utmost importance that development of precipitating HRS. Also, progression of pre-renal ARF and HRS into ATN should be prevented at an early stage.

Abbreviations

HRS-Hepatorenal syndrome, ATN-Acute tubular necrosis, ARF-acute renal failure,MARS-Molecular absorbents recycling systeme,TIPSS-Transjugular intrahepatic portsystemic shunt, FENa-Fractional excretion of sodium

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

K C Das, Sumeet david, Rohit Roland, Rohit Massey were involved in the clinical assessment and writing the study. All authors read and approved the final manuscript.

Consent

Full written consent was received for the manuscript to be published.

Acknowledgements

I would like to extend my thanks to my team doctors for their efforts for composing this study and managing these sick patients.

REFERENCES

Afessa, B. and Kublis, P. S. 2000. Upper gastrointestinal bleeding in patients with hapatic cirrhosis: clinical course and mortality predication. *Am. J .Gastroenterology,* 95:484-489.

Alessandria, C., Venon, W. D., Marzono, A., Barletti, C., fadda, M. and Rizzetto, M. 2002. Renal failure in cirrhotic patients: role of terlipressin in clinical approach of hepatorenal sydnorme type 11. *Eur J Gastroentrol Hepatol,* Dec:14 (12):1363-68.

Angeli P, Volpin R, Gerunda G. *et al*. 1999. Reversal of type 1 hepatorenal syndrome with the administration of midodrine and cotreotride. *Hepatology,* 29: 1690 – 7

BacqY, Gaudin C, Hadengue A *et al*. 1991. Systemic, splanchnic and renal hemodynamic effects of a dopaminergic dose of dopamine in Patients with cirrhosis. *Hepatology,* 14:483-87.

Bataller R, Gines P,Guevara M. and Arroyo V. 1997. Hepatorenal sydrome in cirrhosis. Semin. Liver Dis. 17:233-47.

Bataller R, Sort P, Gines P. and Arroyo V. 1998. Hepatorenal sydrome:defination, pathophysiology, clinical features and mangement. Kidney Int, 53(suppl 66):S43-S53.

Blendis L. And Wong F. 1999. Intravenous albumin with diuretics. Protean lessons to be learn? *J Hepatol.,* 30:727-30.

Bomzon A, Jacob G. and Better OS. 1996. Jaundice and the kidney. In :Epstein M (ed) The kidney in liver disease. 4Th edition. Hanley and Belfus. Philadelphia. pp423-446.

Cade R, Wagemaker H, Vogel S, *et al*. 1987. Hepatorenal sydrome studies of the effect of vascular volume and intraperitoneal pressure on the renal and hepatic function. *Am J Med.,* 82: 427-38.

Capling RK. and Bastani B. 2004. The clinical course of patients with type1 hepatorenal sydrome maintained on hemodialysis. Ren Fail. 26(5):563-68.

Cardenas A, Gines P, Uriz J. *et al*. 2001. Renal failure after upper gastronitestinal bleeding in cirrhosis: incidence, clinical course, predictive factors, and short-term prognosis. *Hepatology,* 34:671-76.

Colle I, Durand F, Pressione F, Rassiat E, Bernuau J. *et al*.

2002. Clinical course, predictive factors and prognosis in patients with cirrhosis and type 1hepatorenal sudrome treated with terlipressin: a retrosepctive analysis. *J Gastroenterol Hepatol*, 17:882-88.

Danalioglu A, Cakaloglu Y, Karaca C *et al*. 2003. Terlipressin and albumin combination treatment in hepatorenal sydrome. *Hepatogastroenterology,* 50:Suppl 2:ccciii-cccv.

Dudley FJ, Kanel GC, WoodL J. and Reynold TB.Hepatorenal for treatment of type-1 hepatorenal sydrome (HRS)

Duvoux c, Zanditenas D, Hezode C, Chauvat A, Mohin JL. *et al*. 2002. Effects of nor-adrenaline and albumin in patients with type-1 hepatorenal syndrome: a pilot study. *Hepatolgy,* 36 [2]; 377-80.

Earey LE. 1979. Presentation of diagnostic criteria of the hepatorenal syndrome. Piccin Medical, Padova, 495-504.

Eckardt KU. 1999. Review: Renal failure in liver disease. *Intensive Care Med.,* 25:5-14.

Feirbinteanu- Braticevici C, Udeanu M, Usvat R. and Andronisco D. 2004. The role of octreotide on renal ffunction in patients with advanced cirrhosis: *Rom J Intern Med.,* 42(1): 173-81.

Fernadez- Esparrach G, Guevara M, Sort P, Padro A, Jimenez W, Gines P. *et al*. 1997. Diuretic requirements after therapeutic paracentesis in non-azotemic patients with cirrhosis. A randomized double blind study of spironolactone versus placebo. *J Hepatol.,* 26:614-20.

Fernandez-Seara J, Prietro J, Quirogo J. *et al*. 1989. Systemic and regional hemodynamics in patients with liver cirrhosis and ascites with and without functional renal faiture. *Gastroentrology,* 97:1304-12.

Gines A, Escorsell A, Gines P, Salo J, Jimenez W, Inglada L, Navasa M. *et al*. 1993. Incidence, predective, factors and prognosis of the hepatorenal syndrome in cirrhosis and ascites. Gastroentology, 105:229-236.

Goldstein H. and Boyle ID. 1965. Spataneous recovery from the hepatorenal syndrome. *N Engl J Med.,* 272:895-98.

Guarner C, Soriano G, Tomas A *et al*. 1993. İncreased serum nitrite and nitrate level in patients with cirrhosis: relationship to endotoxemia. *Hepatology,* 18:1139-43.

Guevara M, Gines P, Fernandez-Esparrach G. *et al*. 1998. Reversibility of hepatorenal syndrome by prolonged administration of ornipressin and plasma volume expansiom. *Hepatology,* 27:35-41

Gulberg V, Biler M. and Gerbes AL. 1999. Long term therapy and retreatment of hepatorenal syndrome type-1 with ornipressin and dopamine. *Hepatology,* 10:870-75.

Hadengue A, Moreau R, Christopher Gaudin *et al*. 1992. Total effective vascular compliance in patients with cirrhosis. A study of the response to acute blood volume expansion. *Hepatology,* 15:809-15.

Kastelan S, liybicic N, Kastelan Z, Ostojic R. and Uravic M. 2004. The role of duplex Doppler ultrasonography in the diagnosis of renal dysfunction and hepatorenal syndrome in patients with liver cirrhosis. Hepatogastroentology 2004; 51(59):1408-12.

Kew MC, Varma RR, Williams HS, Brunt PW, Hourgin KJ. and Sherlock S. 1971. Renal and itrarenal blood-flow in cirrhosis of the liver. *Lancet,* 2:504-510.

Klingler EL JR. and Cronin RJ. 1972. Renal failure in cirrhosis of the liver. Observations during intermittent hemodialysis. Abstract. *Am Sc Art Int Org.*, (April 16 -18):p26.

Koppel MH, Coburn JW, Mins MM, Goldstein H, Boyle JD, and Rubini ME. 1969. Transplantation of cadaveric kidneys from patients with hepatorenal syndrome. *E Engl,* 280:1367-71.

Lenz K, Hortnagel H, Druml W *et al.* 1991. Ornipressin in the treatment of functional renal failure in decompensated cirrhosis. Effects on renal hemodynamics and arterial natriuretic factor. *Gastroenterology,* 101:1060-7.

Maroto A, Gines, Salo J, Claria J, Gines P, Anibarro L, Jimenez W Arroyo V, Rodes J. 1994. Diagnosisof functional kidney failure of cirrhosis with Doppler sonography: prognostic value of resistive index. *Hepatology*, 20:839-44.

Mitzner SR, Stange J, Klammt S *et al*. 2000. İmprovement of hepatorenal syndrome with extracorporeal albumin dialysis MARS:Results of a prospective, randomized, controlled clinical trial. Liver Transpl, 6:277-86.

Moore K, Wendon J, Frazer M, KaraniJ, Williams R, Bard K. 1992. Plasma endothelin immunoreactivity in liver disease and the hepatorenal syndrome. *N Engl J Med*., 327:1774-8.

Moreau R, Durand F, Paynard T. *et al*. 2002. Terilpressin in patients with cirrhosis and type 1 heaptorenal syndrome: a retroscopective multicentre study. *Gastroenterology,* 122:923-930.

Navasa M, Follo A, Filella X, JimenezW, Francitorra A, Planas R, Rimola A. *et al*. 1988. Tumor nercosis factor and interleukin-6 in spontaneous bacterial peritonitis in cirrhosis. Relationship with the development of renal impairment and mortality. *Hepatology,* 27:1227-1232.

Ortega R, Gines P, Uriz J, Cardenas A, Calahorra B. *et al*. 2002. Terlipressin therapy with and without albumin for patients with hepatorenal syndrome: Results of a prospective, non randomized study. *Hepatology,* 36:941-48.

Papper S. 1983. The hepatorenal syndrome. In: Epstein M,ed. The kidney liver disease. 2nd ed, New York: *Elsevier Biomedical*, 8:106.

Parson S, Wilkinson SP. and Weston MJ. 1975. Use of dialysis in treatment of renal failure in liver disease. *Post grad Med J*., 1975; 51:515-520.

Platt JF,Eills JH, Rubin JM, Merion RM, Lucey MR. Renal duplex Doppler ultrasonography: noninvasive predictor of kidney dysfunction and hepatorenal failure in liver disease. *Hepatology*, 1994; 20:362-69.

PomierLG, PaquinSc, Hassoun Z, Lafortune M, Tran A. 2003. Octreotide in hepatorrenal syndrome: a randomized, double-blind, placebocontrolled, crossover study. *Hepatology,* 38[1]: 238-43.

Rasaratnam B, Kaye D, Chin-Dusting J, Gennings G. Dudly F. 2000. Effect of selective intestinal decontimation on the peripheral arterial vasodilatation in cirrhosis [abstract]. *Hepatology*, 32 [part 2 of 2]: 310A.

Ruiz-del-Arbol L, Monescillo A, Jimenez W, Garcia –Plaza A, Arroyo V. and Rodes J. 1997. Paracentesis-induced circulatory dysfunction: mechanism and the effect on hepatic hemodynamics in cirrhosis, *Gastroenterology,* 113:579-586.

Saner FH, Fruhauf NR, Schafers RF, Lang H *et al*. 2003. Terlipressin plus hydroxyethyl starch infusion: An effective treatment for hepatorenal syndrome. *Eur J Gas troentrol Hepatol.,* 15(8):925-27.

Shear L, Kleinerman J. and Gabuzda GJ. 1965. Renal failure in

patients with cirrhosis of the liver. *Am J MED*, 39:184-198.

Sherlock S, Senewiratne B, Scott A. and Walker JG. 1966. Complications of diuretic therapy in hepatic cirrhosis. *Lancet*, 1: 1049-55.

Solanki P, Chawla A, Garg R, Jain M *et al*. 2003. Beneficial effect of terlipressin in hepatorenal syndrome for a prospective, randomized, placebo-controlled cinical trial. *J Gastroeterol Hepatol.,* 18(2):152-56.

Soper CPPR, Latif AB. Bending MR. 1996. Amelioration of hepatorenal syndrome with selective endothelin-A antagonist. *Lancet,* 347: 1842-43.

Sort P, Navasa M, Arroyo V, Aldeguer X, Planas R, Ruiz-del-Arbol, Castells L, *et al*. 1999. Effect of intraveneous albumin on renal impairment and morality in patients with cirrhosis and spontaneous bacterial peritonitis. *N Engl J Med*., 341:403-409.

Stange J, Hassanein TI, Mehta R, Mitzner SR, Bartlitt RH. 2002. The molecular absorbents recycling system as a livr support system based on albumin dialysis: a summary of pre-clinical investigations, prospective, randomized, controlled clinical trials and clinical experience from 19 centers. *Artif Organs.*, 26 (2):103-10

Tristani FE. amd Cohn JN. 1967. Systemic and renal hemodynamics in oliguric hepatic failure: effect of volume expansion. *J Clin Invest,* 46:1894-1906.

Uriz J, Gines P, Cardenes A. *et al*. 2000. Terlipresin plus albumin infusion: an effective and safe therapy of hepatorenal syndrome, *J Hepatol.,* 33:33-48.

Watt K, Julia Uhanova J, Minuk GY. 2002. Hepatorenal syndrome; Diagnositc accuracy, clinical features and outcome in a tertiary care centre. *Am J Gastroeterology*, 97(8):2046-50.

Wilkinson SP. 1982. Renal failure. In: Wilkinson SP, ed. Hepatorenal disorders. New York: Marcel Dekker, Inc., 1-54.

Wong F and Blends L. 2001. New challenges of hepatorenal syndrome: prevention and treatment. *Hepatology,* 34(6): 1242-51.

Wong F, Pantea L, Sniderman K. 2004. Midodrine, octreotide, albumin and TIPS in selected patients with cirrhosis and type 1 hepatorenal syndrome. *Hepatology,* 40 (1): 16-18.

Zussman RM, Axelrod I. and Tolkoff-Rubin N. 1977. The treatment of hepatorenal syndrome with intra renal administration of prossstalglandin E1. *Prostaglandins,* 13:819-30.

****

.