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Incidence, causes, and outcomes of renal failure among cirrhotic patients

LIVER

Khairy H. Morsy[1], Mohamed A. Mekky[2], Mohamed O. Abdel-Malek[2], Wael A. Abbas[3]

[1]Department of Tropical Medicine and Gastroenterology, Sohag University Faculty of Medicine, Sohag, Egypt
[2]Department of Tropical Medicine and Gastroenterology, Assiut University Faculty of Medicine, Assiut, Egypt
[3]Department of Internal medicine, Assiut University Faculty of Medicine, Assiut, Egypt

Original Article

ABSTRACT

Background/Aims: To evaluate the incidence, risk factors of RF among cirrhotic and its impact on patient's outcome.

Materials and Methods: A total of 573 cirrhotic patients were evaluated for renal failure (RF) and its causes, 212 patients (37%) were enrolled.

Results: Majority of the patients had post hepatitis C liver disease (n=190, 89.6%) with Child-Pugh score C (88.2%), HCC was in 21.2% of cases baseline characteristics. Infections were observed in 45.8% (n=97) of patients whereas, spontaneous bacterial peritonitis (SBP) was the most type of infection (19.3%) among cirrhotic patients with renal failure, followed by pneumonia (9.9%). Infection-induced represents 30.2% followed by hypovolemia (29.7%), whereas HRS was in 11.3%. Reversibility of the condition was seen in 81 patients (38.2%), whereas mortality was seen in 58 (27.4%) patients of RF. The reversibility was more common in the patients with infection, followed by hypovolemia. Mortality was higher in the patients with HRS followed by parenchymal renal disease.

Conclusion: Infection-induced and hypovolemic-induced RF represent the most common and also the most correctable causes and must be considered in management protocols for early detection and treatment that will serve for a better prognosis.

Keywords: Renal failure, liver cirrhosis, hepatorenal syndrome, bacterial infection, parenchymal renal disease

INTRODUCTION

Liver cirrhosis is now considered as a systemic disease with a various circulatory changes that worsen in parallel to the deterioration in liver function (1). With the occurrence of end-stage liver disease (ESLD), and as a response to these circulatory upsets, the burden of renal failure (RF) among patients with ascites is a common finding (2). The real incidence and the different etiologies may have a great burden on the prognosis and the outcome. It has been known for many years that patients have a reduced survival than patients without renal failure (3). Liver and renal dysfunction often present together, either secondary to single organ failure or as part of multi-organ failure. There is also an increased frequency of complications and reduced survival after liver transplantation in these patients, as compared with those without renal failure (4). Moreover, recently, the prognosis was shown to be dependent on the etiology of the RF and severity of liver disease (5).

Compared with the abundance of studies that show the prognostic value of renal function parameters, particularly serum creatinine, it is not known whether the cause of renal failure is relevant to prognosis or not. This information may be important not only for clinical management of patients and classification of patients in therapeutic trials but also in decision making in liver transplantation.

The estimated frequencies of RF is 30% in liver cirrhosis with infections, 11% in upper GI bleeding and 45-50% in critically ill liver cirrhosis patients admitted to intensive care units (ICU) (6).

In spite of most articles tackled this concern deal with the causes of renal failure, as a subsequent on infection-induced, intrinsic renal disease or prerenal, the real life is not as simple as described with an overlap. Most of the cases as an insult of multifaceted pictures of infection, prerenal hypovolemia and intrinsic renal diseases.

Address for Correspondence: Wael A. Abbas, E-mail: drwaelabbas@yahoo.com
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Therefore, we aimed to design a prospective, hospital-based study to evaluate patterns of renal failure among cirrhotic patients and its impact on prognosis.

MATERIALS AND METHODS

Patients' recruitment

After obtaining our local ethical committee approval, a hospital-based, prospective study was designed to include all consecutive cirrhotic patients admitted to the Departments of Gastroenterology, Assiut University Hospital, and Sohag University Hospital, Egypt, over six months period (from July 2014 to December 2014). The diagnosis of cirrhosis was made by the finding of clinical examination, laboratory test and ultrasonographic imaging.

Patients were subjected to:

Clinical evaluation (medical history and physical examination),

abdominal ultrasonography examination with special comments on renal parenchymal status and the presence of ascites, portal Vein diameter, repeated urine analysis, liver function test, prothrombin time estimation, complete blood count, serial blood urea and serum creatinine level estimation every two days, serum sodium and potassium, blood glucose level, ascitic fluid study in suspected spontaneous bacterial peritonitis (SBP).

Study design

Renal function assessed at admission and at regular intervals throughout hospital stay.

Study definitions

Liver cirrhosis: Its diagnosis was made by the pooled results of clinical examination, laboratory tests and imaging. The etiology of liver cirrhosis and the reason for hospitalization was established in all patients. In the case of more than one cause for admission, the main cause was reckoned based on the following hierarchy: GI bleeding, infection, hepatic encephalopathy, tense ascites and mixed. Severity of liver cirrhosis was assessed by the Child-Pugh score (CPS).

Renal failure: Patients have 2 consecutive reading of raised serum creatinine more than 1.5 mg/dL (133 mol/L) during 48-hour. This value of serum creatinine was used because it has been selected in several consensus conferences as a cut off to define renal failure in cirrhosis (7). The baseline serum creatinine was considered as first value obtained on the first day of this admission. Renal failure was either: 1. reversible, if serum creatinine was reversed to its baseline or 2. irreversible, if it did not reverse and or still greater than 1.5 mg /dL during the hospital stay or death.

Patients were classified into 5 different categories: 1. Infections-induced RI: when an overt infection was diagnosed on a solid clinical, laboratory, and/or imaging findings. Spontaneous bacterial peritonitis (SBP) was defined by polymorphonuclear count greater than 250 per mm^3 in ascitic fluid in the absence of a source of infection in the peritoneal cavity (8); spontaneous bacteremia was defined by positive blood cultures without an evidence of infection. 2. Prerenal Hypovolemia-induced RI: when evidence of body fluid losses prior to admission (because of bleeding, diuretics, or other causes, mainly gastrointestinal fluid losses) without evidence of other renal causes. 3. Intrinsic renal parenchymal disease: when proteinuria more than 500 mg/24 hours, and or urine contain more than ≥50 RBC/HPF, and or abnormal renal imaging changes. 4. Hepatorenal syndrome: The diagnosis of HRS was made after exclusion of other potential renal disorders. 5. Combined etiologies: when there was an overlap between the first three etiologies.

- Inclusion criteria: All hospitalized patients with liver cirrhosis and RF, according to our criteria.
- Exclusion criteria: Patients with a hospital stay or survival of less than 48 hours after admission were excluded from the study.
- Our local ethical committee approved this study and informed consent obtained from patients.
- Renal failure was managed as follow: 1. drugs that may potential induce failure such as diuretics or nephrotoxic drugs stopped immediately; 2. patients with volume loss were treated by volume expanders, and the original cause were managed according to the original etiology; 3. infection treated with the proper antibiotic according to our local guidelines; 4. HRS treated with albumin and terlipressin; and 5. hemodialysis was done in indicated patients (9).

Statistical analysis

Frequency and percentage of different variables were determined. Chi square test and student's t-test were used as appropriate. P-value less than 0.05 was considered statistically significant. The data was analyzed using Statistical Package for Social Sciences (SPSS) version 16.0 for Windows (SPSS Inc.; Chicago, IL; USA).

RESULTS

A total of 573 cirrhotic patients were evaluated for the presence of renal failure (RF) and its causes. Among them, 212 patients (37%; 158 males (74.5%), with age range 48-80years) were recognized according to our inclusion criteria. Majority of the patients had their liver disease secondary to hepatitis C (n=190, 89.6%) with Child-Pugh score C (n=187, 88.2%), HCC was presented in 21.2% of cases baseline characteristics are described in Table 1.

Basic laboratory characteristics of cirrhotic patients with renal failure are described in Table 2.

Infections were observed in 45.8% (n=97) of patients whereas, spontaneous bacterial peritonitis (SBP) was the most type of infection (19.3%) among cirrhotic patients with renal failure, followed by pneumonia (9.9%) as described in Table 3.

As regard the patterns and types of renal failure observed in the studied group, infections (30.2%) and hypovolemia (29.7%) were responsible for majority of the causes of renal failure, whereas HRS was seen in 11.3% of the cases as described in Table 4.

On assessing the outcome and the in-hospital mortality, reversibility of the condition was seen in 81 patients (38.2%), whereas mortality was

Table 1. Basic characteristics of cirrhotic patients with renal failure (n=212)

Characteristics	
Age (years)*	59.5 (48–80)±7.1
Sex (M:F) %	158 (74.5%):54 (25.5%)
Hospital stay (days)*	6.7 (4–15)±2.9
Possible predisposing factors n (%)[§]	
Hematemesis/melena	25 (11.8%)
Vomiting/diarrhea	9 (4.2 %)
HE	29 (13.7%)
Infection	44 (20.8%)
Tense ascites	5 (2.4%)
Bleeding/HE	26 (12.3%)
Ascites/HE	17 (8%)
Infection/HE	23 (10.8%)
Bleeding/infection	10 (4.7%)
Ascites/infection	4 (1.9%)
Bleeding/HE/infection	20 (9.4%)
Prior NSAIDs	0 (0%)
Presence of coexisted HCC	45 (21.2%)
Etiology of cirrhosis, n (%)	
HCV:HBV:combined	190 (89.6):16 (7.5%):6 (2.8%)
Child-Pugh score, n (%)	
A:B:C	5 (2.4%):20 (9.4%):187 (88.2%)

*mean(range)±SD
[§]some overlap was found between cases
HE: hepatic encephalopathy; HCC: hepatocellular carcinoma; NSAIDs: non-steroidal anti-inflammatory drugs; HCV: hepatitis C virus; HBV: hepatitis B virus

Table 2. Basic laboratory characteristics of cirrhotic patients with renal failure (n=212)

Characteristics	Mean±SD
HB level (g/dL)	8.4±7.1
Platelet level	116.6±54
WBC count	9.6±4.4
RBC count	3.4±0.8
Total bilirubin (mg/dL)	7.1±5.5
Serum albumin (g/dL)	2.1±0.6
Prothrombin concentration (%)	55.1±14.9
Serum creatinine (mg/dL)	3.2±1.2
Serum sodium (mEq/L)	128±8
Serum potassium (mEq/L)	4.5±0.7
MELD score (mean±SD)	25±7

HB: hemoglobin; WBC: white blood cell; RBC: red blood cell; MELD: model for end-stage liver disease

seen in 58 (27.4%) patients of RF. The outcome was shown to be affected by the cause of RF; as the reversibility was more common in the patients with infection, followed by hypovolemia. Mortality was higher in the patients with HRS followed by Parenchymal Renal disease (Table 5).

DISCUSSION

Chronic liver diseases are common in Egypt due to high incidence of viral hepatitis. End stage liver disease is usually associated with multiorgan failure that affect most of body systems (9). The high morbidity and mortality is often related to renal dysfunction, either alone or in combination with other organ dysfunction. Studies concerning the evaluation of the predictors of survival in cirrhosis, found that renal failure was the most predictor of poor prognosis in decompensated cirrhosis, with Child-Pugh score and its components (5,10,11).Three pattern of liver-kidney interactions; simulta-

Table 3. Types of infection among cirrhotic patients with renal failure (n=212)

Characteristics	
SBP	41 (19.3%)
Pneumonia	21 (9.9%)
Empyema	11 (5.2%)
UTI	16 (7.5%)
Combined[§]	8 (3.8%)
No infection	115 (54.2%)

[§]some overlap was found between cases
SBP: spontaneous bacterial peritonitis; UTI: urinary tract infection

Table 4. Types of renal failure among studied group (n=212)

Characteristics	
HRS	24 (11.3%)
Infection-induced RF	64 (30.2%)
Hypovolemic pre-renal failure	63 (29.7%)
Parenchymal Renal disease	20 (9.4%)
Combined	41(19.3%)

HRS: hepatorenal syndrome; RF: renal failure

Table 5. Course and in-hospital mortality among cirrhotic patients with renal failure (n=212)

	Course of renal failure		
Cause of renal failure	Reversible	Irreversible	Mortality
HRS (24)	4 (16.7%)	20 (83.3%)	16 (66.7%)
Infection-induced RF (64)	38 (59.4%)	26 (40.6%)	9 (14%)
Hypovolemic pre-renal failure (63)	34 (54%)	29 (46%)	10 (15.9%)
Parenchymal renal disease (20)	0 (0%)	20 (100%)	11 (55%)
Combined (41)	5 (12.2%)	36 (87.8%)	12 (29.3%)
Total (212)	81 (38.2%)	131 (61.8%)	58 (27.4%)

p<0.001 (chi-square test)
HRS: hepatorenal syndrome; RF: renal failure

neously affection of both, or a primary disorder affecting either of them at first with secondary affection of the other later (12).

Renal dysfunction secondary to hepatic disease is usually non organic (functional disorder). However, this may be complicated with intrinsic renal changes (13).

Renal failure in liver cirrhosis is often challenging. It is associated with a high morbidity and mortality in these patients. Its estimated incidence in previous studies was ranged between 30-40% in most studies (6,14,15). In our study we observed RF in about 37% of our enrolled cirrhotic patients that match with the previous mentioned series. Renal failure in our patients settings was noted to occur in advanced liver disease with; mainly Child C patients and in more elder populations (age around 60) that similar to the findings of Qureshi et al. (14).

In the current study, infection was the commonest cause of renal failure (30%), followed by hypovolemic pre-renal failure, HRS and renal parenchymal disease and combined causes. Most of studies also, commented on the high incidence of infection-induced RF as the most common (30-40%), and reversible, predisposing factor (6,13,14). The pathogenic mechanism of renal failure in liver cirrhosis and infections is not completely understood, but it is thought to be secondary to a circulatory dysfunction due to circulatory vasodilation by the presence of vasoactive bacterial products (16).

Our results indicate that almost any bacterial infection may cause renal failure in cirrhosis, yet the most frequent are spontaneous bacterial peritonitis (20%) and spontaneous bacteremia, followed by respiratory and urinary tract infections. Our findings go with those reported by others. Follo et al. (17) concluded that renal dysfunction is frequent in cirrhotics with spontaneous bacterial peritonitis that occurs mainly in patients with kidney failure before infection and found that renal failure is an important predictor of survival especially in the presence of SBP. Also, the same conclusion was mentioned in the study of Ruiz-del-Arbol et al. (18) as patients with SBP frequently develop a progressive severe renal and hepatic failure, and even death, despite of the resolution of infection and is usually associated with an extremely poor prognosis. These observations give an alarm for the emergency-pattern of combating coexisted infections in patients with ESLD to prevent these comorbidities and poor prognosis.

Hypovolemia-related renal failure was the second cause of renal failure in the current series. The most common causes of hypovolemia were gastrointestinal bleeding followed by diuretics, which accounted for almost 75% of cases of renal failure related to hypovolemia. Most patients with hypovolemia developed renal failure in the absence of hypovolemic shock. Gastrointestinal bleeding leads to reduced intravascular volume, renal hypoperfusion and reduction in glomerular filtration rate. Gastrointestinal bleeding in cirrhotic patients also predisposed to bacterial infections and this may adversely affect renal function (19). In spite of the observation that infection-induced and hypvolemic-induced etiologies are the most frequent finding, they are reversible and even preventable in most of clinical settings. Therefore, early detection and immediate management might help in reducing the co-morbidity and in-turn the prognosis.

In our study, we found that more than one third of cases had a reversible pattern (38.2%) regardless the etiology and this percentage was better than that reported by Carvalho et al. (6) who reported about 29% of their cohort had a reversible pattern although their study were retrospective type. Moreover, we found that infection-induced RF was the commonest cause of reversible renal failure and exhibited the least mortality (59.4%) which is lower than that reported by Fasolato et al. (78%) (20) and better than that reported in the study of Carvalho et al. (6). This notion augment our previous recommendation of early detection of infections coincidentally occurred with ESLD and the subsequent early aggressive management will serve as a crucial step in management protocols. The second reversible cause in the present study was the hypovolemic pre-renal failure that was the exact percentage reported in the study of Carvalho et al. (6) (54%). From these observation, it worth noted that, both infection induced and hypovolemic-induced renal failure together may represent more than half of the causes of renal failure with the best prognosis and highest reversibility (88%) and least mortality (32.7%). So, the workup management protocols must contain clear statements about how to prevent, early detect, and the possible lines of treatment of these causes. Also, we found that patients with parenchymal renal disease and HRS were exhibited the least reversibility rates that was similar to that by Carvalho et al. (6) and in contradiction to that of Martín-Llahí et al. (14) who mentioned the best prognosis where found in those with renal parenchymal disease. In spite of these results, avoidance of nephrotoxic drugs and early detection of patients with preexisted parenchymal renal diseases will reduce the prognosis. Another serious point was noted in the current series, that a considerable percentage of our patients had a combined pattern of risk factors (19.3%) and also a combined pattern of causes of renal failure that will add a heavy burden on the bad prognosis.

In our design we aimed to highlight the presence of some cases that presented with a combined pattern either in the risk factor; such as a combined pre-renal hypovolemia and infections, and also, in the classification of the etiology. Martín-Llahí et al. (14) discussed this drawback by the absence of specific markers that may help in the identification of the cause of renal failure in cirrhosis. We also recommend the need to exert an effort to build-up a new battery of laboratory markers of renal failure that may be useful for the differential diagnosis.

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. Also, the definition of renal failure in our study was depend on the guidelines published by Arroyo et al. (7) which looks an old criteria, therefore we also recommend a recent prospective study to evaluate the RF among cirrhotic with the adoption of the recently published guideline in 2015 by Angeli et al. (21).

In conclusion, the infection-induced and hypovolemic-induced RF represent the most common and also the most correctable causes of RF among cirrhotic and must be considered in management protocols for early detection and treatment that will serve for a better prognosis.

Ethics Committee Approval: Ethics committee approval was received for this study.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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REFERENCES

1. Nadim MK, Kellum JA, Davenport A, et al. Hepatorenal syndrome: the 8th International Consensus Conference of the Acute Dialysis Quality Initiative Group. Crit Care 2012; 16: R23. [CrossRef]
2. Gines P, Schrier RW. Renal failure in cirrhosis. N Engl J Med 2009; 361: 1279-90. [CrossRef]
3. Wu CC, Yeung LK, Tsai WS, et al. Incidence and factors predictive of acute renal failure in patients with advanced liver cirrhosis. Clin Nephrol 2006; 65: 28-33. [CrossRef]
4. Trawalé JM, Paradis V, Rautou PE, et al. The spectrum of renal lesions in patients with cirrhosis: a clinicopathological study. Liver Int 2010; 30: 725-32. [CrossRef]
5. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. J Hepatol 2006; 44: 217-31. [CrossRef]
6. Carvalho GC, Regis Cde A, Kalil JR, et al. Causes of renal failure in patients with decompensated cirrhosis and its impact in hospital mortality. Ann Hepatol 2012; 11: 90-5.
7. Arroyo V, Ginès P, Gerbes AL, et al. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. International Ascites Club. Hepatology 1996; 23: 164-76. [CrossRef]
8. Rimola A, Garcia-Tsao G, Navasa M, et al. Diagnosis, treatment, and prophylaxis of spontaneous bacterial peritonitis: a consensus document of the International Ascites Club. J Hepatol 2000; 32: 142-53. [CrossRef]
9. Angeli P, Sanyal A, Moller S, et al. on behalf of the International Club of Ascites (Current limits and future challenges in the management of renal dysfunction in patients with cirrhosis: report from the International Club of Ascites) Liver International (2012).
10. Lim YS, Larson TS, Benson JT, et al. Serum sodium, renal function, and survival of patients with end-stage liver disease. J Hepatol 2010; 52: 523-8. [CrossRef]
11. Krag A, Bendtsen F, Henriksen JH, et al. Low cardiac output predicts development of hepatorenal syndrome and survival in patients with cirrhosis and ascites. Gut 2010; 59: 105-10. [CrossRef]
12. Betrosian AP, Agarwal B, Douzinas EE. Acute renal dysfunction in liver diseases. World J Gastroenterol 2007; 13: 5552-9 [CrossRef]
13. Moreau R, Lebrec D. Acute renal failure in patients with cirrhosis: perspectives in the age of MELD. Hepatology 2003; 37: 233-43. [CrossRef]
14. Martín-Llahí M, Guevara M, Torre A, Fagundes C, et al. Prognostic importance of the cause of renal failure in patients with cirrhosis. Gastroenterology 2011 Feb; 140: 488-496.e4. [CrossRef]
15. Qureshi MO, Shafqat F, Dar FS, Salih M, et al. Renal failure in patients with end stage liver disease and its impact on clinical outcome. J Coll Physicians Surg Pak 2014 Sep; 24: 628-31.
16. Terra C, Guevara M, Torre A, et al. Renal failure in patients with cirrhosis and sepsis unrelated to spontaneous bacterial peritonitis: value of MELD score. Gastroenterology 2005; 129: 1944-53. [CrossRef]
17. Follo A, Llovet JM, Navasa M, et al. Renal impairment after spontaneous bacterial peritonitis in cirrhosis: incidence, clinical course, predictive factors and prognosis. Hepatology 1994; 20: 1495-501. [CrossRef]
18. Ruiz-del-Arbol L, Urman J, Fernandez J, et al. Systemic, renal, and hepatic hemodynamic derangement in cirrhotic patients with spontaneous bacterial peritonitis. Hepatology 2003; 38: 1210-8. [CrossRef]
19. Makhlouf NA, Morsy KH. Renal failure after upper-gastrointestinal bleeding among cirrhotic patients in Upper Egypt. Arab J Gastroenterol 2012; 13: 139-44. [CrossRef]
20. Fasolato S, Angeli P, Dallagnese L, et al. Renal Failure and Bacterial Infections in Patients with Cirrhosis: Epidemiology and Clinical Features. Hepatology 2007; 45: 223-9. [CrossRef]
21. Angeli P, Gines P, Wong F International Club of Ascites. Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites. Gut 2015; 64: 531-7. [CrossRef]