

## THE COMPARATIVE ANALYSIS OF RENAL FUNCTION IN LIVER DISEASES USING COCKCROFT-GAULT FORMULAE AND CREATININE CLEARANCE

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### ABSTRACT

#### BACKGROUND

Kidney dysfunction in liver disease can be due to different aetiologies 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 glomerular filtration rate. Renal dysfunction in chronic liver disease usually follows a progressive course- the final phase being Hepatorenal Syndrome (HRS).

#### MATERIALS AND METHODS

This study included patients with chronic liver disease being treated as inpatients in the Department of General Medicine, Konaseema Institute of Medical Sciences, Amalapuram. 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) or tissue diagnosis (positive liver biopsy for cirrhosis).

#### RESULTS

Eighteen percent, i.e. 5 out of the 28 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 done by timed urine collection P value calculated was found to be less than 0.0001, which is statistically significant.

#### CONCLUSION

In chronic liver disease, serum creatinine alone is not a reliable marker to assess renal dysfunction. Calculating creatinine clearance by using Cockcroft-Gault formula overestimates renal function in cirrhotics. Creatinine clearance measured by timed urine collections should be done routinely to assess renal reserve in advanced liver disease. Alcoholism appears to have adverse effect on renal function when compared with other aetiologies of cirrhosis.

#### KEYWORDS

Renal Function, Chronic Liver Disease, Serum Creatinine.

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#### BACKGROUND

Kidney dysfunction in liver disease can be due to different aetiologies 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 glomerular filtration rate. Renal dysfunction in chronic liver disease usually follows a progressive course- the final phase being Hepatorenal Syndrome (HRS).<sup>1</sup>

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

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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 impressions and hence alternative methods to determine renal reserve must be used. Detection of renal insufficiency is clinically important, because it contributes significantly to high morbidity and mortality in cirrhosis. Moreover, renal dysfunction 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.<sup>2</sup>

#### Aim of Study

- To determine the usefulness of serum creatinine and creatinine clearance as parameters in assessing renal function abnormalities in patients with chronic liver disease.



- To find if aetiology of chronic liver disease has a bearing on renal dysfunction.

**MATERIALS AND METHODS**

**Inclusion Criteria-** This study included patients with chronic liver disease being treated as inpatients in the Department of General Medicine, Konaseema Institute of Medical Sciences, Amalapuram.

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) or tissue diagnosis (positive liver biopsy for cirrhosis).

**Exclusion Criteria**

- Elderly patients (>60 years).
- Overt renal failure (S. creatinine >1.5).
- Known primary renal disease.
- Diabetes mellitus/hypertension.
- Grade 4 hepatic encephalopathy.
- Recent gastrointestinal bleed.

**Methodology-** Inpatients in the medical ward/IMCU admitted with chronic liver disease with seemingly normal renal function were included in this analytical study, which was conducted from June 2015 to October 2017. 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 predesigned pro forma. Diuretics were withheld for 3 days before carrying out lab investigations. Lab investigations including complete liver function test, renal function tests, viral marker for hepatitis B, 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) x V. This was divided by 1440 to get the value in mL/minute. Creatinine clearance was also calculated using the Cockcroft-Gault formula (CGF) (140- age) x weight/(serum creatinine x 72).<sup>3</sup>

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.

**Observations and Analysis-** 50 patients with chronic liver disease were enrolled in the study. 7 patients did not satisfy inclusion criteria and were excluded. So, a total of 43 patients were included.

The following observations were made-

**Age and Sex-** Age of the patients ranged from a minimum of 22 years to a maximum of 58 years. The mean age was 42.14 years.

The age distribution is as follows-

Age Group	Number of Patients
Less than 30 years	2
30 to 39 years	9
40 to 49 years	24
Above 50 years	8

**Table 1. Age and Sex Distribution**

Of the patients included in the study, 35 were males, while remaining 8 were females.

**Aetiology-** Out of the 43 patients of cirrhosis, the cause of liver disease was attributed to alcoholism in 21 patients. 6 patients were found to be positive for hepatitis B surface antigen. One patient was a case of Wilson’s disease and another patient was found to have autoimmune hepatitis. In the other 14 patients, causative aetiology could not be ascertained.

Aetiology	Number of Patients	Percentage
Alcoholism	21	48.83%
Hepatitis B	6	13.95%
Wilson’s	1	2.33%
Autoimmune hepatitis	1	2.33%
Unknown	14	32.56%

**Table 2. Aetiology Distribution**

**Blood Urea Levels-** There was no significant variation in blood urea levels in all the three groups suggesting that estimation of blood urea will not be of much use in determining renal impairment. Mean blood urea level was 22.42 mg/dL.

**Serum Creatinine-** Only patients with creatinine levels less than 1.5 mg/dL were included in this study. It was seen that in 7 patients with creatinine clearance less than 30 mL/mt, serum creatinine levels failed to rise above 1.2 mg/dL suggesting that moderate-to-severe renal dysfunction maybe masked by seemingly normal creatinine levels. The mean serum creatinine level was 1.01 mg/dL.

**24-Hour Urine Volume-** Patients with greater amount of renal impairment were found to have lesser urine output, thus suggesting that eliciting history of oliguria in a patient with normal serum creatinine levels should call for a high index of suspicion of renal dysfunction. The mean 24-hour urine volume was 1317.44 mL.

**Measured Creatinine Clearance by Timed Urine Collection-** The patients were grouped into three based on their creatinine clearance. Measurement of creatinine clearance using the Cockcroft-Gault Formula (CGF) showed significantly high values suggesting overestimation of GFR by this method.

	Group I	Group II	Group III
Blood urea mg/dL	22.43	22.42	22.4
Serum creatinine mg/dL	0.90	1	1.2
24-hour urine volume mL	2010.71	1136.84	690
Creatinine clearance (U x V/P) mL/mt	85.33	43.41	18.55
Creatinine clearance (CG formula) mL/mt	85.02	63.87	44.90

**Table 3. Renal Profile**

Group	Creatinine Clearance	Number of Patients
Group I	>60 mL/minute	14
Group II	30-60 mL/minute	19
Group III	<30 mL/minute	10

**Table 4. Creatinine Clearance**

Creatinine Clearance	By (U x V)/P	By Cockcroft-Gault Formula
<20 mL/minute	6 (13.95%)	0 (0%)
20-40 mL/minute	12 (27.90%)	4 (9.30%)
40-60 mL/minute	11 (25.58%)	11 (25.58%)
60-80 mL/minute	5 (11.63%)	17 (39.54%)
>80 mL/minute	9 (20.93%)	11 (25.58%)

**Table 5. Creatinine Clearance Based on Different Formulae**

**Renal Function According to Aetiology**

Eighteen percent, i.e. 5 out of the 28 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 done by timed urine collection P value calculated was found to be less than 0.0001, which is statistically significant.

Aetiology	Number of Patients		
	Group I	Group II	Group III
Alcoholism	5	10	6
Hepatitis B	3	2	1
Wilson's	0	0	1
Autoimmune	0	1	0
Unknown	6	6	2

**Table 6. Renal Function According to Aetiology**

Mean serum albumin was 3.37 mg/dL. The distribution of serum albumin in the three groups was as follows-

Serum Albumin (mg/dL)	Group I	Group II	Group III
>3.5	8	2	0
3.2-3.5	4	14	3
<3.2	2	3	7

**Table 7. Distribution of Serum Albumin**

Average serum albumin (mg/dL) in the three groups was-

- Group I - 3.59
- Group II - 3.34
- Group III - 3.11

Serum albumin was found to have direct correlation with renal function, i.e. patients with higher rates of creatinine clearance were seen to have higher albumin levels.

**Serum Bilirubin and Renal Function-** The distribution of serum bilirubin levels in the three groups were as follows-

Serum Bilirubin (mg/dL)	Group I	Group II	Group III
<1.2	2	2	3
1.2-2	8	12	4
>2	4	5	3

**Table 8. Serum Bilirubin and Renal Function**

**DISCUSSION**

This study followed 43 patients with chronic liver disease with special emphasis on renal function. Many patients with cirrhosis and ascites will have a glomerular filtration rate of less than 60 mL/minute, but a normal serum creatinine level. Our study showed that serum creatinine alone in patients with advanced liver disease is of limited value for identification of renal dysfunction. This is in agreement with the findings in a study by McAulay et al.<sup>4,5</sup> Another prospective study of a large number of cirrhotic patients by Papadakis and Arieff also indicated that the glomerular filtration rate can be very low even when the serum creatinine is less than 1.0 mg/dL.<sup>6</sup> The level of serum creatinine required for the diagnosis of HRS is 1.5 mg/dL in the absence of diuretic therapy. Although, this value may seem rather low, patients with cirrhosis and a serum creatinine above 1.5 mg/dL have a GFR below 30 mL/min.<sup>7</sup> Hence, patients with creatinine levels more than 1.5 mg/dL were excluded from our study.

Our study also shows that calculating creatinine clearance by Cockcroft-Gault formula overestimates renal function. This is probably due to discrepancies in weight due to fluid retention, which is one of the consequences of renal impairment in cirrhotics. As weight is one of the variables in the numerator of the formula, an increase in weight due to oedema or ascites will give a spuriously high creatinine clearance. The study by McAulay also supports this finding.<sup>4</sup> This overestimation of renal function was highest in patients with lower GFR, which was observed in our study also.

MacAulay et al observed that among the Cr-based GFR formulas, the MDRD formula had the best overall accuracy. This formula developed by the Modification of Diet in Renal Disease (MDRD) Study Group is based on the patient's creatinine levels, age, sex, race and serum urea nitrogen and serum albumin levels and it showed a larger proportion of agreement with radionuclide GFR in patients with advanced liver disease. MacAulay summarised that in clinical practice, the MDRD is the best formula for detection of moderate renal dysfunction among those with cirrhosis.<sup>4</sup> But, the above-mentioned study didn't include any formulas requiring urine collection. As MDRD formula requires web-based calculations, it will be impractical to rely on it as a parameter of assessing renal function in a resource limited setup.

Measured creatinine clearance from timed urine collections is a relatively inexpensive, accessible method used in clinical practice. Our study showed that it provides a better estimate of renal reserve than serum creatinine or predicted creatinine clearance by Cockcroft-Gault formula.

A systematic review and meta-analysis of patients with cirrhosis by Proulx et al 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).<sup>7</sup> This overestimation is substantial especially in the low GFR range where important decisions relative to drug dose adjustment, the staging of CKD and the pre-liver transplant evaluation maybe required.

The meta-analysis proved that direct measurement of GFR using inulin clearance (Cin) is the most accurate estimate of renal reserve.<sup>8</sup> But, in routine clinical practice, GFR estimation by this method is not very feasible because of the complexity, expense and limited availability of testing and overall patient inconvenience, few articles have examined alternative GFR markers using cystatin C or radioisotopes and two studies support the use of the renal clearance of either (<sup>51</sup>Cr) EDTA or (<sup>125</sup>I) iothalamate to estimate GFR in patients with liver cirrhosis, which again will be impractical in our setup.

The study by Papadakis and Arrief was a prospective evaluation of 23 non-azotaemic cirrhotic patients with ascites over a three-year interval.<sup>6</sup> It showed that the serum creatinine levels frequently failed to rise above normal even when the glomerular filtration rate was very low (less than 25 mL/minute) and creatinine clearance overestimated inulin clearance. However, this study also suggested that creatinine clearance was an aid in determining true glomerular filtration rate (when inulin clearance was not available) and maybe a useful clinical test in the evaluation of renal insufficiency in cirrhotic patients with normal serum creatinine values.

Our study has 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 Amrapurkar et al and El-Minshawy O et el.<sup>9,10</sup> This latter study also denoted direct correlation between chronicity of liver disease and renal dysfunction. It also showed a higher mortality in patients with lower creatinine clearance especially 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.<sup>11</sup> The same study showed no significant differences in age, aetiology of cirrhosis, serum levels of bilirubin, prothrombin time, encephalopathy, bacteraemia, urinary tract infection or occurrence of oesophageal 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 our 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. Our study showed that patients with alcoholic liver disease were predisposed to develop renal

impairment when compared with liver disease of other aetiologies. Only 20% of alcoholic patients had a creatinine clearance of more than 60 mL/minute as compared to 50% of cirrhotic patients due to hepatitis B.

Our 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. Blood urea nitrogen levels may also vary in the absence of GFR changes. The reasons for this being-

1. Blood urea levels may be lower than expected in patients with liver disease because of reduced hepatic synthesis.
2. Blood urea levels may also increase because of gastrointestinal haemorrhage or catabolic states. Hence, blood urea levels cannot be relied on to assess renal dysfunction.

Similarly, serum creatinine measurements may underestimate changes in GFR,<sup>12</sup> because of-

1. Decreased synthesis of creatinine from liver and more importantly,
2. Decreased endogenous production of creatinine in cirrhotics due to decreased muscle mass as a result of severe wasting.

Hence, to check for renal dysfunction in advanced liver disease, routine tests like blood urea and serum creatinine will be insufficient. Other methods like measured creatinine clearance should be employed to get an accurate picture of the renal status.

## CONCLUSION

In chronic liver disease, serum creatinine alone is not a reliable marker to assess renal dysfunction. Calculating creatinine clearance by using Cockcroft-Gault formula overestimates renal function in cirrhotics. Creatinine clearance measured by timed urine collections should be done routinely to assess renal reserve in advanced liver disease. Alcoholism appears to have adverse effect on renal function when compared with other aetiologies of cirrhosis.

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