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ASSESSMENT OF RENAL FUNCTIONS IN PATIENTS OF CHRONIC LIVER DISEASES

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Abstract

Background: Renal involvement is one of the dreaded consequences of chronic liver disease associated with high mortality and morbidity. The cause of this renal dysfunction is either multi-organ involvement in acute conditions or secondary to advanced liver disease. The present study aimed to assess the incidence and causal relationship of various factors for different types of renal failure in cirrhotic patients.

Material & Method: After approval from the IEC this prospective cross-sectional study was undertaken in Department of General Medicine, IMCHRC, Indore. 100 patients admitted with chronic liver disease were included after considering the inclusion criteria. Patients were clinically examined and laboratory investigations to diagnose the aetiology of chronic liver disease, and assess the severity of liver and renal dysfunction were done.

Results: M:F ratio of 4.5:1 (mean age 44.68yrs). 70% patients had alcoholic liver disease, followed by 20% which had hepatorenal syndrome, 12% patients who had chronic Hepatitis-B, 10% patients developed acute kidney injury and 14% had IgA deposition. A statistically significant distribution was observed for serum urea and creatinine across the categories of Child Pugh classification.

Conclusion: Renal impairment in patients with advanced liver disease is a common finding, more commonly associated with a more advanced disease. Presence of PHTN and various signs of decompensation increase the chances of renal derangements in these patients. This study emphasizes the fact that we should be more vigilant when treating CLD patients, regarding their renal function, as proper screening, prevention and treatment of renal dysfunction can decrease morbidity and mortality.

Keywords: Acute kidney injury, renal impairment, chronic kidney disease, hepatorenal syndrome.

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INTRODUCTION

Chronic liver disease is one of the most commonly prevalent clinical problem in India. CLD involves a process of progressive destruction and regeneration of liver parenchyma leading to fibrosis and cirrhosis [1]. Renal involvement in patients of chronic liver disease (CLD) is one of the most dreaded complications associated with a steep rise in mortality and morbidity. A few conditions which account for the structural renal disease involving either glomerulus or the collecting system like glomerulonephritis, renal tubular acidosis, interstitial nephritis, etc. can be associated with liver involvement where basic pathology lies in kidney and is independent of hepatic involvement [2].

Acute kidney injury, chronic kidney disease and the evaluation of various exogenous and endogenous measures of kidney function continue to be the focus of much research different patient population [3]. The presence of renal impairment depreciates the prognosis in kidney disease is a poor prognostic indicator. Hepato-renal syndrome is a unique form of renal failure associated with advanced liver disease or cirrhosis and is characterized by functional renal impairment without significant changes in renal histology [4].

Chronic liver disease and cirrhosis are frequently complicated with renal dysfunction and this combination leads to significant morbidity and mortality [5]. There is considerable evidence that renal failure in patient with cirrhosis primarily related to disturbances in circulatory function-mainly, a reduction in system vascular resistance due to primary arterial vasodilatation in the splanchnic circulation, triggered by portal hypertension [6]. Intrinsic renal diseases may occur in patient with hepatitis B or hepatitis C and alcoholic cirrhosis. Moreover, patients with cirrhosis may develop a specific acute renal failure called type-I hepatorenal syndrome. Independent of event that leads to acute renal failure, patient with cirrhosis may have diseases, such as diabetes mellitus or hypertension and atherosclerosis, which may cause chronic renal injury [7,8]. In clinical practice plasma creatinine level and endogenous creatinine clearance are commonly used as more convenient but less accurate method for glomerular filtration rate assessment [9].

Derangements in various homeostatic mechanisms marked by abnormal hepatic and other parameters due to CLD have been associated with renal impairment in these patients and studies on renal failure in CLD are scarce in our population. In advent of same the present study was undertaken to assess the renal function in chronic liver diseases and find out the association of alteration of renal function with gradation of liver disease and to find out the association of alteration of renal function among the different aetiologies of chronic liver disease.

MATERIAL & METHOD

After approval from the IEC this cross-sectional, observational study was undertaken in Department of General Medicine, IMCHRC, Indore during the study period from July 2022 to July 2023. 100 patients admitted with chronic liver disease of different aetiologies were included after considering the inclusion and exclusion criteria. Patients were clinically examined and laboratory investigations to diagnose the aetiology of chronic liver disease, and to assess the severity of liver and renal dysfunction were done.

Inclusion criteria:

Patients diagnosed with chronic liver disease (CLD) and have a definite aetiology for the CLD such as: Alcoholic chronic liver disease, Viral (Hepatitis B, Hepatitis C), Non-alcoholic steatohepatitis and Autoimmune (Wilson's disease, cryptogenic).

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Exclusion Criteria:

Unconscious patients, known patients of kidney disease, patients taking any nephrotoxic drugs and patients of chronic diseases such as tuberculosis, malignancy, diabetes mellitus were excluded from the study.

Methodology & Procedure:

After obtaining approval from IEC the present prospective cross-sectional study was conducted on 100 patients diagnosed with CLD of different aetiologies and qualifying the inclusion criteria. During the study period 125 patients were admitted with chronic liver disease but among them 25 were excluded as they had existing kidney disease or had a positive history of consuming nephrotoxic drug or had other chronic diseases like tuberculosis, malignancy or diabetes mellitus. Therefore, the number of study population was 100. Written Informed consent was obtained from each patient enrolled in the study.

Patients were interviewed about duration of the disease, presence of alcoholism, presence of yellowish discoloration of urine, vomiting of blood and passage of black stool. General examination was done to assess presence of anemia, jaundice, clubbing and oedema. The patients were also examined for presence of ascitis, hepatosplenomegaly, distented veins, everted umbilicus, spider naevi, palmar erythema, gynaecomastia, testicular atrophy, and bleeding manifestation to assess the severity of liver dysfunction.

Investigations

- Biochemical examination like blood for hemoglobin, total count, differential count, ESR, and fasting and post prandial sugar was done.
- Laboratory investigations like total bilirubin with conjugated and un-conjugated fraction, Alanine amino transferase, Aspartate amino transferase S, Alkaline Phosphatase, total protein, albumin, globulin, prothrombin time, HbSAg, Antinuclear antibody, Anti Liver Kidney Microsomal antibodies 1, 2 & 3 were done.
- Ascitic fluid was examined to assess the aetiology and severity of chronic liver disease.
- For assessment of kidney function serum urea, creatinine, seum sodium and potassium were examined.
- Radiographic examination like ultrasonography of upper abdomen and Kidney, Ureter, Bladder was done.
- Upper gastrointestinal endoscopy was done for detecting gastro-oesophagial varices.
- Routine and microscopic examination of urine, 24 h protein excretion and measurement of 24 h urine volume was also done.

Statistical Analysis

The data analysis was performed using IBM SPSS ver. 20 software. Frequency distribution and cross tabulation was used to prepare the tables. Quantitative variables were expressed as the mean and standard deviation. Categorical data was expressed as percentage. Microsoft office was used to prepare the graphs. Student t-test and ANOVA was used to compare the means. Mann Whitney and Kruskal Wallis test were used to compare the data. P value of < 0.05 is considered as significant.

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RESULTS

A prospective cross-sectional study was conducted among 100 patients to evaluate the assessment of renal function in chronic liver disease. Distribution of patients according to Age Majority of the patients [32(32%)] were in the age group of 31-40 years followed by 21% in the age group of 41-50 years, 17% in the age group of 61- 70 years, 15% in the age group of 51-60 years, 10% patients in the age group of 21-30 years and 5% in the age group of >70 years. The mean age of the patients was 44.78 ± 13.17 years. [Table 1]

Parameter	No. of patients (N)	Percentage
Age		
21-30	10	10%
31-40	32	32%
41-50	21	21%
51-60	15	15%
61-70	17	17%
>70	5	5%
Total	**100**	100%
Mean ± SD	**45.78 ± 13.19**	
Etiology		
Alcoholic chronic liver disease	73	73%
Hepatitis B virus	13	13%
Hepatitis C virus	11	11%
Nonalcoholic steatohepatitis	3	3%
Total	100	100%

Table 1: Distribution of patients according to age and etiology

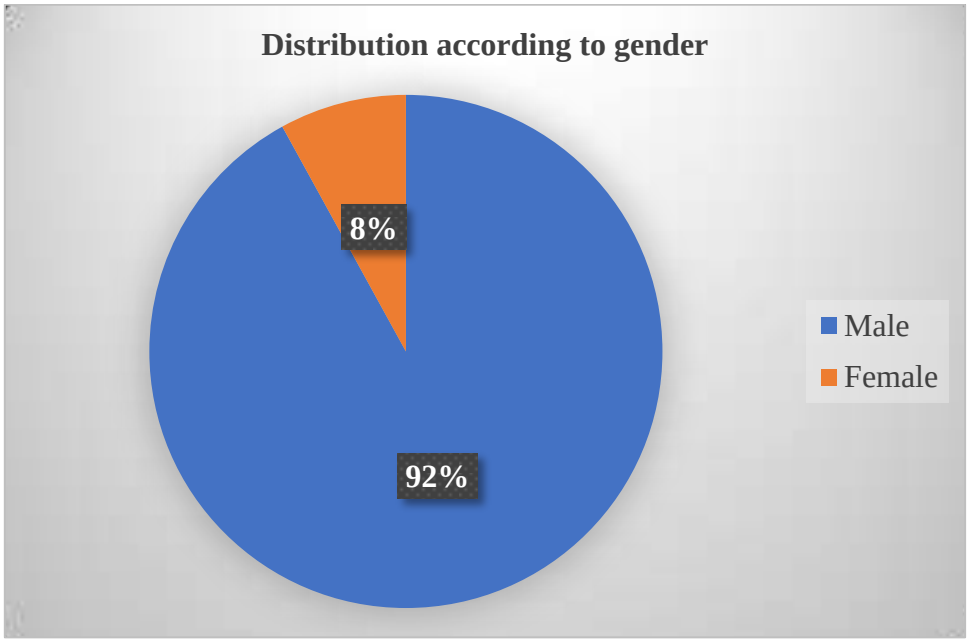

Figure 1: Distribution of patients according to sex

There was male preponderance [92(92%)] whereas female patients constituted 8% of the study group with a M:F ratio of 11.5:1. [Figure 1]

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Distribution of patients according to etiology: It was observed that found that 73 (73%) patients suffered from Alcoholic liver disease while 13 (13%) and 11 (11%) patients had chronic Hepatitis-B and chronic Hepatitis-C respectively. 3 (3%) patients had Nonalcoholic steatohepatitis. [Table 1]

Distribution of patients according to Renal Dysfunction: It was observed that 36 (36%) patients had renal dysfunction with Acute Kidney Injury (AKI) being the most common 21(58.33%) followed by Hepatorenal Syndrome (HRS) i.e.,15(41.67%). [Figure 2]

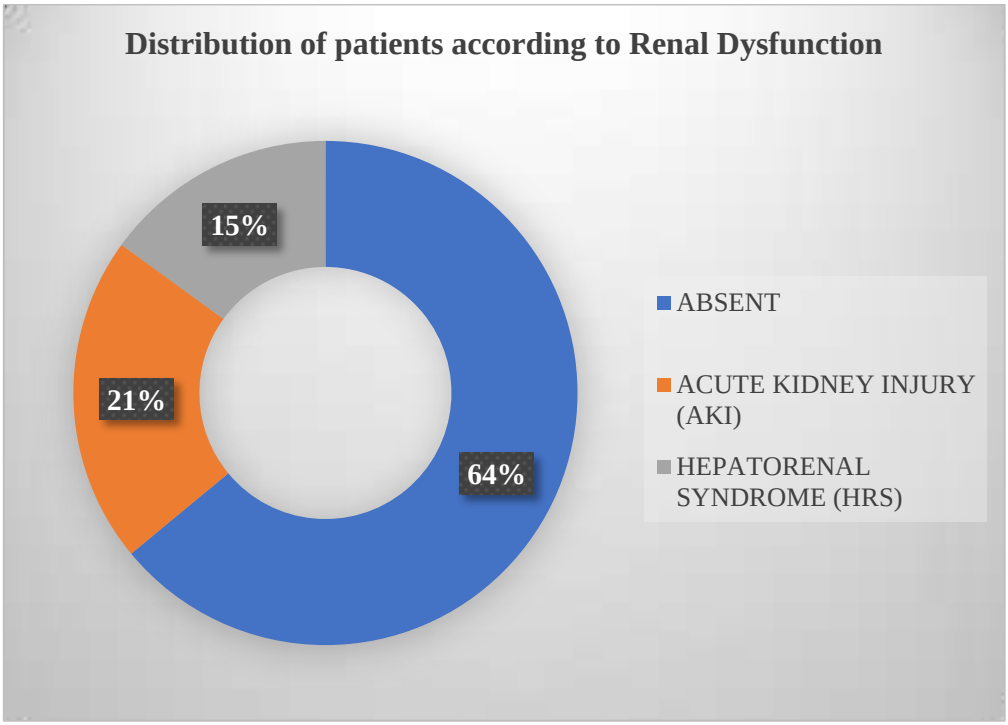

Figure 2: Distribution of patients according to Renal Dysfunction

Association of Etiology and Renal Dysfunction: Majority of the cases of renal dysfunction (29 out of 36; 80.5%) were associated with chronic alcoholic liver disease. However, there was statistically insignificant association between the etiology and renal dysfunction as per Chi-Square test (p>0.05). [Table 2]

Etiology	Normal Dysfunction		Renal Dysfunction		Chi-Square Value	p Value
	N	%	N	%		
Alcoholic chronic liver disease	44	44%	29	29%	1.426	>0.05
Hepatitis B virus	10	10%	3	3%		
Hepatitis C virus	8	8%	3	3%		
Nonalcoholic steatohepatitis	2	2%	1	1%		
Total	64	64%	36	36%		

Table 2: Association of Etiology and Renal Dysfunction

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Renal Function Profile of patients: 75 (75%) patients had serum urea in the range of 15-50 mg/dl while 48(48%) patients had serum creatinine level of 1 mg/dl. 76 (76%) patients had serum sodium level in the range of 137-145mEq/L while 89 (89%) patients had serum potassium in the range of 3.5-5.1mEq/L. 86 (86%) patients had serum chloride level in the range of 97-110mEq/L while 91 (91%) patients had uric acid level in the range of 2.5-7.0 mg/dl. [Table 3]

Liver Function Profile of patients: 74 (74%) patients had total bilirubin level >3 mg/dl while 56 (86%) patients had serum Alanine amino transferase (ALT) <100u/L. 51(51%) patients had serum Aspartate amino transferase (AST) <100 u/L and 60 (60%) patients had serum Alkaline phosphatase (ALP) within the range of 100-200 u/L. 94 (94%) had serum albumin level <3gmdl while 83 (83%) patients had serum globulin in the range of 2.5-4 gm/dl. [Table 4]

Parameters	**N**	**%**
Serum Urea (mg/dl)		
15-50	75	75%
>50	25	25%
Serum Creatinine (mg/dl)		
1	48	48%
2	24	24%
3	18	18%
4	10	105
Serum Sodium (mEq/L)		
<137	15	15%
137-145	76	76%
>145	9	9%
Serum Potassium(mEq/L)		
<3.5	6	6%
3.5-5.1	89	89%
>5.1	5	5%
Serum Chloride(mEq/L)		
<97	10	10%
97-110	86	86%
>110	4	4%
Uric acid(mg/dl)		

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2.5-7.0	91	91%
>7.0	9	9%

Table 3: Renal Function Profile of patients

Parameters	**N**	**%**
Total bilirubin (mg/dl)		
<2	18	18%
02-Mar	8	8%
>3	74	74%
Serum ALT(U/L)		
<100	86	86%
100-200	6	6%
>200	8	8%
Serum AST(U/L)		
<100	51	51%
100-200	34	34%
>200	15	15%
Serum ALP(U/L)		
<100	34	34%
100-200	60	60%
>200	6	6%
Serum albumin(gm/dl)		
<3	94	94%
3-3.5	4	4%
>3.5	2	2%
Serum globulin(gm/dl)		
<2.5	2	2%
2.5-4	83	83%
>4	15	15%

Table 4: Liver Function Profile of patients

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Association of Serum Urea and Child-Pugh classification: It was observed that there was statistically significant increase in abnormal value of serum urea with increase in the severity of liver disease as per Chi-Square test ($p<0.05$). [Table 5]

Association of Serum Creatinine and Child-Pugh classification: It was observed that there was significant increase in abnormal value of serum creatinine with increase in the severity of liver disease as per Chi-Square test ($p<0.05$). [Table 6]

Association of Renal Dysfunction and Child-Pugh classification: 5 (5%) patients each corresponded to Child–Pugh A class and Child–Pugh C class while 90 (90%) patients corresponded to Child–Pugh B class. There was significant increase in renal dysfunction with increase in the severity of liver disease ($p<0.05$; Chi Square test). [Table 7]

Classification	Normal		Abnormal		Chi-Square Value	p Value
	N	%	N	%		
Child-Pugh A (n=2)	2	6.25%	0	-	28.6	<0.05
Child-Pugh B (n=30)	28	87.5%	2	50%		
Child-Pugh C (n=4)	2	6.25%	2	50%		
Total	32	100%	4	100%		

Table 5: Association of Serum Urea and Child-Pugh classification

Classification	Normal		Abnormal		Chi-Square Value	p Value
	N	%	N	%		
Child-Pugh A (n=2)	2	6.25%	0	-	25.783	<0.05
Child-Pugh B (n=30)	29	90.60%	1	25%		
Child-Pugh C (n=4)	1	3.12%	3	66.67 %		
Total	32	100%	4	100%		

Table 6: Association of Serum Creatinine and Child-Pugh classification

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Classification	Normal		Abnormal		Chi-Square Value	p Value
	N	%	N	%		
Child-Pugh A (n=2)	2	6.25%	0	-	25.783	<0.05
Child-Pugh B (n=30)	28	90.60%	1	25%		
Child-Pugh C (n=4)	1	3.12%	3	66.67 %		
Total	32	100%	4	100%		

Table 7: Association of Renal Dysfunction and Child- Pugh classification

DISCUSSION

A prospective cross-sectional study was conducted among 100 patients in Department of Medicine, IMCHRC, Indore to evaluate the assessment of renal function in chronic liver disease. The prevalence of CLD has been increasing since last few years which can both be attributed to early diagnosis and an increased incidence.[10] One of the major concerns associated with CLD is its unrelenting course, as no therapies have been found to prevent its progression to advanced stages which are marked by fibrosis and cirrhosis as final outcome.

Advancement of liver disease is generally associated with various consequences such as PHTN (Portal Hypertension), upper GI bleed, ascites and SBP (Spontaneous bacterial peritonitis). Deranged liver physiology has a profound effect on the homeostatic mechanisms of the body affecting various other organs, including lungs and kidneys.

Importance of renal involvement in CLD has long been recognized by many workers. [1,11] Renal dysfunction has been recently emphasized by Choi et al. in a retrospective study, where they concluded that renal derangement in CLD was not an uncommon phenomenon. [12] Renal failure in patients with CLD, particularly with advanced liver disease, seems to be common; however, the exact incidence is unknown and is probably underestimated. This may be explained by the fact that patients with cirrhosis tend to have falsely low SCr levels due to decreased hepatic creatinine synthesis and decreased skeletal muscle mass. ARF in patients with cirrhosis frequently accompanies complications such as bacterial peritonitis, sepsis or hypovolemia from gastrointestinal bleeding, excessive diuretic therapy or administration of nephrotoxic drugs/contrast agents. [13] The probability of the occurrence of HRS in patients with cirrhosis and ascites at 1 and 5 years is 18% and 39%, respectively, with mortality approaching 100% in type 1 HRS without specific therapy. The median survival time in these patients without liver transplantation was only 12 days after diagnosis in one study. [14] However, this seems to have improved with terlipressin and albumin therapy.

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The development of ARF in patients with advanced liver disease has significant prognostic importance. [15] In patients with cirrhosis admitted to hospital with acute upper gastrointestinal hemorrhage, development of ARF forms an independent predictive factor for death. [16] There is considerable evidence that ARF in cirrhosis is primarily related to disturbances in circulatory function, mainly a reduction in systemic vascular resistance as a result of primary arterial vasodilatation in the splanchnic circulation, triggered by PHTN. [17] Furthermore, an intrinsic defect in cardiac performance termed cirrhotic cardiomyopathy lead to attenuated cardiac function, also contribute to renal dysfunction in cirrhotics particularly when exposed to stressful events like sepsis. [18]

The diagnosis of ARF in cirrhosis is traditionally made by a 50% increase in sCr with setting a fixed sCr threshold of ≥1.5mg/dl. [31] However, final consensus has not been reached yet on classification of cirrhosis-AKI. In the last decade, several attempts have been made. In 2002, the ADQI Working Group developed RIFLE criteria for AKI. Subsequent evidence that even small increase in sCr (as small as 0.3mg/dl) also has a negative impact on survival led to a modification of the RIFLE criteria called AKIN. [14]

More recently, the KDIGO criteria have been developed to reach a consensus drawing consolidating elements of both RIFLE and AKIN on staging AKI. [44] Whether these criteria improve the traditional criterion (a final threshold value for sCr of 1.5mg/dl) in terms of a better prediction of mortality is still a matter of debate. [19]

In the present study, majority of the patients [32(32%)] were in the age group of 31-40 years followed by 21% in the age group of 41-50 years, 17% in the age group of 61- 70 years, 15% in the age group of 51-60 years, 10% patients in the age group of 21-30 years and 5% in the age group of >70 years. The mean age of the patients was 44.78 ± 13.17 years. There was male preponderance [92(92%)] whereas female patients constituted 8% of the study group with a M:F ratio of 11.5:1. This is similar to the studies of Das N et al, [1] Mohan J et al, [20] Aggarwal HK et al, [2] and Zhou F et al. [21] Das N et al, [1] Mohan J et al, [20] Aggarwal HK et al, [2] also found a higher no. of males patients in their study with mean age 43.58 years, 48.32 ± 10.19 years, 46.12±11.33 years respectively . Zhou F et al, [21] found median age of the patients was 55.68±12.56 years, and 63.06% (n=210) of the patients were male.

In our study, majority of patients [73 (73%)] suffered from Alcoholic liver disease followed chronic Hepatitis-B and chronic Hepatitis-C i.e., 13 (13%) and 11 (11%) patients respectively. Only 3 (3%) patients had Nonalcoholic steatohepatitis. This is in concurrence with studies of Das N et al,[1] Mohan J et al,[20] Aggarwal HK et al,[2] and Zhou F et al. [21] Das N et al,[1] reported most common cause of chronic liver disease was alcohol 34 (68%) followed by Hepatitis B and Hepatitis C. Mohan J et al, [20] reported most common etiology of cirrhosis was alcohol [85% (85/100)], followed by Hepatitis B [11% (11/100)] and C virus [4% (4/100)].

Renal dysfunction was observed in 33.3% (5/15) of cirrhotic cases with viral etiology. There is no significant association between the etiologies of cirrhosis and renal disorders ($p = 0.25$). Aggarwal HK et al, [2] reported major etiology to be alcohol (n=88) and all the patients in this group were males. Other etiologies included cryptogenic (n=5), hepatitis B (n=4), hepatitis C (n=2) and alcohol with hepatitis B (n=1). Zhou F et al, [21] reported most common etiology of cirrhosis was HBV infection (n=232, 69.7%), followed by miscellaneous (n=40,12%), Alcohol (n=30, 9%), Cholestasis (n=17, 5.1%), and Autoimmune (n=14, 4.2%).

It was observed in our study that 24 (36.9%) patients had renal dysfunction. This was similar to results obtained by Mohan J et al, [20] who stated renal diseases prevalence in 22% (22/100) of cirrhotic patients. The most common type of renal dysfunction in our study was

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Acute Kidney Injury (58.3%) followed by Hepatorenal Syndrome (42.7%). This is concordant to the studies of Mohan J et al,[20] Zhou F et al. [21] and Bucsics Tet al [23]. Bucsics T et al, [23] study summarized that Renal dysfunction is a common complication of liver cirrhosis and of utmost clinical and prognostic relevance. Patients with cirrhosis are more prone to developing acute kidney injury (AKI) than the noncirrhotic population. Pre-renal AKI, the hepatorenal syndrome type of AKI (HRS-AKI, formerly known as 'type 1') and acute tubular necrosis represent the most common causes of AKI in cirrhosis. Mohan J et al, [20] reported AKI as the most common type of renal dysfunction in liver cirrhotic 12% (12/100) of patients followed by HRS (7%, 7/100) and CKD (3%, 3/100). Zhou F et al, [21] reported prevalence of AKI in cirrhotic patients was 18.01% by the KDIGO criteria, and 25.22% by the 'Delta-sCr' system.

It was observed in the present study that majority of the cases of renal dysfunction (29 out of 36; 80.5%) were associated with alcoholic chronic liver disease. However, there was statistically insignificant association between the etiology and renal dysfunction ($p>0.05$; Chi-Square test). Mohan J et al, [21] reported no statistically significant difference in renal parameters in different etiologies of liver cirrhosis.

Renal function profile showed that in our study, showed a statistically significant increase in abnormal value of serum urea and serum creatinine with increase in the severity of liver disease ($p<0.05$; Chi-Square test) Similar observations were noted in the studies of Aggarwal HK et al, [2]and Das N et al. [1]

It was observed in the present study that there was significant increase in abnormal value of serum urea and serum creatinine with increase in the severity of liver disease as per Chi-Square test ($p<0.05$).. There was significant increase in renal dysfunction with increase in the severity of liver disease ($p<0.05$). This is similar to the studies of Mohan J et al,[20] Das N et al,[1] Al-Mamun A et al,[24] and Fornari F et al. [25] Mohan J et al,[20] reported that there is an increase in the number of renal disorders with increase in the severity of cirrhosis. In the cirrhotic patients with higher severity of cirrhosis (Child Pugh class B and C), renal dysfunction was developed much more (OR=3.37; CI=1.08-10.5; P = 0.03). Das N et al,[1] reported distribution of serum urea and creatinine, according to the severities of liver disease as per Child Pugh classification, was statistically significant, but serum creatinine level on day 1 and day 3 was not found to be significantly distributed among different aetiologies of chronic liver disease. Al-Mamun A et al,[24] reported no statistically significant relation between Child-Pugh score and serum creatinine. Fornari F et al,[25] study showed 30% of patients with cirrhosis had gall stones, risk of developing stones most strongly associated with Child's grade C & alcoholic cirrhosis with a yearly incidence of about 5%.

Limitation: The study was done with limited patients admitted in a hospital so for generalization derivation from of the results, a further study with larger sample and in different settings would be required.

CONCLUSION

Assessment of renal function is crucial in the evaluation of patients with cirrhosis. It guides diagnostic and therapeutic management as well as helping determine the prognosis of these patients. This study emphasizes the fact that we should be more vigilant when treating CLD patients, regarding their renal function, as proper screening, prevention and treatment of renal dysfunction can decrease morbidity and mortality.

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None

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DECLARATIONS

Conflicts of interest

There is no conflict of interest with publication of manuscript or an Institution or product that is mentioned in the manuscript and/or is important to outcome of study presented.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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