Journal of Cardiovascular Disease Research

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 10, 2023

Original Research Paper

A STUDY ON RENAL FUNCTION TESTS IN CHRONIC LIVER DISEASE AT TERTIARY CARE CENTRE

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ABSTRACT:

Background: Kidney damage in a patient with liver illness could have many different reasons. Intravascular volume reduction, gastrointestinal haemorrhage, sepsis, and nephrotoxins are common causes. [(1)] Kidney dysfunction typically progresses in hepatic cirrhosis patients and eventually results in hepatorenal syndrome (HRS). Early on, it was understood that there was a connection between hepatic disease and kidney impairment, and since then, this relationship has been extensively investigated.

OBJECTIVES:

• To assess the adequacy of serum creatinine, creatinine clearance and other routine renal function tests in evaluating renal dysfunction for patients with chronic liver disease.

• To find if renal functional abnormalities were influenced by the etiology of the chronic liver disease.

MATERIAL & METHODS: Study Design: Prospective cross sectional study. **Study area:** Department of Medical Gastroenterology, NRI Academy of medical sciences, Chinakakani, Guntur, Andhra Pradesh.

Study population: The study was performed amongst the patients admitted in medical wards and Intensive care units. **Sample size**: Study consisted a total of 86 subjects. **Sampling Technique:** Convenience sampling. For this study chronic liver disease was defined as hepatic injury with progressive destruction of liver parenchyma. Data regarding demographic variables (age, sex and weight), clinical features (presenting complaints, ascites, jaundice, urine output, features of encephalopathy, history of alcoholism, etc) and clinical examination findings of liver cell failure were collected using a predesigned proforma.

Results: For the patients in this present study, the urine output was measured for 24 hours. Mean value of 24-hour urine volume of all the patients in Group-I was 2010.71 ml with a standard deviation of 203.8. This was followed by mean value of 1136.84 ml with a SD of 217.4 in group-II patients, and a mean of 690 ml in group-III with a SD of 169.8. Patients with more severe renal impairment were found to have lesser amounts of urine output. The mean 24-hour urine volume of all the patients was 1317.4 ml.

CONCLUSION: In chronic liver disease, serum creatinine alone was not a reliable marker to assess renal dysfunction. Routine renal function tests like blood urea and serum creatinine will not be sufficient to check for adequacy of renal function. Other methods like measured creatinine clearance should be employed to get an accurate picture of the renal status.

Keywords: hepatorenal syndrome, serum creatinine, Routine renal function tests

INTRODUCTION:

Kidney damage in a patient with liver illness could have many different reasons. Intravascular volume reduction, gastrointestinal haemorrhage, sepsis, and nephrotoxins are common causes. [(1)] Kidney dysfunction typically progresses in hepatic cirrhosis patients and eventually results in hepatorenal syndrome (HRS). Early on, it was understood that there was a connection between hepatic disease and kidney impairment, and since then, this relationship has been extensively investigated. In roughly 20% of patients hospitalised for decompensating liver cirrhosis, acute kidney injury (AKI), defined as a sudden increase in the blood creatinine level of at least 0.3 mg/dL, takes place. [(2)]

Renal failure in a patient with liver cirrhosis should unquestionably be assessed because renal insufficiency increases mortality and morbidity in those patients. Renal insufficiency is also important for people who are waiting for liver transplants. When compared to patients without renal failure, people with hepatic cirrhosis experience more problems.

Hepatic disease's renal impairment can have a variety of aetiologies and symptoms. The main functional factors that contributed to renal failure in hepatic cirrhosis included sodium retention, decreased free water excretion, and renal vasoconstriction. [(3)] Despite the fact that HRS is functioning, it has a bad prognosis. [(4)]

It is yet unclear how liver illness and kidney impairment are related to one another. Although research in this area has advanced significantly in recent years, further study was still required. It was challenging to evaluate renal function in a patient with hepatic cirrhosis because standard renal function tests like BUN and blood creatinine could produce false results. As a result, it was necessary to apply alternative techniques to accurately test the renal function in such patients.

OBJECTIVES:

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• To find if renal functional abnormalities were influenced by the etiology of the chronic liver disease.

MATERIAL & METHODS:
Study Design: Prospective cross sectional study.
Study area: Department of Medical Gastroenterology, NRI Academy of medical sciences, Chinakakani, Guntur, Andhra Pradesh.
Study Period: 6 months.
Study population: The study was performed amongst the patients admitted in medical wards and Intensive care units.
Sample size: Study consisted a total of 86 subjects.
Sampling Technique: Convenience sampling.

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 hepatic echotexture) (Or)
- Tissue diagnosis (positive liver biopsy for cirrhosis)

Exclusion criteria:
a) Elderly patients (>60 years)
b) Overt renal failure (S. creatinine >1.5)
c) Known primary renal disease
d) Diabetes mellitus / Hypertension
e) Grade 4 hepatic encephalopathy
f) Recent gastrointestinal bleed.
Patients above 60 years were excluded as the glomerular filtrate rate (GFR) decreases with age. False low GFR thus calculated could interfere with the findings of this study leading to misinterpretations.
Diabetes and/ or Hypertension can impair the kidney function, hence patients with those above co-morbid conditions were excluded. Similarly, recent gastrointestinal bleed impairs renal function temporarily, hence was excluded.
Ethical consideration: Institutional Ethical committee permission will be taken prior to the commencement of the study.

Study tools and Data collection procedure:
For this study chronic liver disease was defined as hepatic injury with progressive destruction of liver parenchyma.
Data regarding demographic variables (age, sex and weight), clinical features (presenting complaints, ascites, jaundice, urine output, features of encephalopathy, history of alcoholism, etc) and clinical examination findings of liver cell failure were collected using a predesigned proforma.
Diuretics were withheld for 2 days before carrying out lab investigations. Lab investigations including complete liver function test, renal function tests, viral markers for hepatitis B, 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 regarding liver echo texture and size, evidence of splenomegaly or portal hypertension, presence of ascites and kidney pathology.

Creatinine clearance for the patient was calculated using timed urine samples by the following formula:

= URINE CREATININE x 24 HOUR URINE VOLUME SERUM CREATININE

$$= \frac{(U / P) \times V}{}$$

This value 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) x WEIGHT** (in kgs) **/ (SERUM CREATININE x 72)**
ml/minute.

This value has to be multiplied by 0.85 if the patient is female.

Serum creatinine values and creatinine clearance calculated by Cockcroft and Gault formula were compared with creatinine clearance by timed urine collection, which is a standard to measure renal function.

Statistical analysis:
The collected data was compiled and analyzed in SPSS Vr. 20 (Trial version). Variation of the variables among the 3 groups was estimated by analysis of variance test (ANOVA) and a p-value of < 0.05 was considered statistically significant. The results were presented in frequencies, proportions, means, standard deviations and graphs.

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OBSERVATIONS & RESULTS:

Table 1: Age wise distribution of the patients

AGE GROUP	NUMBER OF PATIENTS (%)
Less than 30 years	4 (4.6%)
30 to 39 years	18 (20.9%)
40 to 49 years	48 (55.8%)
Above 50 years	16 (18.6%)

Age of the patients ranged from a minimum of 24 years to a maximum of 58 years. The mean age was 42.2 years. There were 48 out of 86 patients (55.8%) in 40-49 years age group, followed by 18 patients (20.9%) in 30-39 years' age group. Among the patients included in the study, 70 patients out of 86 (81.4%) were males, while remaining 16 (18.6%) were females.

Table 2: Etiological distribution of the patients

ETIOLOGY	NO. OF PATIENTS (Total - 86 patients)	PERCENTAGE
ALCOHOLISM	42	48.83%
HEPATITIS B	14	16.28%
HEPATITIS C	12	13.95%
AUTO IMMUNE HEPATITIS	2	2.33%
UNKNOWN	16	18.60%

The patients in this study group distributed according to the etiology of the liver disease in each of them. Out of the 86 patients with hepatic cirrhosis, the cause of liver disease was attributed to alcoholism in 42 patients (48.8%). This was followed by viral hepatitis consisting of hepatitis B surface antigen (HBs Ag) positive and Anti-hepatitis c antibody (anti-HCV Ab) positive patients. Among them others 14 out the total 86 patients (16.28%) were found to be positive for Hepatitis B surface antigen. 12 out of the 86 patients (13.95%) were Hepatitis C antibody positive. Together viral hepatitis constitutes 26 of the total study group (30.2%). Another 2 patients were found to have autoimmune hepatitis. In the remaining 16 patients, causative etiology could not be completely ascertained.

ASSESSMENT OF RENAL FUNCTION BY DIFFERENT METHODS:

Out of the 86 patients, renal function was assessed by blood urea, serum creatinine and creatinine clearance. The creatinine clearance was estimated by two methods. They were creatinine clearance by timed urine collection method [(UxV)/P] and creatinine clearance by Cockcroft and Gault formula (CGF). The patients were grouped into three groups, based on their creatinine clearance from timed urine collection method [(UxV)/P] :

Group-I consists of patients having values more than 60 ml/min, Group-II were with values 30-60 ml/min and Group-III was with values less than 30 ml/min.

The mean value of the three groups was calculated individually and the combined data was tabulated and analysed.

Table 3: "ANOVA TEST" WITH MEANS OF QUANTITATIVE VARIABLES

	GROUP- I		GROUP – II		GROUP - III			
	M	SD	M	SD	M	SD	'f'	'p'
BUN	22.43	3.0	22.42	3.5	22.40	2.5	0.0	1
S.Creatinine (P)	0.9	0.09	1.0	0.16	1.2	0.15	28	0.000*
24 hr urine Volume (V)	2010	204	1137	217	690	169	274	0.000*
Ur.Creatinine (U)	54.84	4.44	54.63	5.83	45.85	3.6	25	0.000*
Cr. Clearance (timed urine collection)	85.33	9.87	43.41	8.68	18.55	5.3	392	0.000*
Cr. Clearance (Cockcroft Gault formula)	85.02	9.23	63.87	13.3	44.9	8.68	78	0.000*

BLOOD UREA LEVELS: In this study, Mean BUN level in Group-I patients was 22.43 mg/dl with a standard deviation of 2.99. This was followed by a mean value of 2.42 with a standard deviation of 3.5 in group-II patients and a mean value of 22.40 with a SD of 2.56.

SERUM CREATININE; Only patients with serum creatinine levels less than 1.5 mg/dl were included in this study. Mean serum creatinine level in Group-I patients was 0.9 mg/dl with a standard deviation of 0.086. This was followed by

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a mean value of 1.0 mg/dl with a standard deviation of 0.16 in group-II patients and a mean value of 1.2 mg/dl with a SD of 0.15 in group-III.

24 HOUR URINE VOLUME: For the patients in this present study, the urine output was measured for 24 hours. Mean value of 24-hour urine volume of all the patients in Group-I was 2010.71 ml with a standard deviation of 203.8. This was followed by mean value of 1136.84 ml with a SD of 217.4 in group-II patients, and a mean of 690 ml in group-III with a SD of 169.8. Patients with more severe renal impairment were found to have lesser amounts of urine output. The mean 24-hour urine volume of all the patients was 1317.4 ml.

Table 4: COMPARISON OF THE MEASURED CREATININE CLEARANCE VALUE ESTIMATED BY THE TWO METHODS IN TERMS OF NUMBER OF PATIENTS IN EACH GROUP

CREATININE CLEARANCE	By TIMED URINE COLLECTION (U x V) /P	By COCKCROFT GAULT FORMULA
<20 ml/min	12 (13.95%)	0
20-40 ml/min	24 (27.90 %)	8 (9.3%)
40-60 ml/min	22 (25.58 %)	22 (25.58 %)
60-80 ml/min	10 (11.63%)	34 (39.54%)
>80 ml/min	18 (20.93%)	22 (25.58%)

In the group of creatinine clearance less than 30 ml/min, there were 20 patients in timed urine collection method and patients were absent in that group when estimated by CGF method. In the group with clearance of 30-60 ml/min, there were 38 patients when calculated by timed urine collection and only 30 patients when calculated using CGF. In the group with clearance of more than 60 ml/min, there were 28 patients when calculated by timed urine collection but 56 patients when calculated using CGF.

Table 5: Etiological distribution of patients into the three groups based on the creatinine clearance

ETIOLOGY	NUMBER OF PATIENTS		
	GROUP-I	GROUP-II	GROUP-III
ALCOHOLISM	10	20	12
HEPATITIS B	6	4	4
HEPATITIS C	6	4	2
AUTO-IMMUNE HEPATITIS	0	2	0
UNKNOWN	6	8	2

The etiologies present in this were alcoholism, Hepatitis-B, Hepatitis-C, autoimmune hepatitis, unknown etiology. Alcoholism consists of 10 patients in Group-I, 20 patients in group-II and 12 patients in group-III. Viral hepatitis consisted of Hepatitis-B and Hepatitis-C. Hepatitis-B had 6 patients in Group-I, 4 patients in group-II and 4 patients in group-III. Hepatitis- C had 6 patients in Group-I, 4 patients in group-II and another in group-III. There were 2 patients of autoimmune hepatitis in group-II. The etiology was unknown in 6 patients of Group-I, 8 patients of group-II and 2 patients of group-III.

Table 6: Distribution of patients based on serum albumin levels into the three groups

SERUM ALBUMIN (mg/dL)	GROUP I	GROUP II	GROUP III
>3.5	16	4	0
3.2-3.5	8	28	6
<3.2	4	6	14

Table 7: Distribution of apatients based on serum bilirubin levels into the three groups

SERUM BILIRUBIN (mg/dL)	GROUP I	GROUP II	GROUP III
< 1.2	4	4	6
1.2 — 2	16	24	8
> 2	8	10	6

Ultrasound abdomen was done in all of the 86 patients. Findings of splenomegaly and altered echotexture of liver were uniformly seen in all these patients. Ascites was present in 76 out of the 86 patients. Liver was shrunken in size in 84

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 10, 2023

patients of the study. The remaining 2 patients showed changes of malignant transformation. Kidney size and corticomedullary differentiation was normal in all the patients in this study group.

DISCUSSION:

In this present study, age of the patients ranged from a minimum of 24 years to a maximum of 58 years. Mean age was 42.2 years, with a standard deviation of 6.6. As the glomerular filtration rate (GFR) tends to decrease through age, patients above the age of 60 years were excluded. If not, findings of the study might be influenced by such false low GFR calculations. In this study it was observed that the maximum number of patients fell in the age group of 40-49 years with 55.8% (48 patients among the total of 86 patients). This was followed in the next place by age group of 30-39 years with 20.9% (18 out of 86 patients). This high number of patients around the age group of 40-49 years may be due to the time taken for the liver disease to manifest in those patients. A study by Hampel et al showed no significant differences in age in cirrhotic patients with or without renal dysfunction. (5)

Out of the 86 patients in this study, majority of the patients were males with 81.4% of the total (70 out of 86 patients). The rest 18.6 % (16 out of 86 patients) were females. This high male preponderance may be due to the habit of consuming alcohol, which was greater in males than females that might have led to chronic liver disease. A study by RW.Wilsnack et al that studied gender and alcohol consumption also found out that alcohol consumption per person and high volume drinking were consistently more prevalent among men than among women. (6)

In this present study, alcoholism was found to be the etiological factor in maximum number of patients, occupying 48.83% of the total study group (42 out of 86 patients). This was followed in the next place by viral hepatitis, occupying 33% of the study group (26 out of 82 patients). Among these, 14 cases were Hepatitis B virus surface antigen (HBs Ag) positive and the other 12 cases were of anti-Hepatitis C virus antibody (anti HCV antibody) positive.

It was noted that Glomerular filtration rate (GFR) was the primary metric for kidney function. And creatinine clearance was used as an approximate measure of glomerular filtration rate. (7) It was also noted that according to J.Traynor et al measurement of creatinine clearance using timed urine collection was a reasonable method of following changes in renal function in patients. (8)

The mean Blood urea nitrogen (BUN) value of group-I was 22.43 mg/dl with a standard deviation (SD) of 2.99, followed by a mean of 22.42 mg/dl with a standard deviation of 3.5 in the group-II, and a mean of 22.40 with a SD of 2.56 in group-III. Patients with serum creatinine levels of less than 1.5 mg/dl were included in this study, because the level of serum creatinine required for diagnostic criteria of HRS was atleast 1.5 mg/dl, in the absence of diuretic therapy. The mean serum creatinine value in group-I was 0.9 mg/dl with a standard deviation (SD) of 0.086, in group-II it was 1 mg/dl with a SD of 0.16, and 1.2 mg/dl with a SD of 0.15 in group-III. These suggest increase in the mean serum creatinine values with corresponding decrease in renal function. This was in agreement with the findings in a study by MacAulay et al. (9) Another prospective study by Papadakis and Arieff , conducted on a large number of cirrhotic patients also indicated that the glomerular filtration rate can be very low even when the serum creatinine was less than 1.0 mg/dl.(10)

In this study the mean value of the 24 hour urine volume of the group-I patients was 2010.71 ml with SD of 203.83. This was followed by a mean value of 1136.84 ml with a SD of 217.38 in group-II patients, and 690 ml with a SD of 169.83 in group-III patients.

The mean value of creatinine clearance by CGF was 85.02 ml/min in group-I, followed by 63.67 ml/min in group-II, followed by 44.9 ml/min in group-III. In this study the patients of group-III (20 out of 86 patients) had creatinine clearance estimated by timed urine collection of <30 ml/hour individually, with a mean value of 18.55 ml/min. Where-as, all those group-III patients were found to have a creatinine clearance of more than 30 ml/min when calculated using CGF, with a mean value of 44.9 ml/min in group-III.

A systematic review and meta-analysis of patients with cirrhosis by Proulx et al showed that creatinine clearance measured by timed urine collections overestimates GFR in patients with hepatic cirrhosis, however, it was a preferable method in clinical practice, as it was more reliable than serum creatinine or predicted creatinine clearance by CGF. (11)

The study by Papadakis and Arrief was a prospective evaluation of 23 non- azotemic cirrhotic patients with ascites over a three-year interval. (10) It showed that the serum creatinine levels frequently failed to rise above normal level even when the glomerular filtration rate was very low (less than 25 ml/minute), and also creatinine clearance overestimated inulin clearance. However, this study also suggested that creatinine clearance was an important aid in determining true glomerular filtration rate (when inulin clearance was not available) and may be a useful clinical test in the evaluation of renal insufficiency in cirrhotic patients with normal serum creatinine values.

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In this study, alcoholism was the etiological factor in maximum number of chronic liver disease patients with 48.8% (42 out of 86 patients in total). This was followed by viral hepatitis as etiology in 30.2% patients (26 out of 86 patients). The viral hepatitis was comprised of Hepatitis B (HBs Ag positive) patients with 16.3% of total study group (14 out of 86 total patients) and Hepatitis C (Anti HCV Ab positive) with 13.9% of the total (12 out of 86 patients). But a study by Hampel et al showed no significant difference in etiology of cirrhosis in cirrhotic patients with or without renal dysfunction. [5]

In this study, the mean serum albumin was highest in group-I patients with a value of 3.59 mg/dl. It was followed by mean value of 3.34 mg/dl in group-II and a value of 3.11 mg/dl in group-III. It was observed that the mean serum albumin decreased as the renal function decreased. This suggests serum albumin was having a direct correlation with renal function, with higher rates of creatinine clearance having higher albumin levels.

The correlation with albumin levels was also noted in a study by Amrapurkar et al. [12] This latter study also denoted a direct correlation between chronicity of liver disease and kidney dysfunction. It also showed a higher mortality in patients with lower values of creatinine clearance, especially with hepatorenal syndrome.

In this study, the mean serum bilirubin was 1.67 mg/dl in group-I patients, 1.61 mg/dl in group-II and 1.64 mg/dl in group-III patients. So serum bilirubin levels were found to have no significant correlation with renal function. This was in agreement with a study by Hampel et al. The latter study showed no significant difference in serum levels of bilirubin in cirrhotic patients with or without renal dysfunction. [5]

In this study, ascites was present in 76 out of 86 patients on ultrasonography scan of the abdomen. The remaining 10 patients were not found to have ascites. It was noted that the patients without ascites had a relatively better renal function, because all those remaining 10 patients belonged to Group-I (Creatinine clearance more than 60 ml/minute). Thus it was noted that ascites may be one of the first changes in worsening of renal function. This was in agreement with a study by Hampel et al, which suggested patients who develop renal dysfunction were more likely to have ascites. [5]

CONCLUSION:

In chronic liver disease, serum creatinine alone was not a reliable marker to assess renal dysfunction. Routine renal function tests like blood urea and serum creatinine will not be sufficient to check for adequacy of renal function. Other methods like measured creatinine clearance should be employed to get an accurate picture of the renal status. Alcoholism appears to have an increased adverse effect on renal function when compared with other major etiologies of cirrhosis like viral hepatitis.

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