Clinical study of renal dysfunction in liver cirrhosis in a tertiary care hospital

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Abstract

Background: Acute Kindney Injury (AKI) is a common complication of Liver Cirrhosis, and is reversible in its initial stage. AKI is seen in 20% of hospitalizations associated with complications related to liver dysfunction. The objective of the study was to study the clinical profile of patients with liver cirrhosis with renal dysfunction. **Materials and Methods:** This was a prospective observational study in diagnosed cases on liver cirrhosis in a tertiary care government hospital in Maharashtra. All the patients were screened for renal dysfunction using International Club of Ascites (ICA) AKI criteria, and patients from stage I onwards were included after taking properly explained written consent. Data on symptoms, clinical presentation investigation was collected through a validated pretested proforma. **Results:** A higher number of males (85%) reported liver cirrhosis and was alcohol-related (81.6%); especially in patients working as unskilled laborers or unemployed. The case fatality rate during hospitalization was 33.33%. Sepsis-related AKI was more common. Hypoalbuminemia was correlated with the disease severity and progression of Acute Kidney Injury (AKI). The mean Model for End-Stage Liver Disease (MELD) score of the study group was 30.67, as those of the non-survivor group were 34.76. MELD was correlated with the progression of AKI as it was counted with baseline creatinine. **Conclusion:** Alcohol-related liver disease was more prevalence in patients with liver cirrhosis with AKI, especially males. MELD can be used as a prognostic indicator to assess the worsening of renal function in patients with liver cirrhosis.

Keywords : Liver cirrhosis, Acute Kidney Injury (AKI), Tuberculosis, Model for End-Stage Liver Disorder (MELD)

Introduction

Cirrhosis is a continuum of events leading to fibrosis with nodule formation in the liver. It is the cumulative outcome that occurs with chronic liver injury. It can present with multiorgan complications at some point in the life of cirrhosis. Acute Kidney Injury (AKI) is one of the common complications of liver cirrhosis; it is a result of possible renal ischemia, which is in earlier stages reversible upon correction of the underlying hemodynamic abnormalities with no permanent impairment. AKI is seen in 20% of hospitalizations associated with some or other complications related to liver dysfunction and is associated with significant mortality[1,2].

The etiologies for acute kidney injury in patients with liver cirrhosis can be grouped into five major categories[3]: Pre-renal, Renal causes, Infections, Severe Systemic Response Syndrome, and Exposure to Nephrotoxic Agents. Pre-renal causes are a group of many conditions. Systemic conditions compromising the renal perfusion pressure can aggravate the azotemia and lead to AKI. Hemorrhage, particularly excessive blood loss, excessive diuresis, overzealous paracentesis, diarrhea mostly related to lactulose use, and poor oral intake due to nausea and vomiting, are also pre-renal causes of acute renal failure. Acute tubular necrosis (progression of pre-renal injury) and intrinsic renal failure/Hepatorenal syndrome are major renal causes of acute kidney failure[4].

AKI is caused by deranged hemodynamics of systemic and splanchnic circulation, especially vasodilatation in the arterial tree and extra-hepatic vasoconstriction seen in advanced stages of cirrhosis. A state of functional renal failure, is correctible with the improvement of underlying defects in the vascular tree. This functional renal failure seen in liver cirrhosis is not associated with any residual structural damage[5]. Table 1 gives primary renal conditions associated with different causes of Liver Cirrhosis[2].

Table 1: Common associations of liver cirrhosis and renal dysfunction

Alcoholic liver cirrhosis	IgA nephropathy
Hepatitis B and C-related cirrhosis	Membranous and membranoproliferative glomerulonephritis
Wilsons disease – cirrhosis	Renal tubular acidosis
Primary Biliary Cirrhosis	Tubule-interstitial nephritis Chronic tubular damage
Non-alcoholic fatty liver disease (NAFLD)	Diabetic glomerulosclerosis and Chronic Kidney Disease

Cirrhotics have increased portal circulation, promoted by Nitric Oxide (NO) production, leading to the development of ascites. Other factors such as dysbiosis, impaired peristalsis, altered gut permeability, and immune dysregulation promote antigenic presentation to the mesenteric lymph nodes. Thus activating further downstream effector arm immunity, activating local inflammatory cytokines, chemotaxis, and nitric oxide, causing further splanchnic vasodilation and creating a persistent state of chronic inflammation in the vascular tree around the gut[6,7].

In the initial phase of cirrhosis, cardiac output increases to cope up with reduced systemic vascular resistance. With the progression of cirrhosis, this degree of cardiac compensation falls short of maintaining adequate circulation and blood supply to vital organs, leading to end-organ damage such as AKI and encephalopathy. Hepatorenal Syndrome (HRS) is the terminal manifestation of the AKI, developing in the setting of liver cirrhosis. In the aspect of renal failure in cirrhosis, histopathology often is non specific and does not show correlating lesions with regards to compromised renal function. As arterio-vascular resistance in the kidneys correlates with the activity of the renin-angiotensin and sympathetic nervous system in cirrhosis, HRS is considered to be an extreme stimulation of these systems[5-7]. It is possible to prevent HRS with appropriate management.

Aim

To study the clinical profile of Renal dysfunction in patients with Liver Cirrhosis in terms of Outcome

Objectives

1. To study the clinical profile of patients with liver cirrhosis with renal dysfunction
2. To monitor renal function tests in patients with liver cirrhosis
3. To observe the correlation between hepatic and renal function tests
4. To study the etiology and outcome of patients with liver cirrhosis

Materials and Methods

Study design

A prospective type of observational study was performed.

Settings

The authors have conducted a current study in a government medical college in Western Maharashtra.

Study period

The investigators conducted the study from 2017 to 2018.

Participants

All admitted newly diagnosed and previously known cases of liver cirrhosis.

Inclusion Criteria

A patient above 12 years, having liver cirrhosis diagnosed on the basis of radiological, laboratory, and clinical grounds, having renal dysfunction documented on laboratory and biochemical parameters.

Exclusion Criteria

A patient having renal dysfunction from other known causes like diabetic or hypertensive nephropathy, which is documented by parenchymal involvement on abnormal urine microscopy or renal ultrasonography, was excluded.

Collection of data

The authors prepared a standardized proforma with due importance to symptomatology, clinical presentation, investigations of all the patients. The proforma was validated and pretested. The format included demographic features and a general examination of the patient.

Symptomatology

History and clinical presentation of all the patients was collected using the clinical proforma. The information about the following variables was collected.

- Jaundice
- Abdominal distension and pedal edema whenever present
- Decreased urine output
- Altered sensorium (as complained by the accompanying relatives)
- Fever
- History of black stools or blood in vomitus
- Any other systemic complaints

All the patients were screened for renal dysfunction using International Club of Ascites (ICA)-AKI criteria, and patients from stage I onwards were included after taking properly explained written consent. We evaluated patients using standard guidelines for renal and liver functions[2,3,8,9]

Operational definitions used in the study

AKI is defined as an acute significant reduction in the Glomerular Filtration Rate (GFR). Serum Creatinine has a few limitations in liver cirrhosis to be used as a biomarker for AKI. The standards for staging are based on serum creatinine. The stages are defined as below;

Stage 1: Increase in Serum creatinine is ≥ 0.3mg/dl or an increase in Serum ≥ 1.5-fold to 2-fold from baseline.

Stage 2: Increase in Serum creatinine > 2-fold to 3-fold from baseline

Stage 3: Increase in Serum creatinine > 3-fold from baseline or Serum creatinine ≥ 4.0 mg/dl with an acute increase ≥ 0.3mg/dl or the initiation of renal replacement therapy

We have followed the ICA criteria for Hepatorenal Syndrome[5] and standard classification Hepatorenal Syndrome[8,9].

Statistical analysis

The data was collected and entered into a Microsoft Excel sheet. Data was evaluated for a number of patients presenting with such symptoms and expressed as a percentage of patients.

Results

Demographic information about the patients is given in Table 2. In this clinical study of 60 cases of liver cirrhosis with renal dysfunction; the male population was high, [Male:Female (M:F= 6:1)]. Three-fourths of the patients were from urban area. The overall case fatality rate during hospitalization was 33.33%. There was no significant difference between the fatality rate among males and females (Fisher's exact test= 0.46; P>0.05).

Table 2: Demographic characteristics of participants

Age (in years)	Male n (%)	Female n (%)	Total n (%)
12-20	0 (0)	2 (3.3)	2 (3.3)
21-30	7 (11.66)	1 (1.66)	8 (13.33)
31-40	14 (23.33)	2 (3.33)	16 (26.66)
41-50	11 (18.33)	1 (1.66)	12 (20)
51-60	15 (25)	2 (3)	17 (28.33)
Above 60	4 (6.66)	1 (1.66)	5 (8.33)
Total	51 (85)	9 (15)	60 (100)

The most common etiology of liver cirrhosis was alcohol-related liver disease, with a high prevalence of alcohol abuse (Table 3). All patients who had alcoholic cirrhosis were male (except one). The incidence of alcoholic liver cirrhosis was higher in occupations such as drivers and laborers, followed by unemployed.

Table 3: Etiologies of liver cirrhosis

Etiologies of Liver Cirrhosis	Male n (%)	Female n (%)	Total n (%)
Alcoholic liver cirrhosis	48 (79.93)	1 (1.67)	49 (81.6)
Non-alcoholic fatty liver disease (NAFLD)	2 (3.32)	3 (4.99)	5 (8.32)
Post viral necrosis - cirrhosis	1 (1.74)	1 (1.74)	2 (3.48)
Cryptogenic liver cirrhosis	0 (0)	4 (6.6)	4 (6.6)

Abdominal distension was the most common complaint on admission, followed by jaundice (Figure 1). Decreased urine output on admission was significantly related to the progression of AKI but not to the final outcome.

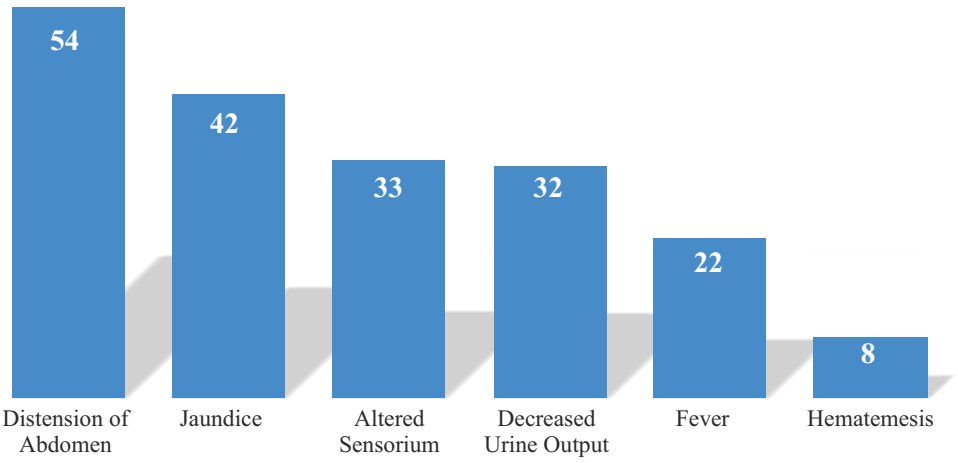

Figure 1: Complaints reported by the participants on admission (in percentage)

Ascites was the most common clinical finding in both sexes; followed by Icterus. Signs of liver cell failure and hepatic encephalopathy were noted in half of the patient population during admission and hospitalization. Tender abdomen was found in 20% of the population, with the most common differential being spontaneous bacterial peritonitis. The palpable spleen was present in half of the population, whereas more than half of the cases were in shock on admission. Hepatomegaly was present in 20% of the patients.

The respiratory system was commonly involved in systemic involvement, where four patients required invasive ventilation in the Intensive Care Unit. Sixteen percent of patients had spontaneous bacterial peritonitis, and 13% of patients had a history of prior hospitalization. Seven patients had infections of the genitourinary tract, leading to the progression of AKI.

Severe anemia with hemoglobin less than 6gm/dl was present in 16% of the patients. Thrombocytopenia was seen in almost the entire population in conjunction with the strong association of portal hypertension and uremia seen in the study group. Leukocytosis was also commonly seen in the study population, with half of the patients having White Blood Cells (WBC) counts of more than 11,000/cmm. The mean International Normalized Ratio (INR) of the study group was 2.2, indicating the prevalence of coagulopathy; 90% of the population had prothrombin time above 14 seconds. Hyponatremia was noted in 72% of the patients evaluated. Severe Hyponatremia was present in 16 (26%) cases (125mEq/ml). Hyponatremia is also known to be aggravating the AKI progression. The majority of the patient (93.33%) had hyperbilirubinemia with total bilirubin above 1.1mg/dl. Hypoalbuminemia was correlated with the disease severity and progression of AKI. Only 10% of the population had normal serum albumin (above 3.5mg/dl).

Very few of the tested population turned out to be HCV-positive. Only one was HBsAg positive with post-viral necrotic etiology of cirrhosis.

The Model for End-Stage Liver Disease (MELD) score of the patient population based on patient characteristics on the day of admission was calculated. The mean MELD of the study group was 30.67 where, as those of the non-survivor group were 34.76. MELD was correlated with the progression of AKI as it was counted with baseline creatinine.

Hepatic encephalopathy was significantly correlated with the AKI progression (Table 4).

Table 4: Showing stratification of AKI based on IAC-AKI criteria

AKI staging	Male n (%)	Female n (%)	Totaln (%)
I	16 (26.61)	3 (4.99)	19 (31.6)
II	12 (19.93)	1 (1.66)	13 (21.6)
III	23 (38.27)	5 (8.32)	28 (46.6)
Total	51 (85)	9 (15)	60 (100)

Stage III AKI had a significant association with mortality in the present study. In a retrospective analysis of the non-survivor group of 20 patients, M:F ratio was 4:1. Majority (90%) of the patient population was in stage III AKI. No patients responded to fluid therapy completely, mandating further use of vasopressors. Maximum number of patients received Fresh Frozen Plasma (FFP), and one fourth patients received IV Albumin. Four patients were offered dialysis as a mode of renal replacement therapy.

Discussion

Male preponderance among patients is usually observed[10,11]. This is a reflection of the consumption of alcohol, which is comparatively lesser among Indian women. Another article on the effect of gender on the prevalence and patient outcomes[12] stated that cirrhosis arising from alcohol abuse is far less common in females, as supported by the population-based study of 8482 Danish patients from 1993 to 2005 in which only 33% of patients were women. Changes in AKI grading at baseline and later during hospitalization are usually bidirectional due to the treatment of deterioration. Varied proportions in grading are observed in various studies[13,14,15]. The proportion of pre-renal azotemia, acute tubular necrosis, intrinsic or HRS was similar to other studies except for septicemia, which was not observed among other studies[13,14,15,16]. We had maximum cases of renal dysfunction due to septicemia-related causes. In 28 out of 60 patients (46%), the cause was entirely related to septicemia. Whereas in 13 cases (21%), the cause was due to septicemia and additional pre-renal factors. Maximum mortality was also seen in patients having renal dysfunction with additional septicemia. Sixteen patients (out of 20) who died had AKI due to septicemia and additional pre-renal etiology. In a similar study conducted by Belcher et al.[15], including 192 patients of AKI with liver cirrhosis, 56 (29%) cases were due to alcoholic cirrhosis, and 17 (9%) were related to NAFLD, cryptogenic cirrhosis was evident in 12 (6%) cases, and HCV

was the cause in 33 cases. In a similar study conducted by Mohan et al.[10], they found that the AKI (12%) was the most common type of renal dysfunction followed by HRS (7%) and Chronic Kidney Disease (CKD) (3%). There was no association between the causes of cirrhosis and renal pathologies. They had six patients with Multi-organ Dysfunction Syndrome (MODS) that complicated the outcome in a very adverse manner. Only one patient had acute pancreatitis, which was managed with conservative therapy.

In a similar study performed by Fasolato et al.[14], Spontaneous Bacterial Peritonitis (SBP) was seen in six (3%) cases, and other systemic infections were involved in another 3% of cases. In another study by Allegretti et al.[13], 15 (38%) of their 120 participants had evidence of systemic infection complicating their hospital stay.

Conclusion

Renal dysfunction is a common complication of Liver Cirrhosis, and AKI in Liver Cirrhosis is a known predictor of mortality in patients with advanced renal dysfunction in the settings of complications of liver cirrhosis. Alcohol-related liver diseases have a rising trend in the urban population, especially in patients working as unskilled laborers or unemployed. Cryptogenic cirrhosis is common in females, with liver cirrhosis being commoner in the male population overall. Sepsis-related AKI is more common in hospitalized patients with liver cirrhosis, followed by pre-renal and intrinsic causes. Hepatorenal syndrome represents its extreme end with the highest mortality. Septicemia and Hepatic encephalopathy are important factors causing the progression of AKI in hospitalized patients. MELD can be considered as a prognostic indicator in the settings of worsening renal dysfunction in liver cirrhosis as it considers both hepatic and renal parameters. Dialysis or renal replacement therapy has no significant difference in the outcome in cirrhotic patients with advanced renal dysfunction.

Conflict of Interest: Nil

Source of Support: Nil

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Ethical consideration

The study was approved by the Institutional Ethics Committee. Informed written consent was obtained from the patient or parent.

Authors' Contribution

MTD: Data Collection, Implementation, Data Analysis and Interpretation, Manuscript Writing; SS: Conceptualization, Design, Monitoring and Supervision, Data Analysis and Interpretation, Manuscript Writing

Data availability statement

Data well be available with corresponding author on request.

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