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FREQUENCY OF ACUTE RENAL FAILURE IN PATIENTS OF LIVER CIRRHOSIS ADMITTED IN A TERTIARY CARE HOSPITAL

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Abstract:

Background: *Kidney failure is a common and potentially life-threatening event in patients with cirrhosis, and underlying mechanisms for renal dysfunction are highly variable. Acute kidney failure occurs in approximately 19% of hospitalized patients with cirrhosis.*

Objective: *To find the frequency of acute renal failure in patients of liver cirrhosis*

Study Design: *Descriptive case series*

Setting: *Unit I, Department of Gastroenterology, Lahore general Hospital, Lahore*

Duration: *6 months: from July 2018 to December 2018*

Data Collection Procedure: *175 patients meeting the inclusion criteria were included in the study. Basic demographics like name, age, gender and weight were noted. Blood sample was obtained by using 5 cc BD syringe. Samples were sent to the pathology laboratory of the hospital daily for serial assessment of serum creatinine and GFR during period of admission. Patients were followed for 48 hours, labs were repeated and ARF was labeled, (as per operational definition). All the data was recorded on especially designed proforma (attached). Data was entered and analyzed with IBM-SPSS version 21. Chi-square test was applied with p ≤0.05 taken as significant.*

Results: *The mean age of the study population was 44.29±7.68 years. Majority of the cases were male 137 (78.3%). Child Pugh class when noted, it was found that majority were in child Pugh class B with frequency of 103 (58.9%). There were 119 (68%) with normal weight. Acute renal failure was noted in 37 (21.1%) and 138 (78.9%) were without this condition.*

Conclusion: *Quite a few of cases have the kidney failure in the population presenting with the liver cirrhosis.*

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INTRODUCTION:

Patients with cirrhosis have multiple risk factors for pre renal dysfunction involving volume depletion, for example; gastrointestinal losses with diarrhea from lactulose, renal losses from diuretics, and large volume paracentesis.[1, 2] . Pre renal dysfunction resulting in renal ischemia may be due to renal hypoperfusion as well as drugs, such as nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and contrast dye. Acute renal failure (ARF) is common in patients with cirrhosis and is frequently precipitated by prolonged prerenal dysfunction.[3]. ARF occurs commonly in patients with advanced cirrhosis. Furthermore, mortality in cirrhosis has been shown to increase progressively in association with an increase in the severity of renal dysfunction.[4] ARF is a common problem for patients with cirrhosis and is associated with poor survival.[5] There is increasing evidence that renal dysfunction in cirrhotic patients also reflects infection/inflammatory-mediated renal tubular failure. Bacterial translocation from the intestinal tract is known to increase production of cytokines, nitric oxide metabolites, and toll-like receptor 4. [6]

Diagnosis is challenging because it is based on serum creatinine, which is used to calculate estimated glomerular filtration rate, which itself is not an ideal measure of renal function in patients with cirrhosis. Finding the exact cause of renal failure in patients with cirrhosis remains problematic due to the limitations of the current diagnostic tests. [2] Neutrophil gelatinase-associated lipocalin is a 25-kD protein that is synthesized in renal tubules and up-regulated after tubular inflammation/failure. Serum and urine levels were significantly higher in patients with HRS compared with stable cirrhotic patients. These studies suggest an important role of inflammation-mediated renal dysfunction in cirrhosis. [7] But there is only one study which reported the frequency of ARF among cirrhotic patients i.e. 12.9%. [8] One study showed that the renal dysfunction was found in 63% cases but not specifically ARF was mentioned.9 One more study showed that renal dysfunction was found in 12% cirrhotic patients only. [10]

Rationale of this study is to find the frequency of ARF in patients of liver cirrhosis. Literature has showed that ARF is common complication of cirrhosis, particularly patients on treatment. But very scant literature is available in this regard and there is also no local evidence present and there is a deficiency of data concerning the extent of problem in local population. So, we conducted this study to find local evidence and implement the results of this study in future, which could help us in planning better management protocols and early screening of ARF and alteration in treatment of cirrhotic patients.

OPERATIONAL DEFINITIONS:

Liver cirrhosis: It is defined as on Ultrasound: presence of coarse or shrunken liver, with Portal Vein Diameter >13 mm, with or without splenomegaly and with or without ascites. On Laboratory values: platelet count ≤150000 /mm3, Prothrombin Time prolonged ≥4 seconds, Serum Albumin ≤3.5 g/dL, Bilirubin ≥2 mg/dl and APRI (serum AST to Platelet Ratio Index) scoring ≥1.5

Acute renal failure: At 48 hours, any one of these: serum Creatinine increased >3 times baseline or GFR falls <75% as calculated by Cockroft Gault equation. (Annex)

MATERIAL AND METHODS:

Study Design:
Descriptive case series

Setting:
Unit I, Department of Gastroenterology, Lahore general Hospital, Lahore

Duration:
6 months : July 2018 to December 2018

Sample Size:
Sample size of 175 cases is calculated with 95% confidence level, 5% margin of error and taking expected percentage of ARF i.e. 12.9% in patients with liver cirrhosis

Sampling Technique:
Non probability consecutive sampling

Selection criteria:
Inclusion Criteria:
Patients of age 18-60 years, either gender with diagnosed cirrhosis (as per operational definition).

Exclusion Criteria:

- Patients having Chronic Kidney Disease as defined by having Glomerular Filtration Rate (GFR) <60 ml/min for > 3 months (calculated using Cockroft Gault equation) (medical record)
- Patients already on Hemodialysis before diagnosis of cirrhosis (medical record)
- Patients diagnosed with Hepatocellular Carcinoma (using Triphasic CT Scan Abdomen and raised serum α FP >500 ng/ml)

Data Collection Procedure:
175 patients meeting the inclusion and exclusion criteria was included in the study through wards of Department of Gastroenterology, Lahore General Hospital, Lahore. Informed consent was taken. Basic demographics like name, age, gender and weight were noted. Blood sample was obtained by using 5 cc BD syringe. Samples were sent to the pathology laboratory of the hospital daily for serial assessment of serum creatinine and GFR during period of admission. Patients were followed for 48 hours, labs were repeated and ARF was labeled, (as per operational definition). All the data was recorded on especially designed proforma (attached).

Data Analysis:
Data was entered and analysed with IBM-SPSS version 21. Mean ±SD was presented for quantitative variables like age, BMI and duration of cirrhosis. Frequency and percentage were computed for qualitative variables like gender, Child Pugh score and ARF. Effect modifiers like age, gender, BMI, Child Pugh class and duration of cirrhosis was controlled by stratification. Post-stratification, chi-square test was applied with $p \leq 0.05$ taken as significant.

RESULTS:
The mean age of the study population was 44.29±7.68 years. Majority of the cases were male 137 (78.3%) and female 38 (21.7%). Child Pugh class when noted, it was found that majority were in child Pugh class B with frequency of 103 (58.9%) (Table #3). There were 119 (68%) with normal weight while 56 (32%) were obese cases. Mean duration passed at the time of presentation was 8.57±3.35 months of liver cirrhosis. Acute renal failure was noted in 37 (21.1%) and 138 (78.9%) were without this condition.

When data was stratified for age, it was noted that there was no significant difference with respect to age as the p-value was 0.50. (Table #7). It was noted that 32 (23.4%) male and 5 (13.2%) female were having the renal failure due to liver cirrhosis, but again the difference was not statistically significant. (Table #8). The only new finding was this that there was significant difference with respect to different child Pugh classes. (Table #9). Body mass index and duration of liver cirrhosis did not contribute differentially for the onset of acute renal failure (Table #10, 11)

Table #1: Distribution of the Mean Age of the Study

Mean	44.29
Std. Deviation	7.68
Minimum	24
Maximum	56

Table #2: Distribution of the Gender in the Study

	Frequency	Percent
Male	137	78.3
Female	38	21.7
Total	175	100.0

Table #3: Distribution of the Child Pugh Class in the Study

	Frequency	Percent
A	29	16.6
B	103	58.9
C	43	24.6
Total	175	100.0

Table #4: Distribution of the Body Mass Index

	Frequency	Percent
Normal	119	68.0
Obese	56	32.0
Total	175	100.0

Table #5: Distribution of the Mean Duration of the Liver Cirrhosis

Mean	8.57
Std. Deviation	3.35
Minimum	3.00
Maximum	15.00

Table #6: Distribution of the Presence of Acute Renal Failure

	Frequency	Percent
Present	37	21.1
Absent	138	78.9
Total	175	100.0

Table #7: Stratification of Renal failure with respect to Age

		Acute renal failure		
		Present	Absent	P-value
Group of Age	18-40	14 21.9%	50 78.1%	0.50
	>40	23 20.7%	88 79.3%	

Table #8: Stratification of Renal failure with respect to Gender

		Acute renal failure		
		Present	Absent	P-value
Gender of patients	Male	32 23.4%	105 76.6%	0.12
	Female	5 13.2%	33 86.8%	

Table #9: Stratification of Renal failure with respect to Child Pugh Class

		Acute renal failure		
		Present	Absent	P-value
Child Pugh class	A	4 13.8%	25 86.2%	0.01
	B	15 14.6%	88 85.4%	
	C	18 41.9%	25 58.1%	

Table #10: Stratification of Renal failure with respect to Body Mass Index

		Acute renal failure		
		Present	Absent	P-value
Body mass index	Normal	24 20.2%	95 79.8%	0.39
	Obese	13 23.2%	43 76.8%	

Table #11: Stratification of Renal failure with respect to Duration of Liver Cirrhosis

		Acute renal failure		P-value
		Present	Absent	
Group duration of liver cirrhosis	1-6 months	14 24.1%	44 75.9%	0.31
	>6 months	23 19.7%	94 80.3%	

DISCUSSION:

Acute kidney failure is characterized by progressive renal failure in the absence of renal parenchymal disease. It is a functional disorder, i.e., the decreased glomerular filtration rate results from renal vasoconstriction, which in turn is due to decreased systemic vascular resistance and increased compensatory activity of the renin-angiotensin-aldosterone axis and of antidiuretic hormone release. [11]

Acute kidney failure often occurs in patients with advanced liver disease. These patients typically have a hyperdynamic circulation (systemic vasodilation, low blood pressure, and increased blood volume) with a low mean arterial pressure and increased renin and norepinephrine levels. Other frequent findings include hyponatremia, low urinary sodium excretion (< 2 mmol/day), and low free water clearance, all of which mark the high systemic levels of antidiuretic hormone and aldosterone. [12,13]

Kidney disease occurs in 20%-25% of patients with liver disease. One must first determine whether the patient is experiencing a process that affects both the kidney and the liver or has kidney disease as a result of liver disease. [14,15]

As can be seen, glomerulonephritis is common. Immunoglobulin A (IgA) deposition is an almost universal finding in patients with liver disease, particularly alcoholic cirrhosis, which may result in the full spectrum of IgA nephropathy. [16] Management strategies are similar to those for the patient with idiopathic IgA nephropathy. Immunosuppressive therapy is not indicated in this setting. Membranous, membranoproliferative, and rapidly progressive crescentic glomerulonephritis are associated with both hepatitis B and C. Membranous is more common with hepatitis B, and membranoproliferative, particularly with cryoglobulinemia, with hepatitis C. [17] Other diseases, such as focal segmental glomerulonephritis and antineutrophil cytoplasmic antibody associated glomerulonephritis, also have been reported. A search for cryoglobulins is indicated in all patients presenting with proteinuria (protein excretion.0.5 g/24 h), low complement level, and typical purpuric rash. Treatment is targeted to the hepatitis virus, and remission of the kidney disease can occur with eradication. However, treatment itself may lead to further deterioration of kidney function. In cases of rapidly progressive kidney failure, plasma exchange with or without rituximab used. [18]

In a study it was noted that out of Six hundred and forty-three patients were admitted, of whom 190 (29.5%), 273 (42.5%), and 180 (28.0%) were Child-Pugh class A, B, and C, respectively. Eighty-three patients (12.9%) were diagnosed with AKI. [19] The prevalence of renal dysfunction has been reported to vary from 14–50% in patients with cirrhosis. The prevalence is estimated to be approximately 50% among patients with cirrhosis and ascites and 20% of patients with advanced cirrhosis admitted to the hospital. [20,21] The wide range in prevalence is likely due to different study populations and varying definitions of renal dysfunction. For example, in one retrospective study on 932 patients with cirrhosis admitted to the intensive care unit (ICU), renal dysfunction as defined by serum creatinine >1.5 mg/dL was reported in 14% of cases. Using the same definition, in a prospective study of 206 cirrhotic (100 with sepsis), the prevalence of renal dysfunction was reported at 17% and was higher among patients with sepsis (27% vs. 8%, $p<0.0001$). [22] The prevalence of AKI as defined by increase in serum creatinine by >0.9 mg/dL was reported in 25% of patients, with 93 cirrhosis patients with baseline creatinine <1.4 mg/dL. [23] While in a Pakistani study, it was noted that out of 523 patients, 261 (49.9%) had RF. Acute kidney injury (AKI) was the most common presentation seen in 160 (61%) patients [24] which has the same results as were noted in this study.

The initial management of AKI should focus on early recognition and correction of potential trigger events and on preventing further hemodynamic deterioration. [25,26] This includes careful review of all medications

including over-the-counter drugs and nephrotoxic agents (e.g. non-steroidal anti-inflammatory drugs [NSAIDs]) need to be withdrawn. The use of drugs that may induce or aggravate arterial hypotension (e.g. vasodilators or non-selective beta-blockers [NSBBs]) should be carefully evaluated.(In volume-depleted patients, diuretic therapy and/or lactulose should be withdrawn and plasma volume should be expanded with albumin, or blood transfusions in anemic patients due to gastrointestinal blood loss. [27,28]

Since bacterial infections are the most common precipitant of AKI in cirrhosis, patients should be thoroughly screened for (e.g. by performing diagnostic paracentesis to rule in/out SBP). Early empiric antibiotic treatment should be initiated already on clinical suspicion and be based on local epidemiology and resistance patterns. [29,30]

In case of therapeutic response, which is defined as a decrease of sCr to a value within 0.3 mg/dL of baseline, patients should be followed closely for early detection of recurrent episodes of AKI. Follow-up assessment of sCr every 2–4 days during hospitalization and every 2–4 weeks during the first 6 months after discharge is advised. [31]

The main limitation in our study was the short duration of the study and the lack of incorporating new adjuvant markers that may help in better differentiation of the possible etiology of renal failure in cirrhotic patients. Therefore, we recommend to investigate new tools for early detection and good delineation of RF among cirrhotic that will reflect on prognosis.

CONCLUSION:

There is substantial number of cases who have presented with the issue of acute kidney failure after having cirrhosis. It is an alarming situation, that the cases who have been suffering from liver related disease, also develop kidney failure. It adds to the sinister effect of the disease and management of such cases becomes difficult. But in order to cope with it, effective monitoring of the patients for their creatinine level during the course of cirrhosis management, can be very useful.

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APPENDIX
PROFORMA

Frequency of acute renal failure in patient of liver cirrhosis admitted in a tertiary care hospital

Case No:_____ **Reg No:**_____ **Date:**_____
Age:_____
Sex: Male □ **Female** □
BMI:_____
Duration of cirrhosis:_____
Child Pugh score: _____
Laboratory findings:
ARF: Present □ **Absent** □

Annexure I: Child-Pugh Score

Measure	1 point	2 points	3 points
Total bilirubin, µmol/L (mg/dL)	<34 (<2)	34-50 (2-3)	>50 (>3)
Serum albumin, g/dL	>3.5	2.8-3.5	<2.8
Prothrombin time, prolongation (s)	<4.0	4.0-6.0	> 6.0
Ascites	None	Mild (or treated with medication)	Moderate to Severe (or refractory)
Hepatic encephalopathy	None	Grade I-II	Grade III-IV

Points	Class
5-6	A
7-9	B
10-15	C