Study of the Relationship between the Cause of Renal Failure and Outcome in Decompensated Liver Cirrhosis

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Abstract: Background: Renal failure is a challenging complication of cirrhosis and is one of the most important risk factors when liver transplantation is being considered. Patients with cirrhosis and renal failure are at high risk for death while awaiting transplantation and have an increased frequency of complications and reduced survival after transplantation, as compared with those without renal failure**. Aims:** To evaluate the causes of renal failure in patients with decompansated liver cirrhosis and its impact on prognosis. **Patients & Methods:** One hundred patients with decompansated liver cirrhosis associated with renal failure (serum creatinine equal to or more than 1.5 mg/dl) were included in our study; they were classified according to the cause of renal failure into 4 groups: hepatorenal syndrome, infection, hypovolemia and parenchymal kidney disease. All patients in the study were subjected to full history taking, complete clinical examination, pelviabdominal ultrasonography, chest X ray and laboratory investigations including blood urea, serum creatinine, urine analysis, ascitic fluid analysis, serum sodium, serum potassium, urinary sodium, and serum osmolarity. **Results:** 37 patients (37%) developed renal failure due to hepatorenal syndrome, 31 patients (31%) due to infection especially spontaneous bacterial peritonitis, 22 patients (22%) due to hypovolemia especially upper and lower gastrointestinal bleeding and 10 patients (10%) due to parenchymal kidney disease. There was statistically non - significant increased incidence of diabetes melllitus among group II (infection group) as compared to other groups (*p*. value 0.054). Prognosis depends on the cause of renal failure as 16 patients of hepatorenal syndrome died within 2 weeks of admission, 5 patients died due to infection, 4 patients died due to hypovolemia and no patients died due to parenchymal kidney disease. There was statistically significant difference in outcome among studied groups (*p*. value 0.001). **Conclusions:** A simple classification of patients with decompansated liver cirrhosis according to cause of renal failure is useful in assessment of prognosis and may help in decision making in liver transplantation.
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1. Introduction

Renal failure is a challenging complication of cirrhosis [1, 2] and is one of the most important risk factors when liver transplantation is being considered. Patients with cirrhosis and renal failure are at high risk for death while awaiting transplantation and have an increased frequency of complications and reduced survival after transplantation, as compared with those without renal failure [3, 4]. In 2002, the Model for End-Stage Liver Disease (MELD) score which derived from measurements of serum bilirubin, the international normalized ratio of prothrombin time, and serum creatinine to evaluate pretransplantation renal function, was introduced as an aid to organ allocation among candidates for liver transplantation. Use of this scoring system has increased the number of patients with renal failure who receive a liver transplant [5, 6] and has reduced mortality among patients awaiting liver transplantation.

Renal failure in patients with cirrhosis is primarily related to disturbances in circulatory function, mainly reduction in systemic vascular resistance due to primary arterial vasodilatation in the splanchnic circulation, triggered by portal hypertension [1, 6, 7]. The cause of this arterial vasodilatation is increased production or activity of vasodilator factors particularly nitric oxide, carbon monoxide, and endogenous cannabinoids mainly in the splanchnic circulation [8, 9].

Patients with cirrhosis who have circulatory dysfunction and arterial underfilling, increased endogenous vasoconstrictor activity affecting the intrarenal circulation, and increased systemic inflammatory responses are particularly prone to renal failure, which may occur spontaneously or may be triggered by a number of events that occur frequently in advanced cirrhosis. Such events include hypovolemia, induced by renal or gastrointestinal fluid losses, and bacterial infections [10]. Hypovolemia as a consequence of gastrointestinal bleeding, diarrhea, or excessive administration of diuretics is a common cause of impaired renal function in cirrhosis [11].

The prognosis for patients with cirrhosis and renal failure is poor. Poor outcome is probably related to the combination of liver and renal failure and depends on

the cause of renal failure. The hepatorenal syndrome is associated with the worst prognosis [12]. The great majority of patients with the hepatorenal syndrome have a poor short-term outcome unless they undergo liver transplantation [13].

Mortality is higher with type 1 hepatorenal syndrome than with type 2 (median survival, 1 month vs. 6 months). Vasoconstrictor therapy has not been shown to improve survival in patients with type 1 hepatorenal syndrome, but patients in whom the hepatorenal syndrome is reversed with vasoconstrictor therapy live longer than patients who do not have a response to such therapy [14, 15]. Many studies were performed in relatively small series of patients, and so larger studies are required to assess more definitively whether vasoconstrictors improve survival in patients with the hepatorenal syndrome [16].

The purpose of the present study is to evaluate the causes of renal failure in patients with decompansated liver cirrhosis admitted to the hospital, as well as to reassess the impact of the cause of renal failure on their survival.

2.Patients and Methods

This study was conducted on patients admitted to Internal Medicine Department in Tanta University Hospital with decompansated cirrhosis and renal failure. Written informed consent was taken from all patients and the protocol was approved by local ethical committee at Tanta Faculty of Medicine. Our patients were divided according to etiology of renal failure into 4 groups: Group I: End stage liver scetic (ESLD) presented with hepatorenal syndrome. Group II: ESLD presented with infection. Group III: ESLD presented with hypovolemia or gastrointestinal bleeding. Group IV: ESLD presented with parenchymal kidney disease. All patients were subjected to full history taking, complete clinical examination, pelvi-abdominal ultrasound, chest x-ray, and laboratory investigations including complete blood count, liver function test, blood urea, serum creatinine, urine analysis, scetic fluid analysis, serum sodium, serum potassium, urinary sodium, and serum osmolarity. Exclusion criteria include all cirrhotic patients with renal failure due to obstructive uropathy. Statistical presentation and analysis of the present study was conducted, using the mean, standard error, unpaired student t-test, chi-square, Analysis of variance [ANOVA] tests, Mann-Whitney and Kruskal-Wallis by SPSS V17 [17].

3.Results

There was no statistically significant difference among studied groups as regards age and sex (*p*. values 0.107 & 0.131 respectively) (Tables 1 & 2). There is non significant increase in the incidence of diabetes and hypertension in group II as compared to other groups (*p*. values 0.054 and 0.119 respectively) (Tables 3 & 4). Serum creatinine level was significantly higher than normal in all studied groups (*p*.value 0.001). Serum creatinine level was significantly higher among patients of group IV as compared to other groups (*p*.value 0.001) (Table 5). Blood urea increased among patients of group IV more than other groups but this increase was statistically not significant (*p*. value 0.213) (Table 6). As regards renal ultrasonography; there was statistically significant increase in the number of patients having abnormal ultrasound kidney in group IV as compared to other groups (*p*. value 0.001) (Table 7). There were no significant statistical differences among studied groups as regards hemoglobin level (*p*. value 0.6), platelet count (*p*. value 0.035), serum albumin (*p*. value 0.150), total bilirubin; both direct and indirect (*p*.value 0.098, 0.128 and 0.283), prothrombin activity and INR (*p*. value 0.985 & 0.408), serum sodium (*p*. value 0.542) and serum potassium (*p*. value 0.034). Total leucocytic count was significantly increased in group II compared with other groups (*p*. value 0.001) (Table 8). Total leucocytic count in ascetic fluid was significantly increased in group II as compared with other groups. (*p*. value 0.001). There was no statistically significant differences regarding to neutrophil percent in ascetic fluid between studied groups (*p*. value 0.212) (Table 9). Urinary sodium was significantly decreased in the hepatorenal syndrome group (group I) as compared with other groups (*p*. value 0.001) (Table 10). Serum osmolarity was significantly increased among patients of hypovolemia group (group III) (*p*. value 0.001). Also serum osmolarity was significantly decreased among patients of hepatorenal syndrome group (Group I) (*p*. value 0.001) (Table 11). As regards the outcome of renal failure within 2 weeks of admission to our hospital among patients of studied groups; group I: 21 patients discharged on follow up (56.76%), no patient discharged on chronic haemodialysis (0.00%), 16 patients died within 2 weeks of admission (43.24%). In group II: 24 patients discharged on follow up (77.42%), 2 patients discharged on chronic haemodialysis (6.45%), 5 patients died within 2 weeks of admission (16.13%). In group III: 18 patients discharged on follow up (81.82%), no patient discarged on chronic haemodialysis (0.00%), 4 patients died within 2 weeks of admission (18.18%). In group IV: 5 patients discharged on follow up (50.00%), 5 patients discharged on chronic haemodialysis (50.00%), no patient died (0.00%). There was statistically significant difference regarding to the outcome among studied groups (*p*. value 0.001) (Table 12).

Table 1: Age distribution among studied groups.

	Age (years)					ANOVA	
	Range			Mean	± SD	F	*p* -value
HRS	45	-	79	62.297	± 8.113	2.087	0.107
Infection	27	-	79	56.355	± 12.257		
Hypovolemia	40	-	72	60.182	± 9.500		
Parenchymal kidney disease	53	-	74	59.600	± 7.090		

HRS: hepatorenal syndrome *p* -value <0.05(significant)

Table 2: Sex distribution among studied groups.

Sex		GROUPS				
		HRS	Infection	Hypovolemia	Parenchymal kidney disease	Total
Male	N	28	20	12	9	69
	%	75.68	64.52	54.55	90.00	69.00
Female	N	9	11	10	1	31
	%	24.32	35.48	45.45	10.00	31.00
Total	N	37	31	22	10	100
	%	100.00	100.00	100.00	100.00	100.00
Chi-Square	X^2	5.623				
	p -value	0.131				

Table 3: Number and percentage of diabetic patients among studied groups.

D M		GROUPS				
		HRS	Infection	Hypovolemia	parenchymal kidney disease	Total
NO	N	32	18	15	8	73
	%	86.49	58.06	68.18	80.00	73.00
YES	N	5	13	7	2	27
	%	13.51	41.94	31.82	20.00	27.00
Total	N	37	31	22	10	100
	%	100.00	100.00	100.00	100.00	100.00
Chi-Square	X^2	7.651				
	p -value	0.054				

Table 4: Number and percentage of hypertensive patients among studied groups.

HTN		GROUPS				
		HRS	Infection	Hypovolemia	Parenchymal kidney disease	Total
NO	N	35	21	20	8	84
	%	94.59	67.74	90.91	80.00	84.00
YES	N	2	10	2	2	16
	%	5.41	32.26	9.09	20.00	16.00
Total	N	37	31	22	10	100
	%	100.00	100.00	100.00	100.00	100.00
Chi-Square	X^2	9.975				
	p -value	0.019				

HTN: hypertensive

Table 5: Level of serum creatinine among patients of studied groups

	Serum Creatinine (mg| dl)					ANOVA	
	Range			Mean	± SD	F	*p* -value
HRS	1.5	-	5.3	2.700	± 1.077	6.342	0.001*
Infection	1.5	-	14	3.668	± 3.213		
Hypovolemia	1.5	-	5	2.105	± 0.771		
Parenchymal kidney disease	2.1	-	9.7	5.170	± 2.168		

Tukey's test					
HRS & Infection	HRS & Hypovolemia	HRS & parenchymal kidney	Infection& Hypovolemia	Infection & parenchymal kidney	Hypovolemia& parenchymal kidney
0.222	0.706	0.006*	0.038	0.192	0.001*

Table 6: Level of blood urea among patients of studied groups.

	Urea (mg|dl)			ANOVA	
	Range	Mean ± SD		F	*p* -value
HRS	24 - 286	139.703 ± 52.174		1.525	0.213
Infection	65 - 315	141.226 ± 62.706			
Hypovolemia	80 - 225	137.455 ± 46.402			
Parenchymal kidney disease	109 - 256	178.300 ± 51.989			

Table 7: Ultrasound of kidney among patients of studied groups

US kidney		GROUPS				
		HRS	Infection	Hypovolemia	parenchymal kidney disease	Total
Normal	N	37	30	22	0	89
	%	100.00	96.77	100.00	0.00	89.00
Abnormal	N	0	1	0	10	11
	%	0.00	3.23	0.00	100.00	11.00
Total	N	37	31	22	10	100
	%	100.00	100.00	100.00	100.00	100.00
Chi-Square	X^2	60.468				
	p -value	<0.001*				

Table 8: Total leucocytic count in blood among patients of studied groups.

	TLC			ANOVA	
	Range	Mean ± SD		F	P-value
HRS	2600 - 13000	5589 ± 2456		5.586	0.001*
Infection	3700 - 86000	13181 ± 14498.9			
Hypovolemia	2200 - 13000	5636.4 ± 3036.22			
Parenchymal kidney disease	4300 - 10400	6370 ± 2030.4			
Tukey's test					
HRS& Infection	HRS & Hypovolemia	HRS & Parenchymal kidney	Infection & Hypovolemia	Infection & Parenchymal kidney	Hypovolemia & Parenchymal kidney
0.002*	1.000	0.994	0.010*	0.125	0.996

Table 9: Total leucocytic count and neutrophil percent in ascetic fluid analysis among patients of studied groups.

		AFA	
		AFA (N)%	AFA (TLC)
		Mean ± SD	Mean ± SD
HRS		78.676 ± 11.031	192.5 ± 278.541
Infection		83.68 ± 11.041	7822.2 ± 13135.2
Hypovolemia		82.727 ± 7.862	170.9 ± 180.469
Parenchymal kidney disease		85.857 ± 12.734	208.6 ± 178.179
ANOVA	F	1.538	5.775
	p -value	0.212	0.001*

Table 10: Urinary sodium among patients of studied groups.

	Urinary Na (mEq/L)		ANOVA	
	Range	Mean ± SD	F	*p* -value
HRS	2 - 19	6.22 ± 3.242	98.041	<0.001*
Infection	12 - 38	18.20 ± 5.630		
Hypovolemia	12 - 24	17.76 ± 3.015		
Parenchymal kidney disease	22 - 38	29.90 ± 5.587		

Tukey's test					
HRS & Infection	HRS & Hypovolemia	HRS & parenchymal kidney	Infection& Hypovolemia	Infection & parenchymal kidney	Hypovolemia& parenchymal kidney
<0.001*	<0.001*	<0.001*	0.985	<0.001*	<0.001*

Table 11: Serum osmolarity among patients of studied groups

	Serum osmolarity (mOsm/kg water)						ANOVA	
	Range			Mean ± SD			F	*p* -value
HRS	210	-	290	240.28	±	24.43	78.61	<0.001*
Infection	230	-	310	277.58	±	23.69		
Hypovolemia	290	-	350	329.09	±	15.40		
Parenchymal kidney disease	270	-	300	281.00	±	9.94		

Tukey's test					
HRS & Infection	HRS & Hypovolemia	HRS & Parenchymal kidney	Infection & Hypovolemia	Infection & Parenchymal kidney	Hypovolemia & Parenchymal kidney
<0.001*	<0.001*	<0.001*	<0.001*	0.972	<0.001*

Table 12: The outcome of renal failure within 2 weeks of admission among patients of studied groups.

Outcome		GROUPS				
		HRS	Infection	Hypovolemia	Parenchymal kidney diseae	Total
Discharged on follow up	N	21	24	18	5	68
	%	56.76	77.42	81.82	50.00	68.00
Discharged on chronic haemodialysis	N	0	2	0	5	7
	%	0.00	6.45	0.00	50.00	7.00
Died	N	16	5	4	0	25
	%	43.24	16.13	18.18	0.00	25.00
Total	N	37	31	22	10	100
	%	100.00	100.00	100.00	100.00	100.00
Chi-Square	X^2	32.161				
	P-value	<0.001*				

4. Discussion

Liver cirrhosis is a worldwide medical problem especially in Egypt. Renal failure is a challenging complication of cirrhosis and one of the most important risk factors when liver transplantation is being considered. Patients with cirrhosis and renal failure are at high risk for death while waiting transplantation and have an increased frequency of complications and reduced survival after transplantation [1-4].

Patients who have ascites, particularly those with hyponatremia, bacterial infections, gastrointestinal bleeding are at high risk for renal failure, as are all patients hospitalized for acute decompensation of cirrhosis [18,19].

In clinical practice, serum creatinine measurement is still the most useful and widely accepted method for estimating renal function in patients with cirrhosis [20]. To date, most studies and consensus conferences have defined renal failure in cirrhosis as a serum creatinine concentration equal to or more than 1.5 mg / dl [21].

It is reported that there are 4 main causes of renal failure in cirrhotic patient which are hepatorenal syndrome (types 1,2), infection (especially spontaneous bacterial peritonitis, urinary tract infection and chest infection), hypovolemia (mainly due to upper and lower gastrointestinal bleeding) and parenchymal kidney disease [22].

Our study Aims to evaluate the causes of renal failure in patients admitted to Tanta University Hospital due to decompensated liver cirrhosis and to assess the impact of the underlying cause of renal failure on survival. It was conducted on 100 patients admitted to the hospital due to decompansated liver cirrhosis associated with renal failure (whose serum creatinine concentration equal to or more than 1.5 mg/dl).

Those patients were classified into 4 groups according to the cause of renal failure which are hepatorenal syndrome, infection, hypovolemia and parenchymal kidney disease.

Analysis of the clinical results of the present work revealed that 37 patients (37%) developed renal failure due to hepatorenal syndrome, 31 patients (31%) due to infection especially spontaneous bacterial peritonitis, 22 patients (22%) due to hypovolemia especially upper and lower gastrointestinal bleeding and 10 patients (10%) due to parenchymal kidney disease.

Also the number of diabetic patients was increased in (Group II) who have different types of infection , this may be due to immune compromisation and increase liability for infection.

It was found that the most common cause of renal failure in those patients with decompansated cirrhosis was hepatorenal syndrome (37%) and the least common cause was parenchymal kidney disease (10%).

These results are in agreement with **Schepke , et al,** whose study revealed that hepatorenal syndrome

was the most common cause of renal failure in patients with decompansated liver cirrhosis. It was present in (40%) of patients, followed by renal parenchymal disease (23%), drug-induced kidney dysfunction (19%) and prerenal failure due to bleeding or infections (15%) [23].

In contrast to our results **Aldo , et al.** found that the most frequent cause of renal failure in those patients was infection (46%), followed by hypovolemia (32%), HRS (13%), and parenchymal nephropathy (9%). The remaining patients had a combination of causes or miscellaneous conditions [24].

Also **Grazielle et al,** stated that bacterial infections (40%) and hypovolemia (32%) were responsible for most of the cases of renal failure followed by parenchymal kidney disease (15%) whereas hepatorenal syndrome was seen in only 12% of the patients with renal failure [25]. These results are not in agreement with our results.

As hepatorenal syndrome was the most common cause of renal failure in our study, also it was found that it led to the worst prognosis as follow: 21 patients discharged on follow up (56.76%), no patient discharged on chronic haemodialysis (0.00%) but 16 patients died within 2 weeks of admission (43.24%).

While among patients with infection 24 patients discharged on follow up (77.42%), 2 patients discharged on chronic haemodialysis (6.45%) and 5 patients died within 2 weeks of admission (16.13%).

Also among patients with hypovolemia 18 patients discharged on follow up (81.82%), no patient discarged on chronic haemodialysis (0.00%) and 4 patients died within 2 weeks of admission (18.18%).

Among patients with parenchymal kidney disease 5 patients discharged on follow up (50.00%), 5 patients discharged on chronic haemodialysis (50.00%), no patient died (0.00%).

So mortality ascribed to renal failure was shown to vary according to its cause. In this respect, hypovolemia and renal parenchymal diseases were associated with lower mortality when compared to bacterial infections and HRS.

This results are inagreement with study done by **Grazielle , et al** [25]. Also in agreement with **Marta, et al,** whose study revealed that prognosis was markedly different according to the cause of renal failure, 3-month probability of survival being 73% for parenchymal nephropathy, 46% for hypovolemia-associated renal failure, 31% for renal failure associated with infections, and 15% for HRS [24].

Diagnosis of hepatorenal syndrome is still associated with a poor prognosis and should therefore prompt transplant evaluation. Effective strategies for the prevention of hepatorenal syndrome in patients with spontaneous bacterial peritonitis, alcoholic hepatitis and after large-volume paracentesis have been established. The current first-line treatment of hepatorenal syndrome type 1 is the combination of vasoconstrictors and albumin. Recent studies demonstrate the beneficial effect of terlipressin on kidney function in patients with hepatorenal syndrome type 1 [26].

Conclusion

It is important to stress on fact that a simple classification of patients with decompansated liver cirrhosis according to cause of renal failure is useful in assessment of prognosis and may help in decision making in liver transplantation.

So strict measures should be taken with those patients to improve their prognosis such as early diagnosis and treatment of any infection occurs in those patients by routine urine analysis, ascetic fluid analysis and chest x ray.

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