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Acute Kidney Injury Complicates Advanced Liver Cirrhosis In Hospitalized Patients: Causes And Short-Term Outcomes

Medical Science

KEYWORDS : Acute kidney injury, Liver cirrhosis, Sepsis, Hyponatremia, Hypoalbuminemia

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ABSTRACT

Acute kidney injury (AKI) is frequent complications in patients with advanced cirrhosis. This is a 12 month retrospective study of AKI and its associated factors in hospitalized patients with cirrhosis. For each patient, we performed initial renal function tests and electrolyte levels, at 48 hours post admission and at discharge. We also obtained all patient's CBC. A total of 49 patients were included in the final analysis. The majority of patients were women (29, 59.2%), mean age was 53 years (SD, 16.5). The most common indication for admission was ascites (34 patients, 69.4%), and spontaneous bacterial peritonitis was present in half (17) of them. Baseline renal dysfunction was present in 21 (43%) patients, and 16 of these patients (32.65% of all patients) had AKI. The risk factors associated with the development of AKI were older age, hypoalbuminemia, elevated white blood cell (WBC) count, sepsis, and, hyponatremia (P=.022, .008, .033 and .06, respectively). Hypoalbuminemia was associated with persistent renal dysfunction at discharge.

Conclusions: *AKI is a common complications our cirrhotic patients, and some patients will not achieve complete renal function normalization after AKI.*

Introduction

Liver cirrhosis is a leading cause of hospital admission and mortality [1,2]. Renal impairment (RI) of variable severity develops in approximately 20 to 50% of hospitalized patients with acute liver cirrhosis complications [3-6]. Acute kidney injury (AKI) is defined as a .3 mg/dL (> 26.4 mol/L in total) elevation in serum creatinine, which is equivalent to a > 50% increase from baseline (or a urine output of <.5 mL/kg per hour for > 6 hours) [3-7].

Several mechanisms are thought to play roles in the development of AKI in cirrhosis cases, including the nephrotoxic effects of medication, sepsis, and volume depletion secondary to gastrointestinal bleeding or diuretic use [7,8]. However, progressive vasodilatation of the splanchnic and systemic vascular systems is also thought to be a major cause of AKI [8]. The spectrum of AKI in cirrhosis varies from prerenal azotemia to severe forms of acute tubular necrosis (ATN) and hepatorenal syndrome (HRS) [3,7,9]. The importance of AKI in cirrhosis comes from its association with high morbidity and mortality in cirrhotic patients.[5,10,11]. In this paper, we studied the rate of AKI in patients who were admitted for acute complications of cirrhosis at a main tertiary academic medical center in the Middle East.

Methods

The research ethics committee at the Faculty of Medicine of King Abdilaziz University approved this study.

The study used a retrospective cohort design.

The following inclusion criteria were applied: patients with decompensated liver cirrhosis who were followed in the outpatient hepatology department; those with baseline renal function testing and electrolyte measurements performed prior to hospital admission; and those admitted to the male or female medical ward at King Abdulaziz University Hospital under hepatology care for an acute complication of cirrhosis. Only the patients who underwent abdominal ultrasound examination during the admission process and were tested for renal function at admission, 48 hours after admission and at discharge were included.

The study period ranged from January 2014 to December 2014.

Patients with incomplete data and patients with liver cirrhosis who were admitted for reasons other than complications of cirrhosis were excluded from the study.

We reviewed the hospital information system and patient electronic medical records for demographic data (sex and age). We noted the diagnosis at admission, and we obtained the results of renal function and electrolyte testing at admission, at 48 hours following admission and at discharge. These data included the serum creatinine, serum urea, serum sodium and serum potassium levels. The following liver function measurements were also recorded at admission: serum alanine aminotransferase (ALT), serum aspartate amino transferase (AST), serum alkaline phosphatase (AlP), serum gamma glutamyl transferase (GGT), serum bilirubin total and direct total (TB, DB), serum total protein (TP) and serum albumin. In addition, we examined the serological testing results for viral markers (for hepatitis B and hepatitis C viruses) and autoimmune hepatitis (AIH) profiles.

AKI was defined according to the Acute Kidney Injury Network (AKIN) criteria as follows: .3 mg/dL (> 26.4 mol/L in total) elevation in serum creatinine, equivalent to a > 50% increase from baseline in serum creatinine equivalent to 1.5 mg/dl increase in serum creatinine (or a urine output of < .5 mL/kg per hour for > 6 hours) [12]. The normal serum creatinine level at our lab is 55-115 µmol/L. We also obtained the complete blood count from each patient at admission, including the hemoglobin (Hg) level, white blood cell (WBC) count and platelet (Plat) count. We examined the results of the ultrasound examinations performed during the same admission for the presence of ascites.

We also reported the length of stay for all patients and the patients' outcomes (i.e., in-hospital mortality) during the same admission or discharge.

We used IBM SPSS 22 for the statistical analysis, and we obtained the descriptive statistics. We used the paired-sample T test to compare the serum creatinine and serum sodium levels at 48 hours and at discharge to the baseline levels and to compare the different variables between patients who developed AKI during the admission and those who did not develop AKI. We used multiple regression analysis to study the relationship between the different analyzed factors and persistent renal dysfunction at the time of discharge, as well as patient mortality.

Results

A total of 52 patients fulfilled the inclusion criteria. Three pa-

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tients were excluded because of incomplete data; thus, 49 patients were included in the final analysis. Eight patients had previous frequent admissions for massive ascites, 2 had frequent previous admissions for variceal bleeding, and one patient had previously undergone liver transplantation for autoimmune hepatitis..

The majority of patients (29) were female (59.2%). The mean patient age was 53 years (SD, 16.5 years), and there was no difference in age between the male and female patients (P=.5)

The majority (27, 55%) of patients had negative serology for hepatitis viruses, autoimmune profiles, (Table 1).

The most common cause of admission was ascites; spontaneous bacterial peritonitis (SBP) was suspected in 17 patients at the time of admission. SBP was confirmed by an elevated neutrophil count of more than 250 cells/cmm or a positive bacterial culture for gram-negative bacteria in the ascitic fluid; the causes for admission are listed in Table 2 (explained in the Discussion section). Four patients had advance liver disease and hepatocellular carcinoma.

RI was present in 21 (43%) patients, and AKI was diagnosed in 16 (32.75) patients at the time of admission. The mean serum creatinine level at the time of admission was 147 umol/L (SD 43.6), and there was no difference between the male and female patients (P=.97) table 3 for lab results and normal values.

The mean serum creatinine levels at 48 hours after admission and at discharge were lower than the mean level at baseline, but the difference was not significant (mean difference, 26.4) umol/L

There was no difference in the AKI rate between males and females. Similarly, there was no difference in the AKI rate in terms of the different causes for admission (7.3 and P=.1 and .8, respectively). However, the mean serum sodium level was below normal, although it showed significant improvement at 48 hours and at discharge (mean difference, 4 and 9.3, mmol/L respectively, and P<.001 for both).

Patients with impaired renal function and AKI were more likely to be older and to have significant hyponatremia, hyperkalemia, and hypoalbuminemia, as well as a high WBC count at the time of admission compared to patients with normal creatinine levels at the time of admission (Table 4).

Multiple regression analysis indicated that the only factor that significantly correlated with persistent renal failure at discharge was low serum albumin (Table 5).

At the time of discharge, the serum creatinine levels had improved, but they did not return to normal in 14 of the 21 (66.6%) patients with elevated serum creatinine and 9 (56%) AKI patients. Two (9.5%) patients continued to experience deteriorating serum creatinine levels; one patients was known to have mild baseline RI, and the other patient had severe sepsis secondary to SBP.

Ultrasound examination showed ascites of variable severity in 25 (51%) patients, and 26 (53%) patients had diuresis with furosemide or furosemide and spironolactone. Patients with massive ascites and AKI underwent therapeutic abdominal paracentesis for ascites.

The majority (37, 75.5%) of the patients received intravenous antibiotics as treatment for SBP or other infections, or as prophylactic for SBP in patients with ascites or acute variceal bleeding.

The most commonly used antibiotic was ceftriaxone (Table 4).

The mean length of stay in the hospital was 5.8 days (SD, 4.3 days) (1-22).

Six patients (2 with AKI, 2 with only RI, and 2 with normal creatinine levels) died during admission, resulting in an in-hospital mortality rate of 12.2%. Sepsis and elevated WBC counts were the main factors (according to multiple regression analysis) associated with mortality (Table 6).

Discussion

Our study found that AKI is common in admitted patients with acute complications of cirrhosis, representing one-third of all patients. This result is similar to those reported by several previous studies [5,6]. Because of its limitations in cirrhosis, serum creatinine is not an accurate marker for defining renal dysfunction in cirrhosis. [3]However, until a simple, accurate and easily available glomerular filtration rate (GFR) test is available, serum creatinine will continue to be used to assess renal injury in cirrhosis. In addition, serum creatinine is readily available and can be easily used as a marker for renal dysfunction. Nevertheless, its accuracy in patients with cirrhosis is hindered by several factors: For instance, the creatinine level is altered by reduced muscle bulk due to wasting in cirrhosis, reduced creatinine production from creatinine by the muscles, increase tubular excretion and increased distribution volume [5,7,13-15]. Together, these factors can cause inaccurate results when measuring creatinine levels, as well as incorrect underestimation of renal dysfunction. Therefore, the use of a more accurate testing method for renal function utilizing the GFR may have resulted in a higher rate of RI and AKI in our cohort.

Another important finding of our study was that more than 10% of patients had RI; however, they did not fulfill the criteria for AKI. This finding cannot be ignored because RI is associated with increased mortality in patients with cirrhosis, and it is part of the Model for End-stage Liver Disease (MELD) score for assessing cirrhotic patients [10,11]. Furthermore, patients with milder degrees of RI and with the same risk factors are expected (in the long run) to progress to more severe forms of AKI [5]. In our cohort, several factors were associated with the development of AKI, including older age and severe liver disease, as reflected by the lower albumin levels. This result can be explained by the deterioration in vascular function and impaired renal blood flow with the progression of cirrhosis [7,8,16].

Hyponatremia was another finding that was associated with AKI in our study. This result is important because several previous reports have related hyponatremia to a high mortality rate in cirrhosis [4,17]. Sepsis, as reflected by elevated WBC counts, is another predictor of AKI and mortality. Several previous reports have shown that sepsis in cirrhosis causes circulatory collapse and impairs renal blood flow, which causes AKI [4,18,19]. Moreover, previous data have demonstrated the importance of sepsis in cirrhosis as a risk factor and predictor for AKI and mortality [20-22]. The presence of underlying renal disease and chronic renal failure in cirrhosis can result in severe deterioration of renal function and the failure of renal functions to return to baseline levels, as was the case for one patient in our cohort [23]. The length of hospital stay was also longer n patients who had severe sepsis, but the majority of patients had short admissions of 3-5 days, which is acceptable for the management of acute complications of cirrhosis because the treatment of SBP and other bacterial infections requires approximately 5 days of intravenous antibiotics [24,25]. The

majority (2/3) of our patients received antibiotics as treatment or prophylaxis. Early treatment of sepsis and prophylactic antibiotics for cirrhosis patients at risk of bacterial infection are expected to reduce the rate of AKI and mortality and to shorten the hospital length of stay [24-26].

Conclusions:

Our data showed that AKI is frequently diagnosed in patients who are admitted for acute complication of cirrhosis. Moreover sepsis is an important risk factor for AKI in cirrhotic. Considerable number of patient will continue to have renal dysfunction at the time of discharge.

Competing interests

The authors declare that they have no competing interests.

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Table 1. Results of serological testing for the causes of cirrhosis

	number of patients	Percent
Negative	*25	51
HBV	7	14.3
HCV	15	30.6
ANA/ SMA	2	4.1
Total	49	100.0

***One patient had alcoholic liver disease, confirmed by history.**

HBV (Hepatitis B virus), HCV (hepatitis C virus) ANA (Antinuclear antibodies) SMA (Smooth Muscle Antibody)

Table 2. Causes of acute deterioration and hospital admission

Admission diagnosis	Number of patients	Percent
Ascites	34	69.4
OV	1	12.2
Ascites encephalopathy, SBP	4	8.2
OV encephalopathy	1	2.0
Sepsis SBP and chest infection	1	2.0
Ascites varices	3	6.1
Total	49	100.0

Table 3. Initial lab results at hospital admission

	Minimum	Maximum	Mean	Std. deviation
Mean serum sodium NA Normal 135-145 mmol/L	112.00	145.00	133.6	8.02863
Serum potassium Normal 3.5-5 mmol/L	3.20	5.80	4.1636	.63798
Serum urea Normal 2.4-6.4 mmol/L	2	57	12.75	12.767
Serum creatinine Normal 53-115 µmol/L	42	800	147.33	143.642
Albumin Normal 35-50 g/L	10	37	23.51	6.919
GGT Normal 5-85 U/L	3.00	1095.00	187.5000	219.33027
ALKP Normal 50-136 U/L	38	911	236.70	211.474
Total bilirubin Normal 0-17 µmol/L	3.00	401.00	59.5366	84.83192
AST Normal 15-37 U/L	16	793	117.88	165.852
ALT Normal 30-65U/L	8	268	62.74	49.957
Total protein Normal 64-82 g/L	38.00	91.00	68.3953	11.58024
Hg Normal 12-15 g/dL	4.2	15.6	10.1	2.3
WBC Normal 4.5-11.5K/ µL	2	28	9.1	5.5
Platelets Normal 150-450K/ µL	33	607	179.7	131

Table 4. The relationship between different lab results and the development of AKI

Factor	N	Mean	Std. deviation	P value
Serum sodium at admission	21	130.21	8.85949	.06
	28	136.00	6.06905	
Serum potassium at admission	21	4.40	.78	.023
	28	3.93	.37	
Serum urea at admission	21	19.56	14.117	.02
	28	7.45	8.646	
Serum albumin at admission	21	20.71	6.302	.008
	28	26.18	6.529	
Age	21	59.29	10.645	.022
	28	49.30	18.104	
Platelets	21	168.8	122.15	.47
	28	201.1	183	
WBC	21	11.17	6.74	.033
	28	7.7	3.81	

Table 5. Relationship between different variables and persistent renal failure at discharge

Module	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
(Constant)	.518	.637		.813	.424
Total bilirubin	-.001	.001	-.204	-1.052	.303
Albumin	-.028	.014	-.407	-2.072	.049
Diagnosis at admission	-.026	.037	-.134	-.687	.499
Diuretics	-.055	.187	-.052	-.296	.770
Age	.014	.007	.345	1.942	.064
Sex	.024	.182	.024	.134	.894

Dependent factor, renal failure at discharge.

Table 6. Association between different factors and mortality during admission

model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
	(Constant)	-.769	1.238		-.621	.539
	Hg	.049	.030	.300	1.631	.113
	WBC	.030	.011	.475	2.784	.009
	Creat1	.000	.000	-.183	-.901	.374
	NA1	.004	.009	.076	.414	.682
	Diagnosis	-.015	.024	-.106	-.634	.531
	Age	.003	.004	.126	.762	.452
	Albumin	-.015	.010	-.289	-1.496	.145
	Sex	-.016	.124	-.021	-.125	.901
	AKI	-.048	.156	-.066	-.308	.760

a. Dependent variable: mortalit y

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