

Study of Relation of Renal Functions in Chronic Liver Disease Patients

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Abstract: ***Background:** The inter relationship between liver disease and renal dysfunction was recognised since ages as this has been the considerable amount of research since then. kidney dysfunction in liver diseases may be due to different etiologies most of them with cirrhosis. Renal dysfunction in chronic liver disease follows a progressive course final being hepato renal syndrome. There is no clear explanation that fully defines the relationship between the diseased liver and disturbances in kidney function, though substantial progress is being made in recent years regarding research in this aspect. **Methodology:** The present study was carried out in the Department of General Medicine, GSL medical college/Hospital, Rajahmundry from NOVEMBER 1st-2015 to APRIL 30th-2017. Total 162 patients with chronic liver disease who satisfied inclusion and exclusion criteria were recruited in present study, with Cross-sectional study design. **Results:** 162 patients with chronic liver disease were evaluated for renal dysfunction. The mean age of patients in the present study was 50.69 years. Majority of cirrhotics were in the age group of 50-59 years. The numbers of males were 144 (88.9%) and the numbers of females were 18 (11.1%). The most common cause of chronic liver disease was alcoholism which was seen in 109 (67.2%) patients. Most of the patients were in group with GFR 30-60 ml/minute. Difference in the values of creatinine clearance calculated by using the Cockcroft Gault formula (CGF) and timed urine collection was found to be statistically significant (p value 0.001). **Conclusion:** Renal dysfunction is very common and is a major risk factor for increased mortality in patients with decompensate cirrhosis. The present study showed that standard measures of renal function, namely blood urea and serum creatinine should not be the only criteria to assess renal reserve in chronic liver disease, as they may seem normal even in gross renal dysfunction. Alcoholism was the most common cause of cirrhosis in the present study and also the most important modifiable causative factor for chronic liver disease and timed urine collections should be done routinely to assess renal reserve in advanced liver disease*

1. Introduction

Chronic liver disease is defined as progressive destruction of the liver parenchyma over a period greater than 6 months leading to fibrosis and cirrhosis. Renal dysfunction is a common and serious problem in patients with advanced liver disease. Particularly, alterations in renal physiology in chronic liver disease/cirrhosis with ascites can predispose patients to a specific functional form of renal failure known as hepatorenal syndrome (HRS) ⁽¹⁾. Renal dysfunction is a serious complication in patients with cirrhosis and associated with significant morbidity and mortality ^(2,3).

The interrelationship between liver disease and renal dysfunction was recognized as early as the era of Hippocrates and this has been the object of a considerable amount of research since then. Patients with chronic liver disease frequently develops renal insufficiency with an estimated prevalence of 20% to 25% ⁽⁴⁾. An Indian study from South India, showed that a 22% patient with cirrhosis presented with renal dysfunction (5), Hence Detection of renal insufficiency is clinically important. glomerular filtration rate. There is no explanation that fully defines the complex relationship between the diseased liver and disturbances in kidney function, though substantial progress is being made in recent years regarding research in this aspect. One of the most difficult issues in the clinical evaluation of patients with cirrhosis is the accurate assessment of renal function. Standard measures of renal function like blood urea nitrogen and serum creatinine are likely to give erroneous results and hence alternative methods to determine renal reserve must be Kidney dysfunction in liver disease can be due to different etiologies and can have diverse manifestations. Most of the

abnormalities of kidney function in cirrhosis are of functional origin namely, sodium retention, impaired free water excretion and renal vasoconstriction with decrease in renal perfusion and used.

Aims and Objectives

- To determine the role of serum creatinine in assessing renal function in patients with chronic liver disease.
- To determine the usefulness of creatinine clearance as a parameter in the assessment of renal function in patients with chronic liver disease.
- To find out whether there is any effect of etiology of chronic liver disease on renal dysfunction.

2. Materials and Methods

The present study was carried out in the Department of General Medicine, GSL medical college/Hospital, Rajahmundry from NOVEMBER 1st-2015 to APRIL 30th-2017. Total 162 patients with chronic liver disease who satisfied inclusion and exclusion criteria were recruited in present study, with Cross-sectional study design.

Inclusion Criteria: Evidence for chronic liver disease being defined by:

A compatible Clinical profile (signs of liver cell failure or reduced liver span) along with Biochemical (altered liver function tests, reversal of albumin-globulin ratio) or Sonographic evidence (altered echotexture of liver)

Exclusion Criteria

- Elderly patients (>60 years)
- Overt renal failure (S. creatinine >1.5)
- Diabetes mellitus / Hypertension

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- Known primary renal disease
- Recent gastrointestinal bleed
- Grade 4 hepatic encephalopathy

Methodology

Inpatients admitted in the medical ward/ICU/AMCU with chronic liver disease with seemingly normal renal function after the institutional ethical committee approval and informed consent taken from patients were included in the study. Data regarding demographic variables (age, weight), clinical features (presenting complaints, ascites, jaundice, encephalopathy, history of alcoholism, etc) and clinical examination findings of liver cell failure were collected using a proforma. Diuretics were stopped for 3 days before carrying out lab investigations.

Lab investigations including complete Liver function test, Renal function tests, Viral markers for hepatitis B and hepatitis C, Urine analysis, 24 hour urine volume and Urine creatinine was done and results noted. Patients were subjected to an ultrasound scan of abdomen with regard to liver echotexture and size, evidence of splenomegaly or portal hypertension, presence of ascites and kidney pathology. Creatinine clearance for the patient was calculated by the formula: (URINE CREATININE / SERUM CREATININE MULTIPLIED BY 24 HOUR URINE VOLUME). $[(UCr / PCr) \times V]$. This was divided by 1440 to get the value in ml/minute. Creatinine clearance was also calculated using the Cockcroft and Gault formula (CGF): $(140 - AGE) \times WEIGHT / (SERUM CREATININE \times 72)$. This value is to be multiplied by 0.85 if the patient is female. Comparison between serum creatinine and creatinine clearance calculated by these two methods were done and the results were noted.

Statistical Methods

- Data entry and statistical analysis were performed with the help of Microsoft excel 2007 and SPSS version 21.0
- Categorical variables were presented as numbers and percentages.
- Chi-square test was used to assess the association among different categorical variables.
- Logistic regression was performed to determine association among continuous and categorical variables.
- Correlation was performed to find out the relation between different continuous variables.
- The statistical significance level was fixed at p value of <0.05.

3. Results

The present study of 162 patients, in the Department of General Medicine, GSL medical college and Hospital, Rajahmundry for a period of one year six months from Nov-2015 to April-2017. In this study, 227 patients with chronic liver disease were enrolled. Out of these 227 patients, 65 patients were excluded based on exclusion criteria. So, a total number of 162 patients were included in this study.

Age of the patients ranged from a minimum of 24 years to a maximum of 60 years. The mean age was 50.69 years.

Patients who were above the age of 60 years were excluded, as GFR reduces with increasing age.

Out of the 162 patients included in this study, 18 (11.11%) members were female and the rest 144 (88.89%) members were male patients.

ETIOLOGY: In these 162 patients with chronic liver disease (cirrhosis), the cause of liver disease was found to be chronic alcoholism in 109 patients; hepatitis-B in 27 patients ; hepatitis-C in 9 patients ; Wilson's disease in one patient. In the remaining 16 patients, the cause could not be found. In these three groups, there was no significant variation in blood urea levels. This suggests that estimation of blood urea will not be of much help in determining renal dysfunction. The mean blood urea level was 21.63 mg/dL. p value for blood urea of the three groups was 0.194, which was statistically not significant.

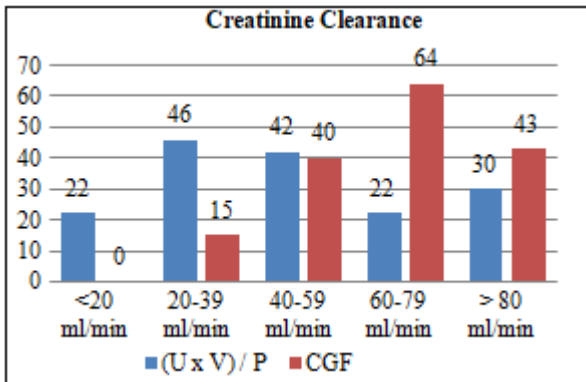
Table 1: Distribution of Study Subjects according to Etiology

Etiology	No: of Patients	Percentage (%)
ALCOHOLISM	109	67.28 %
HEPATITIS-B	27	16.67 %
HEPATITIS-C	9	5.5 %
WILSON'S DISEASE	1	0.62 %
UNKNOWN	16	9.8 %

SERUM CREATININE: In this study, only the patients with creatinine levels less than 1.5 mg/dL were included. It was observed that in 27 out of 39 patients with creatinine clearance less than 30 ml/min, serum creatinine levels failed to rise above 1.2 mg/dL, suggesting that moderate to severe renal dysfunction may be masked by seemingly normal creatinine levels, even though the p value was 0.001 for these three groups, which was statistically significant. The mean serum creatinine level was 0.98 mg/dL.

Table 2: Assessment of Renal Function based on Different Parameters

	Group A Mean (SD)	Group B Mean (SD)	Group C Mean (SD)	p Value
Blood Urea (mg/dl)	21.05 (3.32)	22.16 (3.52)	21.43 (3.40)	0.194
Serum Creatinine (mg/dl)	0.84 (0.14)	1.009 (0.18)	1.138 (0.19)	0.001
24hour Urine Volume ml	1836.53 (218)	1310.56 (360)	723 (192)	0.001
Creatinine Clearance (UXV/P) ml/min	81.81 (13.72)	43.99 (9.32)	19.75 (4.66)	0.001
Creatinine Clearance (CGF) ml/min	85.22 (11.74)	64.79 (12.84)	47.2 (10.8)	0.001



Graph 1: Comparison of Creatinine Clearance Measured by Timed Urine Collection and Cockcroft Gault Formula

21 (i.e., ~20%) out of 107 patients with creatinine clearance more than 60 ml / minute by Cockcroft-Gault formula were found to have creatinine clearance values less than 40 ml/minute when measured by timed urine collection. p value calculated was found to be 0 found to be statistically not significant. The mean serum protein level was 6.2 g/dL. p value was 0.98. The association between serum total protein and severity of renal dysfunction was found to be statistically not significant.

Ultrasound Observations: Ultrasound abdomen was done in all the 162 patients. Findings of splenomegaly and altered echotexture of liver were uniformly seen in all these patients. Ascites was present in 153 out of the 162 patients. Nine patients did not have ascites. This suggested that ascites may be one of the first changes in worsening renal function. Kidney size and corticomedullary differentiation were found to be normal in all these 162 patients. Liver was found to be shrunken in size in 156 of the study subjects. 5 out of 6 with malignant transformation belonged to group C (i.e., <30 ml/minute). This observation suggests that most of the patients with malignant transformation have worsened renal function.

.001 which is statistically significant. Out of the 109 alcoholic liver disease patients, only 26 (23.8 %) had creatinine clearance more than 60 ml/minute, whereas 14 (51.8%) out of the 27 HBsAg positive patients had creatinine clearance more than 60 ml/minute. 5 (55%) out of 9 HCV positive patients had creatinine clearance more than 60 ml/minute. 7 (43.7%) out of 16 patients with liver disease of unknown etiology had creatinine clearance of more than 60 ml/minute.

The association between alcoholism as etiology of chronic liver disease and severity of renal dysfunction was found to be statistically significant. p value was 0.004. The association between hepatitis-B as etiology of chronic liver disease and severity of renal dysfunction was found to be statistically not significant. p value was 0.052. The association between hepatitis-C as etiology of chronic liver disease and severity of renal dysfunction was found to be statistically not significant. p value was 0.281. Other etiologies association were also

4. Discussion

This study included 162 patients admitted in GSL General Hospital, with chronic liver disease with emphasis on renal function. The mean age in the present study was 50.69 years concordance with other studies like Jaiganesh et al and MacAulay et al (5, 6) The reported mean age of Indian cirrhotic patients is around 51 years (50). In the present study, majority of cirrhotics were in the age group 40-59 years. This is in concordance with other Indian studies like Ahmed et al, Devasia et al, Mohanavalli B et al, Xavier S et al studies (7, 8, 9, 10). In present study, 88.9% of stroke patients are males and 11.1% are females, which is comparable with Devasia, et al study (81.4%, 18.6%) (8), Ahmed et al study (85%, 15%) (7), Aggarwal et al study (96%, 4%) (12) Jaiganesh et al study (95%, 5%) and Nupur Das et al study (86%, 14%) (11).

In India, alcoholism is more prevalent among men. According to various studies, alcoholism is the most common cause of chronic liver disease. In the present study, the most common cause of chronic liver disease was alcoholism, which was seen in 67.2% patients. This is comparable to other studies, Devasia, et al study (48.8%) (8), Ahmed et al study (68.7%) (7), Aggarwal et al study (88%) (12), Nupur Das et al study (68%) (11) and Jaiganesh et al study (85%) (5). In all these studies, the most common cause of chronic liver disease was also alcoholism.

Table 3: Distribution of Study Subjects according to Etiology in Other Studies

Study	Alcoholism	Hepatitis B	Hepatitis C	Wilson's disease	Autoimmune	Unknown
Present Study	67.2%	16.6%	5.5%	0.6%	0	9.8%
Devasia, et al (8)	48.8%	13.9%	0	2.3%	2.3%	32.5%
Ahmed et al (7)	68.7%	11.2%	11.2%	0	1.25%	7.5%
Aggarwal et al (12)	88%	4%	2%	0	0	5%
Nupur Das et al (11)	68%	14%	6%	4%	2%	0
Jaiganesh et al (5)	85%	11%	4%	0	0	0

The second most common cause of chronic liver disease was chronic hepatitis-B, which was seen in 16.6% patients in the present study,

Table 4: Distribution of Study Subjects according to Creatinine Clearance in Other Studies

Group	Creatinine Clearance	Present Study	Devasia et al Study
Group A	>60 ml/minute	52 (32.09%)	14 (32.55%)
Group B	30-60 ml/minute	71 (43.82%)	19 (44.18%)
Group C	<30 ml/minute	39 (24.07%)	10 (23.25%)
Total	-	162 (100%)	43 (100%)

In the present study, the 162 patients were grouped into three groups based on their creatinine clearance from timed urine collection [(UxV)/P]. Group A having values more

than 60 ml/min, Group B 30-60 ml/min and Group C less than 30 ml/min. In the present study, most of the patients belonged to Group B (43.82%) followed by Group A (32.09%) and lastly Group C (24.07%). In the Devasia et al study also, most of the patients belonged to the group with GFR 30-60 ml/minute (44.18%) and least were in the group with GFR <30 ml/minute (23.25%)⁽⁷⁾.

In the present study, the mean serum creatinine level of total patients was 0.98 mg/dL. In the Devasia et al study was 0.9 mg/dl⁽⁸⁾. In the present study, 27 out of 39 patients with creatinine clearance less than 30 ml/min, serum creatinine levels failed to rise above 1.2 mg/dL This suggests that even severe renal dysfunction may be masked by seemingly normal creatinine levels.

Table 5: Comparison Of Mean Serum Creatinine Level with Other Studies

Study	Mean Serum Creatinine Level in Mg/Dl
Present Study	0.98
Devasia, et al ⁽⁸⁾	0.9
MacAulay et al ⁽⁶⁾	0.984

Serum creatinine measurements may underestimate changes in GFR because of

- 1) Hepatic production of creatinine is impaired in cirrhosis^(13, 14) and
- 2) Decreased endogenous production of creatinine in cirrhotics due to decreased muscle mass as a result of severe wasting; increased tubular secretion in cirrhosis further reduces the serum creatinine level and decrease the accuracy of serum creatinine in assessing the renal function

Hence, to check for renal dysfunction in advanced liver disease, routine tests like blood urea and serum creatinine will not be sufficient. We have to depend on other renal function tests like creatinine clearance estimation using timed urine collection or eGFR formula like Cockcroft Gault formula, among which creatinine clearance estimation using timed urine collection method was found to be more accurate when compared to Cockcroft Gault formula based creatinine clearance estimation. In the present study, patients with greater amount of renal impairment were found to have lesser urine output. This suggests that a patient with history of decreased urine may have renal dysfunction even with normal creatinine levels. 21 out of 107 patients with creatinine clearance more than 60 ml / minute by Cockcroft Gault formula were found to have creatinine clearance values less than 40 ml/minute when measured by timed urine collection. p value calculated was found to be 0.001 which is statistically significant.

Most of the patients with cirrhosis and ascites will have a GFR of less than 60 ml/minute but a normal serum creatinine level compared with study with MacAulay et al⁽⁶⁾. The level of serum creatinine required for the diagnosis of HRS is 1.5 mg/dL, in the absence of diuretic therapy MacAulay et al.⁽⁶⁾ observed that among the creatinine-based glomerular filtration rate formulas, the MDRD formula developed by the modification of diet in renal disease (MDRD) study group is the best formula for detection of moderate renal dysfunction among those with cirrhosis. This

formula is developed based on the patient's creatinine levels, age, sex, race and blood urea nitrogen and serum albumin levels and it showed a larger proportion of agreement with radionuclide GFR in patients with advanced liver disease.

A systematic review and meta-analysis of patients with cirrhosis by Proulx et al⁽¹⁵⁾ showed that although creatinine clearance measured by timed urine collections overestimates GFR in patients with liver cirrhosis, it is a preferable method in clinical practice, as it is more reliable than serum creatinine or predicted creatinine clearance (by CGF). Proulx et al⁽¹⁵⁾ also suggested that creatinine clearance was an aid in determining true GFR when inulin clearance was not available or feasible and may be a useful clinical test in the evaluation of renal insufficiency in cirrhotic patients with normal serum creatinine values. Inulin clearance⁽¹⁶⁾, along with other more accurate methods like radioisotopes 99mTc-DTPA, 169Yb-DTPA, or 125I-iothalamate to estimate glomerular filtration rate is not feasible in routine clinical practice because of the complexity, cost, and limited availability^(17, 18).

The present study showed that standard measures of renal function, namely blood urea and serum creatinine should not be the only criteria to assess renal reserve in chronic liver disease, as they may seem normal even in gross renal dysfunction. Hence, to check for renal dysfunction in advanced liver disease, routine tests and other methods like measured creatinine clearance should be employed to get an accurate picture of the renal status. In the study by Nupur Das et al⁽¹¹⁾, 94% of study subjects had serum albumin level less than 3 g/dL, 4% patients between 3-3.5 g/dl and 2% had more than 3.5 g/dL. In the Nupur Das et al⁽¹¹⁾ study also, it was found that serum albumin levels have significant correlation with severity of renal dysfunction.

The present study had shown a direct correlation between serum albumin levels and renal function. This may also indicate that renal dysfunction is more with advancing classes of Child-Pugh classification. The correlation with albumin levels has also been noted in a study by Amarapurkar et al⁽¹⁹⁾. It also showed a higher mortality in patients with lower creatinine clearance especially in patients with hepatorenal syndrome. But a study by Hampel et al showed no significant difference in serum levels of albumin and did not consider it as a risk factor for renal dysfunction⁽²⁰⁾. The same study showed no significant differences in age, etiology of cirrhosis, serum levels of bilirubin, encephalopathy, prothrombin time, urinary tract infection, bacteremia, or occurrence of esophageal variceal bleeding in cirrhotic patients with or without renal dysfunction. Patients who developed renal dysfunction were more likely to have ascites. This was seen in the present study also.

The study by Hampel et al also showed aminoglycoside treatment as a strong risk factor for renal dysfunction, independent of the severity of liver disease or spontaneous bacterial peritonitis⁽²⁰⁾. In the present study, the least value of serum total protein was 5.4 g/dL and the highest value was 7.1 g/dL. The mean serum protein level was 6.2 g/dL. p value was 0.98. The association between serum total protein and severity of renal dysfunction was found to be

statistically not significant among the three groups of this study. Mean serum bilirubin (of the total 162 patients) was 1.67 mg/dL. p value of serum bilirubin among the three groups of the present study was 0.826 which was statistically not significant even when compared with other studies.

In the present study, ascites was present in 153 (94.44%) out of the 162 patients. It was noted that the patients without ascites had relatively better renal function. This suggested that ascites may be one of the first changes in worsening renal function. This finding is also in agreement with the study by Hampel et al⁽²⁰⁾. In the present study, kidney size and corticomedullary differentiation were found to be normal in all these 162 patients, suggesting that there was renal dysfunction which no parenchymal changes. In the present study, liver was found to be shrunken in size in 156 of the study subjects. The remaining 6 which were not shrunken, showed changes of malignant transformation. Five of these six patients with malignant transformation belonged to group C (i.e., <30 ml/minute). This observation suggests that most of the patients with malignant transformation have worsened renal function.

5. Conclusions

Renal dysfunction is very common and is a major risk factor for increased mortality in patients with decompensated cirrhosis. An attempt should always be made to identify it early and categorize patients in different groups as treatment and prognosis differs in these subgroups. Patients usually have downhill course once hepatorenal syndrome develops while patients with AKI because of pre-renal azotemia can be successfully treated if detected early.

The present study comprised of 162 subjects, aged less than 60 years, with chronic liver disease and were admitted to GSL General Hospital between 1st November 2015 and 30th April 2017. It is concluded from the present study that alcoholism is the most common cause and also the most important modifiable causative factor for chronic liver disease and timed urine collections should be done routinely to assess renal reserve in advanced liver disease.

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