Acute kidney injury network criteria as a prognostic factor in cirrhotic patients with spontaneous bacterial peritonitis

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Background and Aim
One of the most common complications of spontaneous bacterial peritonitis (SBP) is renal injury. The aim of the study was to detect the frequency of AKI as a problem in end stage liver disease patients with SBP, evaluate the role of acute kidney injury network criteria (AKIN) as a prognostic factor for kidney insult in cirrhotic patients complicated by SBP and lastly.
Settings and Design
A single center, observational, prospective study.
Patients and methods
The study was conducted on 150 cirrhotic patients complicated by SBP who were admitted in hepatology unit, Mansoura Specialized Medical Hospital, Mansoura University. After that, all patients were followed up for three months duration.
Statistical analysis used
Data analysis was performed using SPSS version 16.0 (SPSS, Inc, USA). Chi-square test (crosstabs) was used to compare the distribution of different clinical finding according to AKI stage.
Results
The obtained results were showed a significant change in the number of patients among the three groups at the end of the study versus at admission indicating progressive deterioration of kidney functions. Moreover, the mortality was high (70.42%), most of them were AKIN stage 2 and 3. There was a significant increase of hospital acquired complication especially (hepatic encephalopathy, ICU admission) more commonly in advanced AKIN stages (stage 3).
Conclusion
AKI, as defined by AKIN diagnostic criteria, is associated with a high mortality rate in cirrhotic patients presented with SBP, especially patients with advanced liver disease (Child B and C, high MELD score) in a stage-dependent pattern.

Keywords:
acute kidney injury network, liver cirrhosis, spontaneous bacterial peritonitis

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Introduction

Spontaneous bacterial peritonitis (SBP) is a common and serious complication of decompensated cirrhosis with a prevalence of 10–30% in hospitalized patients [1]. Its association with high rates of complications and mortality is precipitated by circulatory derangement causing liver failure and renal injury [2].

Renal failure is the major predictor of mortality in SBP. Acute kidney injury (AKI) is common in patients with cirrhosis and ascites [3].

The acute kidney injury network (AKIN) classified AKI in cirrhosis into three stages: 1, 2, and 3 [4,5]. This score can predict clinical outcomes such as mortality in patients with cirrhosis with ascites [6].

Patients and methods

This prospective cohort study recruited 150 decompensated patients with cirrhosis complicated by SBP (105 male and 45 female), with mean age of 57.08±8.69 years. All patients were selected from the Hepatology Unit, Mansoura Specialized Medical Hospital, Mansoura University, during the period from November 2014 to December 2015. The study was approved by the Research Ethics Board of Mansoura University. Informed consent was obtained from all patients in the study.

Table 1 Acute kidney injury criteria for staging acute kidney injury [7,9]

AKI stage	Serum creatinine criteria	Urinary output criteria
Stage 1	Increase in serum creatinine ≥0.3 mg/dl within 48 h or an increase of ≥150–200% (1.5–2 folds) from baseline	<0.5 ml/kg/h (>6 h)
Stage 2	Increase in serum creatinine to 200–299% (2–3 folds) from baseline	<0.5 ml/kg/h (>12 h)
Stage 3	Increase in serum creatinine >300% (>3 folds) from baseline or if baseline serum creatinine ≥4 mg/dl, with an acute increase of ≥0.5 mg/dl or initiation of renal replacement therapy	<0.3 ml/kg/h (24 h) or anuria (12 h)

AKI, acute kidney injury.

Only 142 patients with cirrhosis with kidney injury who were diagnosed based on the clinical, laboratory, and radiological findings complete the study, whereas the other eight patients were considered as dropouts owing to missing data. All patients were grouped according their kidney insult on the basis of serum creatinine level at the time of admission using the AKIN criteria [7]. Only change in serum creatinine level was considered because the urinary output usually was inconsistent. In addition, baseline creatinine was selected from the latest stable outpatient measurements recorded within the last 3 months before admission. All patients were subclassified accordingly to the peak AKIN stage during hospitalization, and severity of liver disease was assessed by Child–Turcotte–Pugh (CTP) and Model for End-stage Liver Disease (MELD score) at baseline and at the time of admission.

Fate of acute kidney injury was subclassified into the following:

(1) Stable course: if there was no change in AKIN stage.
(2) Progressive course: if there was increased in at least one AKIN stage.
(3) Regressive course: if there was decreased in at least one AKIN stage.

Inclusion criteria

The inclusion criteria were as follows:

(1) Polymorphonuclear neutrophil leukocyte/μl more than or equal to 250 in ascetic fluid with absence of any features suggestive of secondary bacterial peritonitis (protein >1 g/dl, glucose <50 mg/dl, and increase lactate dehydrogenase).
(2) Absence of other systemic infections and gastrointestinal bleeding.

Table 2 Child–Turcotte–Pugh score

Measures	1 point	2 points	3 points
Total bilirubin (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) OR	<4.0	4.0–6.0	> 6.0
INR	<1.7	1.7–2.3	>2.3
Ascites	None	Mild (or suppressed with medication)	Moderate to severe (or refractory)
Hepatic encephalopathy	None	Grades I–II	Grades III–IV

INR, international normalized ratio.

(3) Presence of AKI (defined as a serum creatinine >1.5 mg/dl) in patients with cirrhosis.

Exclusion criteria

The exclusion criteria were as follows:

(1) Prior liver or renal transplant.
(2) Chronic kidney disease.
(3) Other known causes of renal insufficiency such as glomerulonephritis or hydronephrosis.

Laboratory investigations

The laboratory investigation included the following:

(1) Liver function tests, such as serum albumin, serum bilirubin, aspartate aminotransferase, alanine aminotransferase, and international normalized ratio.
(2) Renal function tests, such as serum creatinine, which was measured on admission, daily, and followed up monthly for 3 months after discharge from the hospital.
(3) Complete blood count.
(4) Serum electrolytes (sodium and potassium).
(5) Random blood glucose.
(6) Urine analysis by urine analysis reagent test strips.

Scores calculation

Score calculation was done using the following:

(1) AKIN criteria (Table 1).
(2) CTP score [8] (Table 2).
Class A (5–6), Class B (7–9), and Class C (10–15).
(3) MELD score: MELD=3.8 [log serum bilirubin (mg/dl)]+11.2 [log international normalized ratio] +9.6 [log serum creatinine (mg/dl)]+6.4.

AdvancedMELD score inpatients with liver cirrhosis is associated with higher risk of mortality in comparison with patients with lower MELD score [10,11].

Table 3 Clinical and demographic baseline characteristics of all patients with cirrhosis based on different acute kidney injury network stages

Groups	AKIN				*P* value
	Whole group	Stage 1	Stage 2	Stage 3	
Number of patients	150	96	26	28	
Parameters					
Age (years)	57.08±8.69	57.95±8.67	57.04±7.38	54.14±9.49	0.125
Sex (males %)	105 (70)	69 (71.9)	18 (69.2)	18 (64.3)	0.74
Diabetes	37 (24.7)	23 (23.9)	7 (26.9)	7 (25)	0.962
Hypertension	6 (4)	5 (5.2)	1 (3.8)	0 (0)	0.522
Hepatocellular carcinoma	40 (26.7)	23 (23.9)	6 (23.1)	11 (39.3)	0.272
MELD	25.03±6.87	22.90±6.39	27.31±5.71	30.21±5.58	**<0.0005**
CTP score					
A	1 (0.7)	1 (1.1)	0 (0)	0 (0)	0.318
B	39 (26)	30 (31.2)	5 (19.2)	4 (14.2)	
C	110 (73.3)	65 (67.7)	21 (80.8)	24 (85.7)	

Data are presented as mean±SD and *n* (%). AKIN, acute kidney injury network; CTP, Child–Turcotte–Pugh; MELD, Model for End-stage Liver Disease. There was a significant increase in MELD score with advancement of AKIN stages ($P<0.0005$).

Table 4 The biochemical characteristics of hepatic patients compared according to stages of acute kidney injury network criteria

Variables	AKIN			*P* value
	Stage 1 (*N*=96)	Stage 2 (*N*=26)	Stage 3 (*N*=28)	
Serum bilirubin (mg/dl)	3.6 (1.8–6.7)	3.6 (1.7–7.3)	4.05 (1.95–11.3)	0.044
Serum albumin (g/dl)	2.23±0.47	2.24±0.38	2.28±0.45	0.86
INR	1.72±0.65	1.81±0.57	1.71±0.45	0.77
ALT (U/l)	36 (22.5–51.5)	23.5 (19–35)	34 (22–55)	0.22
Hb (g/dl)	10.55±1.67	10.10±1.54	10.60±1.29	0.41
Platelets (/cmm^3)	121 (74.5–150)	120 (70–156)	97 (63–184)	0.81
WBCs (/cmm^3)	9.85±5.22	8.53±3.53	10.43±4.001	0.317
Serum K^+ (mEq/dl)	4.36±0.74	4.49±0.87	4.45±0.77	0.713
Serum Na^+ (mEq/dl)	128.96±6.31	126.85±8.20	129.42±6.62	0.299
Serum cholesterol	108.82±36.8	101.15±22.70	110.29±42.15	0.577
Serum triglycerides	86.12±20.57	90.77±58.98	94.82±43.62	0.480

Data are presented as mean±SD or median (IQR). AKIN, acute kidney injury network; ALT, alanine aminotransferase; Hb, hemoglobin; INR, international normalized ratio; WBC, white blood cell.

Table 5 Biochemical characteristics of ascetic fluid in different stages of acute kidney injury

Variables in ascetic fluid	AKIN stages				P value
	Whole group (*N*=150)	Stage 1 (*N*=96)	Stage 2 (*N*=26)	Stage 3 (*N*=28)	
WBCs (10^3/ml)	2922.20±4622.02	3092.71±5106.62	2748.08±4777.25	2499.29±2165.29	0.820
Protein	442.85±245.35	450.05±257.15	448.00±221.73	413.39±229.95	0.782
Glucose	192.91±106.33	199.34±113.17	169.85±89.09	192.29±96.51	0.458
LDH	275.1±526.2	232.8±302.7	413.9±1070.7	287.1±303.2	0.300

Data are presented as mean±SD. AKIN, acute kidney injury network; LDH, lactate dehydrogenase; WBC, white blood cell.

Table 6 Outcome of hepatic patients who classified according to stages of acute kidney injury

AKIN stages	Number of patients/total (%)	%	Outcome [*n* (%)]			*P* value
			Morbidity	Mortality	Healthy	
Stage 1	91/142 (64.08)	64.1	4 (4.39)	56 (61.53)	31 (34.06)	0.021
Stage 2	26/142 (18.30)	18.3	0 (0)	21 (80.76)	5 (19.23)	0.021
Stage 3	25/142 (17.60)	17.6	1 (4)	23 (92)	1 (4)	0.021

AKIN, acute kidney injury network.

The estimated 3-month mortality, which is dependent upon the MELD score, is represented as follows [12]:

MELD score	Estimated 3-month mortality (%)
40 or more	71.3
30–39	52.6
20–29	19.6
10–19	6
<9	1.9

Results

Table 3 showed there was only a significant increase in MELD score with advancement of AKIN stages ($P<0.0005$).

P value less than or equal to 0.05 was considered significant.

Table 4showed that there was a statistically significant increase in serum bilirubin in advanced AKIN stages.

Table 7 Effect of sex and associated comorbidities on outcome

Variables	Number of patients/ total (%)	Morbidity [*n* (%)]	Mortality [*n* (%)]	Healthy [*n* (%)]	*P* value
Male sex	98/142 (69.01)	4 (4.08)	70 (71.42)	24 (24.48)	0.73
DM	35/142 (24.64)	2 (5.71)	26 (74.28)	7 (20)	0.57
Hypertension	6/142 (4.22)	0 (0)	5 (83.33)	1 (16.66)	0.75
HCC	36/142 (25.35)	0 (0)	31 (86.11)	5 (13.88)	**0.043**

DM, diabetes mellitus; HCC, hepatocellular carcinoma. There was a significant increase in mortality in HCC patients.

Tables 5–8 show the changes in the number of hepatic patients among the three stages of AKIN at the end of the study versus at admission. There was a significant change in the number of patients among the three groups at the end of the study versus at admission, indicating progressive deterioration of kidney function.

Table 9 shows the morbidities associated with AKI and their prevalence in different AKIN stages. There was a significant increase of hospital-acquired complication (hepatic encephalopathy, ICU admission) after development AKI in patient with SBP.

Table 10 shows a statistically significant increase in frequency of morbidities such as hepatic encephalopathy and ICU admission because of septicemia ($P<0.0005$ for both) in nonsurvivors more than survivors.

Table 11 shows the rate of mortality in relation to time of follow-up. There was a significant increase of percent of death with advanced AKIN stages, and during period of hospitalization.

Discussion

SBP is a common and serious complication of cirrhosis-associated ascites, with a prevalence of 10–30% in hospitalized patients [1,13]. It is association with high rates of complications and mortality. It is precipitated by circulatory derangement causing liver failure and renal injury, which promote in-hospital mortality up to 30% despite resolution of the infection [2].

Table 8 Changes in acute kidney injury network stages at the end of the study or occurrence of death

AKIN stage	Number of patients/total (%)	AKIN stage at the end of study/death [*n* (%)]				*P* value
		Stage 1	Stage 2	Stage 3	Creatinine return to normal value	
Stage 1	91/142 (64.08)	53 (58.24)	7 (7.69)	7 (7.69)	24 (26.37)	<0.0005
Stage 2	26/142 (18.30)	4 (15.38)	20 (76.92)	0 (0)	2 (7.69)	<0.0005
Stage 3	25/142 (17.60)	0 (0)	1 (4)	22 (88)	2 (8)	<0.0005

AKIN, acute kidney injury network.

Table 9 Prevalence of morbidities associated with acute kidney injury in different acute kidney injury network stages

Morbidity	AKIN stage [*n* (%)]				*P* value
	Number of patients/total (%)	Stage 1	Stage 2	Stage 3	
Hepatic encephalopathy	80/142 (56.33)	41 (51.25)	18 (22.5)	21 (26.25)	**0.001**
Hematemesis	12/142 (8.45)	5 (41.66)	2 (16.66)	5 (41.66)	0.069
ICU admission (septicemia)	72/142 (50.70)	36 (50)	17 (23.61)	19 (26.38)	**0.001**
Dialysis	3/142 (2.11)	1 (33.33)	0 (0)	2 (66.66)	0.093

AKIN, acute kidney injury network. There was a significant increase of hospital-acquired complication (hepatic encephalopathy, ICU admission) after development AKI in-patient with SBP.

The development of AKI in the setting of cirrhosis denotes a bad prognosis and is known to be independently predictive of death in patients with SBP and variceal hemorrhage [14]. The diagnosis of AKI in cirrhosis has been discussed by AKIN, which categorizes kidney dysfunction into stages of increasing severity based on changes in serum creatinine and/or urinary output [6]. This score has been shown to predict clinical outcomes such as mortality in patients with cirrhosis presented by SBP [7].

Our study was conducted to assess the magnitude of AKI as a common problem in end stage liver disease (ESLD) and its effect on the outcome of these patients regarding morbidity and mortality.

The frequencies of stages 1, 2, and 3 AKI were 64, 17.33, and 18.66%, respectively, in our study. Other published series such as Belcher *et al.* [6] found percentages of 48% for stage 1, 29% for stage 2, and 23% for stage 3. Moreover, Scott [19] reported 40% for stage 1, 29.1% for stage 2, and 30.9% for stage 3.

In accordance with Fang and colleagues and Belcher and colleagues, serum bilirubin was found to be significantly higher in AKIN stage 3 than other two stages and in nonsurvivors compared with survivor group. This is in agreement with Salgado *et al.* [7] and Fang *et al.* [15]. This could be explained by that cholestasis is a common complication of bacterial infections and sepsis. This is documented by elevated leukocyte count, which was significantly higher in nonsurvivors than survivor group and associated with more deterioration of liver function [16].

In addition, in agreement with Fang *et al.* [15], there was no significant difference in serum albumin in nonsurvivors versus survivors group.

Regarding the hemoglobin level and platelets count, there was no significant difference in survivors versus nonsurvivors. This goes hand in hand with Fang *et al.* [15] and could be attributed to low incidence of bleeding in those patients.

Serum sodium level was found to be insignificantly different between both survivors and nonsurvivors group. Fang *et al.* [15] and Belcher *et al.* [6] found similar results. This might be related to the severity of the liver disease, as most of our patients were CTP classes B and C.

Concerning the effect of hepatocellular carcinoma (HCC) on the outcome of AKI in our patients, there was a significant increase in the rate of death in those patients (86.11% of all patient with HCC). This result was also supported by de Carvalho and colleagues. On the contrary, the presence of diabetes mellitus and hypertension as comorbidities had no significant difference, and this was similarly found by other studies [7,15,16].

MELD is a reliable measure of mortality risk in patients with ESLD. It is used as a disease severity index to help prioritize allocation of organs for transplant. Moreover, it is considered a good predictor of 3-month mortality in patients with cirrhosis [16]. MELD score was found to be significantly higher in stage 3 compared with stage 2 and stage 1. This is concomitant with other published data [7,15,17,18]. Moreover, it was found that MELD score was significantly higher in nonsurvivors group than survivors group. This result is in agreement with Belcher *et al.* [6], and Piano *et al.* [18].

Table 10 Prevalence of morbidities associated with acute kidney injury in survivors and nonsurvivors

Morbidities	Survivors [*n* (%)]	Nonsurvivors [*n* (%)]	*P* value
Hepatic encephalopathy	5 (3.52)	75 (52.81)	<**0.0005**
Hematemesis	0 (0)	12 (8.45)	0.064
ICU admission (septicemia)	1 (0.7)	71 (50)	<**0.0005**
Dialysis	0 (0)	3 (2.11)	0.525

There was a statistically significant increase in frequency of morbidities as hepatic encephalopathy and ICU admission because of septicemia ($P<0.0005$ for both) in non-survivors more than survivors.

Table 11 Mortality of spontaneous bacterial peritonitis patients associated with acute kidney injury in relation to time of follow-up

AKIN stage	Time of death [*n* (%)]				*P* value
	During hospitalization	1st month	2nd month	3rd month	
Stage 1 (*N*=91) (64.08%)	35 (38.46)	14 (15.38)	6 (6.59)	1 (1.09)	0.001
Stage 2 (*N*=26) (18.30%)	20 (76.92)	1 (3.84)	0 (0)	0 (0)	0.001
Stage 3 (*N*=25) (17.60%)	22 (88)	1 (4)	0 (0)	0 (0)	0.001

AKIN, acute kidney injury network.

CTP score is commonly used as a simple descriptive or predictive indicator in patients with cirrhosis. Unlike the MELD score, it does not comprise a marker of renal dysfunction, though it could be supposed that ascites, bilirubin, and encephalopathy are probable markers of kidney injury. It is not unexpected that a higher mortality rate was associated with increasing of liver disease severity in a stage-dependent way as measured by the CTP score. This was observed in our study as most of our patients were CTP class C (80/100). Similar results were found by de Carvalho and colleagues, who found that most nonsurvivors were Child C (52/63). Scott and colleagues, and Piano and colleagues also supported these results [17–19].

Our study revealed that there was a significant increase of hospital-acquired complications such as hepatic encephalopathy and ICU admission in advanced AKIN stage 3 (21/25 and 19/25, respectively). This result is in accordance with Belcher and colleagues who found that 65 patients developed encephalopathy and 62 patients need ICU admission from a total of 95 patients with advanced AKIN stage 3. In addition, they stated that there was no significance regarding other complications such as upper GI bleeding (12/142) [6].

Concerning the relation between hospital-acquired complication and mortality rate, there was a highly significant increase in occurrence of complications (hepatic encephalopathy and ICU admission), especially among nonsurvivors more than survivors (75/80 for hepatic encephalopathy and 71/72 for ICU admission). This is concomitant with other published data who found that the incidence of hepatic encephalopathy and ICU admission was higher in nonsurvivors than survivors group (75/135 for encephalopathy and 51/55 for ICU admission), and this is also supported by Belcher and colleagues, and Fang and colleagues [6,15,20].

In this study, the overall mortality was high (70.42%), and the vast majority of mortality was found to occur during hospitalization (77% of total mortality), which was similar to the result confirmed by de Carvalho and colleagues who found that patients with AKI had a hospital mortality rate of 52.7%. High mortality rate has been attributed to some other factors. First, most of the cases selected in our study presented with decompensated cirrhosis and consequently a more advanced stage of the disease. Second, patients were either CTP class B or C and had relatively high MELD scores, which represent more severe liver dysfunction and therefore higher mortality [17].

Patients with more severe stages of AKIN (2 and 3) appear to have a higher risk of mortality (92% for stage 3, and 80.8% for stage 2) when compared with AKIN 1 (61.5%). The results of Jenq *et al.* [21], de Carvalho *et al.* [17], Belcher *et al.* [6], and Scott and colleagues, go hand in hand with our results [17,21].

It is notable that the hazard ratio of death has increased in hepatic patients with kidney injury from AKIN stage 1 to stage 3. This is concomitant with the results published by Melcarne and colleagues; Wong and colleagues; Huelin and colleagues; and de Araujo and Alvares-da-Silva. In contrast to this, there was a significant decrease in the cumulative survival from AKIN stage 1 to stage 3 [22–25].

Conclusion

AKI, as defined by the AKIN diagnostic criteria, is associated with a high mortality rate in patients with cirrhosis presented with SBP, especially patients with advanced liver disease (Child B and C and high MELD score) in a stage-dependent pattern. Our study has some limitations, such as, it is a single-center study and the outcome was targeted to short term, for only 3 months.

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Conflicts of interest

There are no conflicts of interest.

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