Acute Kidney Injury Network Criteria as a Predictor of Hospital Mortality in Cirrhotic Patients With Ascites

Juliana Ribeiro de Carvalho, MD, Cristiane Alves Villela-Nogueira, MD, PhD,* Ronir Raggio Luiz, PhD,† Paula Lustosa Guzzo, MD,* Juliana Maria da Silva Rosa, MD,* Eduardo Rocha, MD, PhD,‡ Henrique Sérgio Moraes Coelho, MD, PhD,* and Renata de Mello Perez, MD, PhD**

Background: Acute kidney injury (AKI) is frequent in cirrhotic patients but its best definition is unclear. Recently, the Acute Kidney Injury Network (AKIN) proposed criteria to define AKI. The aims of this study were to apply AKIN criteria to cirrhotic patients with ascites and to evaluate its association to hospital mortality.

Study: In this retrospective study, cirrhotic patients with ascites admitted to a university hospital in Brazil between November 2003 and December 2007 were included. AKIN criteria were applied in the first 48 hours of hospitalization, considering 2 values of creatinine in this period. Association of AKI at admission and hospital mortality was analyzed.

Results: Of the 198 patients in the study, 91 (46%) presented AKI at hospital admission. Overall hospital mortality was 40.4%. Patients without AKI had a hospital mortality rate of 29.9%, whereas the same rate for patients with this complication was 52.7% (odds ratio = 2.6; 95% confidence interval, 1.5-4.7; $P = 0.001$). In a logistic regression analysis, 4 variables were independently associated to hospital mortality: infection, hepatic encephalopathy, Child score, and AKI. A receiver operating characteristic curve analysis revealed that the variation in creatinine proposed by AKIN had the best combination of sensitivity and specificity in relation to hospital mortality.

Conclusions: In cirrhotic patients with ascites, prevalence of AKI at hospital admission is high. Patients with renal dysfunction defined by AKIN have significant higher hospital mortality. AKIN criteria are useful in cirrhotic patients with ascites, as it identifies earlier patients with worse prognosis.

Key Words: acute kidney injury, ascites, hospital mortality, liver cirrhosis, renal failure.

(*J Clin Gastroenterol* 2012;46:e21–e26)

Acute kidney injury (AKI) is a common complication in patients with cirrhosis and has a negative impact on survival.[1–3] Cirrhotic patients might suffer renal injury related to prerenal, intrinsic, or postrenal causes, and a specific type of AKI called hepatorenal syndrome.[4,5]

The susceptibility of kidney function to any type of injury in these patients is related to the hemodynamic consequences of cirrhosis, such as increased intrahepatic vascular resistance, splanchnic vasodilation, and activation of vasoconstrictive and antinatriuretic systems that ultimately lead to renal vasoconstriction.[2] Thus, patients with more advanced liver disease, such as those with ascites, are especially prone to renal impairment.[6]

Despite its importance in the course of cirrhosis, AKI is difficult to define in this group of patients.[2] Decreased production of creatinine by the liver, increased tubular secretion of creatinine, reduced muscular mass, and malnutrition are all factors that contribute to inadequate estimates of glomerular filtration rate.[7]

Recently, members of important societies in critical care and nephrology established the Acute Kidney Injury Network (AKIN), a collaborative network to facilitate research and progress in the field of acute renal failure.[8] They proposed the term "acute kidney injury" and a set of consensus criteria to define acute renal failure, taking into account recent evidence that smaller increments in serum creatinine have impact on prognosis.[9–12] Recent reviews of renal failure in cirrhosis have considered that these new criteria could be useful in this group of patients.[3,13] Furthermore, a working group consisted of members of the Acute Dialysis Quality Initiative and the International Ascites Club has now adopted AKIN criteria to define AKI in cirrhosis to establish uniform standards for the diagnosis of renal dysfunction in these patients.[14] However, there are no data evaluating the association between AKI defined by AKIN and mortality in cirrhotic patients.

The aims of this study were to apply AKIN criteria to cirrhotic patients with ascites at hospital admission and to evaluate its association to hospital mortality.

MATERIALS AND METHODS

Study Design

The study was held at the University Hospital of the Federal University of Rio de Janeiro, Brazil. It is a tertiary hospital and a reference for treatment of liver diseases. The medical records of all cirrhotic patients with ascites aged at least 18 years old and admitted between November 2003 and December 2007 were retrospectively reviewed. These records were identified by the registries of ascitic fluid analysis in the hospital laboratory during this period, as it is a routine to perform a diagnostic paracentesis in every cirrhotic patient admitted with ascites. Exclusion criteria

Received for publication April 14, 2011; accepted July 19, 2011.
From the *Hepatology Service, Internal Medicine Department; †Institute of Public Health Studies (IESC); and ‡Nephrology Service, Internal Medicine Department, Federal University of Rio de Janeiro, Brazil.
Funding Sources: There was no funding for this study.
Conflict of interest disclosure: Henrique Sérgio Moraes Coelho is a member of the scientific board of Merck-Sharp & Dohme (no relation to this article). The other authors declare that they have nothing to disclose.
Reprints: Juliana Ribeiro de Carvalho, MD, Avenida Alexandre Ferreira, 86/402-Lagoa, Rio de Janeiro, RJ CEP: 22470-220, Brazil (e-mail: jucarvalho@openlink.com.br).

were: dialysis in the previous 6 months, previous transplantation (of any tissue or organ, including liver transplantation), positive human immunodeficiency virus serology, malignancy (except hepatocellular carcinoma), hospital stay for < 24 hours, and insufficient data for analysis. If a patient had more than 1 admission during the study period, only data concerning the first admission was considered for analysis.

The study was approved by the local Ethics Committee and conformed to the ethical guidelines of the 1975 Helsinki Declaration. Data were held only by researchers involved in the study and privacy and anonymity of patients were guaranteed.

Definitions

Cirrhosis

The diagnosis of cirrhosis was based on a combination of physical signs and biochemical, endoscopic, or imaging findings compatible with the disease. The presence of ascites was confirmed by a diagnostic paracentesis after being suspected either by physical examination or by ultrasonography.

AKI

The criteria proposed by AKIN[8] were applied to define AKI in the first 48 hours of hospitalization. AKIN criteria are shown on Table 1. In this study, only serum creatinine was considered for these criteria, as data on urine output were not available. Two serum creatinine values measured in the first 48 hours of hospitalization (labeled creatinine 1 and creatinine 2) were used to define the presence of AKI, considering a difference of at least 0.3 mg/dL between the 2 values. These data were also used to classify patients according to different stages shown on Table 1.

Statistical Analysis

Statistical analysis was performed using SPSS version 11.0 (SPSS Inc, Chicago, IL). Normally or near-normally distributed variables were reported as means with SD and compared by Student t test. Non-normally distributed continuous data were reported as medians and range and compared by Wilcoxon signed rank test. Categorical variables were expressed as proportions and compared using χ^2 test. Variables that could be related to mortality were assessed by univariate analysis. Those that were related to cirrhosis and presented a P value < 0.20 were included in a multiple logistic regression model. An analysis of the area under a receiver operating characteristic curve (AUROC) was performed to calculate sensitivity and specificity of different variations in creatinine values in relation to mortality. Data are presented as odds ratio and 95% confidence interval. Statistical significance was assumed at $P < 0.05$.

RESULTS

There were 729 admissions of cirrhotic patients with ascites during the period of study. Of these admissions, 295 were excluded for the following reasons: dialysis in the previous 6 months (25 cases), previous transplantation (27 cases), positive human immunodeficiency virus serology (11 patients), malignancy apart from hepatocellular carcinoma (14 cases), hospital stay for < 24 hours (33), and insufficient data (185 cases).

TABLE 1. Classification/Staging System for Acute Kidney Injury According to AKIN

AKI Stage	Serum Creatinine Criteria	Urine Output Criteria
AKI stage 1	Increase in serum creatinine ≥ 0.3 mg/dL or increase to ≥ 150-200% from baseline	Urine output < 0.5 ml/kg/h for > 6 h
AKI stage 2	Increase of serum creatinine to > 200-300% from baseline	Urine output < 0.5 ml/kg/h for > 12 h
AKI stage 3	Increase of serum creatinine to > 300% from baseline or serum creatinine ≥ 4.0 mg/dl after a rise of at least 0.5 mg/dL or treatment with renal replacement therapy	Urine output < 0.3 mL/kg/hour for 24 h or anuria for 12 h

AKI indicates acute kidney injury; AKIN, Acute Kidney Injury Network.[8]

Of the 434 admissions left, only the first admission of each patient was selected. This way, there were 198 admissions eligible for the study.

Baseline demographic, clinical, and laboratorial characteristics of patients included in the study are shown on Table 2. This table also includes Child-Pugh score, Model for End-Stage Liver Disease (MELD) score, previous complications of cirrhosis, and the complications developed during hospitalization. The most frequent source of infection not related to spontaneous bacterial peritonitis observed was urinary (25%), followed by pulmonary (23.7%) and cutaneous infection (23.7%).

When applying AKIN criteria in the first 48 hours of hospitalization, AKI was observed in 91 patients (46%). Of these, 83 patients (41.9%) were classified as AKIN stage 1, 5 (2.5%) as AKIN stage 2, and 3 (1.5%) as AKIN stage 3. Mean creatinine values in patients with AKI were 1.9 ± 1.2 mg/dL for creatinine 1 and 2.0 ± 1.4 mg/dL for creatinine 2, whereas the mean values in patients without AKI were 1.3 ± 0.7 mg/dL and 1.3 ± 0.6, respectively ($P < 0.001$ for comparison of both creatinine values between the groups). Overall hospital mortality was 40.4%, occurring in 80 patients of the sample. Table 2 includes an analysis comparing patients with and without AKI in respect to the characteristics exposed on this table and also a comparison between survivors and nonsurvivors. Table 3 compares mortality in patients with and without AKI.

Variables included in the multivariate analysis were: spontaneous bacterial peritonitis, infection, hepatic encephalopathy, hepatocellular carcinoma, AKI defined by AKIN, and Child-Pugh score, all of which represent complications of cirrhosis or are related to hepatic failure. Table 4 shows the final results of the multivariate analysis. The probabilities of death according to the presence of the independent variables obtained in the logistic regression are shown on Table 5.

An ROC curve analysis was performed using the difference between creatinine 1 and creatinine 2 and hospital mortality. The difference in creatinine values with the best sensitivity and specificity was 0.3 mg/dL (sensitivity = 60%;

TABLE 2. Demographic, Clinical, and Laboratorial Characteristics of Patients and Their Association to Acute Kidney Injury and Mortality

	Total	AKI	No AKI	*P*	Nonsurvivors	Survivors	*P*
N	198	91	107	—	80	118	—
Age in years, mean ± SD	59.1 ± 12.5	59.2 ± 11.9	59.2 ± 13.1	0.986	59.4 ± 12.2	59.1 ± 12.8	0.857
Male sex, n (%)	120 (60.6%)	59 (64.8%)	61 (57%)	0.261	48 (60%)	72 (61%)	0.886
Etiology of cirrhosis, n (%)							
Hepatitis C	95 (48%)	44 (48.4%)	51 (47.7%)	0.740	35 (43.8%)	60 (50.8%)	0.762
Alcohol	44 (22.2%)	19 (20.9%)	25 (23.4%)		16 (20%)	28 (23.7%)	
Hepatitis B	13 (6.6%)	5 (5.5%)	8 (7.5%)		6 (7.5%)	7 (5.9%)	
Cryptogenic	14 (7%)	7 (7.7%)	7 (6.5%)		6 (7.5%)	8 (6.9%)	
Other*	16 (8.1%)	7 (7.6%)	9 (8.4%)		6 (7.5%)	10 (8.5%)	
Unknown	16 (8.1%)	9 (9.9%)	7 (6.5%)		11 (13.7%)	5 (4.2%)	
Child-Pugh at admission							
A/B/C (n)	0/50/91†	0/21/42	0/29/49	0.635	0/11/52	0/39/39	**< 0.001**
Score (mean ± SD)	10.3 ± 1.8	10.5 ± 1.8	10.2 ± 1.8	0.308	11.2 ± 1.6	9.5 ± 1.5	**< 0.001**
MELD score at admission (mean ± SD)	19.8 ± 7.4	22.2 ± 7.8	17.9 ± 6.5	**< 0.001**	24.2 ± 7.3	16.5 ± 5.4	**< 0.001**
Diabetes, n (%)	48 (24.2%)	21 (23.3%)	27 (25.2%)	0.757	18 (22.5%)	30 (25.6%)	0.614
Hypertension, n (%)	51 (25.8%)	22 (24.4%)	29 (27.1%)	0.671	21 (26.3%)	30 (25.6%)	0.924
Drugs at admission, n (%)							
Diuretics	157 (79.3%)	73 (81.1%)	84 (78.5%)	0.651	65 (81.3%)	92 (78.6%)	0.654
Beta-blockers	111 (56.1%)	53 (58.9%)	58 (54.7%)	0.557	43 (53.8%)	68 (58.6%)	0.499
Previous complications of cirrhosis, n (%)							
Gastrointestinal bleeding	65 (32.8%)	30 (34.1%)	35 (34%)	0.987	21 (28.4%)	44 (37.6%)	0.190
SBP	29 (14.6%)	13 (14.8%)	16 (15.4%)	0.906	10 (13.3%)	19 (16.2%)	0.583
Hepatic encephalopathy	93 (47%)	39 (45.9%)	54 (52.4%)	0.372	32 (45.1%)	61 (52.1%)	0.347
Hepatocellular carcinoma	34 (17.2%)	18 (20%)	16 (15%)	0.350	20 (25.3%)	14 (11.9%)	**0.014**
Ascites	183 (92.4%)	85 (95.5%)	98 (91.6%)	0.273	71 (91%)	112 (94.9%)	0.284
Serum sodium at admission, mean ± SD	133.4 ± 6.8	132.7 ± 6.0	133.9 (7.4)	0.212	130.5 ± 6.8	135.2 ± 6.2	**< 0.001**
Complications during hospitalization, n (%)							
Gastrointestinal bleeding	65 (32.8%)	31 (34.1%)	34 (31.8%)	0.732	30 (37.5%)	35 (29.7%)	0.249
SBP	60 (30.3%)	27 (30%)	33 (31.1%)	0.864	31 (39.2%)	29 (24.8%)	**0.031**
Hepatic encephalopathy	135 (68.2%)	64 (71.1%)	71 (66.4%)	0.474	75 (94.9%)	60 (50.8%)	**< 0.001**
Hepatocellular carcinoma	46 (23.2%)	23 (25.8%)	23 (21.5%)	0.475	25 (32.1%)	21 (17.8%)	**0.021**
Infection (not related to SBP)	76 (38.4%)	39 (42.9%)	37 (34.6%)	0.233	45 (56.3%)	31 (26.3%)	**< 0.001**
Sepsis	49 (24.7%)	30 (33.3%)	19 (17.8%)	**0.013**	48 (60%)	1 (0.8%)	**< 0.001**
Vasopressor amines	55 (27.8%)	30 (33.3%)	25 (23.4%)	0.120	51 (64.6%)	4 (3.4%)	**< 0.001**
Mechanical ventilation	52 (26.3%)	30 (33%)	22 (20.6%)	**0.048**	49 (61.3%)	3 (2.5%)	**< 0.001**
Hemodialysis	14 (7.1%)	9 (9.9%)	5 (4.7%)	0.153	13 (16.3%)	1 (0.8%)	**< 0.001**
Lenght of hospitalization (d)	15.9 ± 14.8	13.3 ± 12.5	18.1 ± 16.3	**0.019**	15.1 ± 11.4	16.4 ± 16.8	0.548

*Autoimmune hepatitis, nonalcoholic steatohepatitis, primary biliary cirrhosis, secondary biliary cirrhosis, hemochromatosis, Wilson disease, congestive hepatopathy.

†Data available in 141 patients.

AKI indicates acute kidney injury; AKIN, Acute Kidney Injury Network; MELD, Model for End-Stage Liver Disease; SBP, spontaneous bacterial peritonitis.

The numbers in bold indicates variables which achieved statistical significance in the analysis.

specificity = 63.6%; AUROC = 0.652). This is the creatinine variation used in AKIN criteria to define AKI. Table 6 shows the coordinates of the ROC curve analysis.

DISCUSSION

There is still no consensus on which would be the best definition of AKI in general.[15,16] This problem is even more difficult to solve in the setting of liver failure, as usual kidney function markers are less robust in this situation.[17,18] AKIN criteria were proposed as a diagnostic and staging tool in the definition of AKI[8] and are now adopted by a working party directed to renal dysfunction in cirrhotic patients.[14] However, these criteria have not been applied to cirrhotic patients.

TABLE 3. Hospital Mortality According to Acute Kidney Injury Status

	Survivors n (%)	Nonsurvivors n (%)	OR	95% CI	*P*
Without AKI	75 (70.1%)	32 (29.9%)		Reference group	
With AKI	43 (47.3%)	48 (52.7%)	2.6	1.5-4.7	0.001
AKIN stage 1	40 (48.2%)	43 (51.8%)	2.5	1.4-4.6	0.002
AKIN stage 2	2 (40%)	3 (60%)	3.5	0.5-30.4	0.208
AKIN stage 3	1 (33.3%)	2 (66.7%)	4.6	0.34-139.9	0.253

AKI indicates acute kidney injury; AKIN, Acute Kidney Injury Network; CI, confidence interval; OR, odds ratio.

TABLE 4. Logistic Regression Analysis—Final Model

Variable	OR	95% CI	*P*
Infection	3.81	1.52-9.54	0.004
Hepatic encephalopathy	4.69	1.36-16.14	0.014
Child score	1.78	1.31-2.42	< 0.001
Acute kidney injury	3.30	1.38-7.92	0.007

CI indicates confidence interval; OR, odds ratio.

In this study, the difference in serum creatinine value proposed by AKIN (0.3 mg/dL) was applied to define the presence of AKI at hospital admission,[8] leading to a prevalence of 46%. This prevalence is higher than those observed in previous studies.[19–22] Follo et al,[19] for instance, observed renal impairment in 33% of patients with spontaneous bacterial peritonitis. Renal failure was observed in 27% of cirrhotic patients with sepsis not related to spontaneous bacterial peritonitis[20] and in 11% of those with gastrointestinal hemorrhage.[22] Lower prevalence values in previous studies are probably related to their different definition of renal impairment, which used greater variations in creatinine such as a rise of at least 50% in baseline serum creatinine with a final creatinine value of more than 1.5 mg/dL.[2] In a study including postliver transplant patients, 3 definitions of AKI were applied and the definition with the smaller rise in creatinine (more than 0.5 mg/dL) resulted in the higher prevalence of AKI (78%).[23] In fact, AKI represents a spectrum of disease and criteria with lower thresholds for the diagnosis (such as AKIN) are expected to select patients on an earlier stage of the disease.[8] This could be of importance, as it allows intervention in less severe phases.

This study used only values of creatinine from the first 48 hours of hospitalization, a strategy that deserves some remarks. First of all, a baseline creatinine was not considered. This could lead to bias, as the first creatinine value could already represent AKI if it was already elevated from the baseline level. However, in clinical practice, physicians are frequently not aware of a previous creatinine value. Therefore, the rationale of using the first 48 hours of hospitalization was to see if AKI at this early point of hospital assistance could define patients with a greater risk of mortality. This is of practical importance, as more aggressive therapy could be applied to this group. The second point is that the study design did not consider the development of AKI during hospitalization. Therefore, both patients with and without AKI could develop renal impairment after the first 48 hours. Once more, the important point was to identify high-risk patients at the beginning of hospitalization. Another aspect that needs a commentary is the fact that AKI was applied considering a bidirectionally variation in creatinine and not only the increase from creatinine 1 to creatinine 2. This way, even if creatinine fell (due to some kind of intervention, for instance), AKI was considered to have occurred. In this context, a decrease in creatinine may represent a reversal or partial reversal of AKI that was already present at hospital admission. In this case, a greater value of creatinine 1 would mean that AKI is present and the smaller value of creatine 2, an improvement in renal function.

TABLE 5. Probabilities of Death Estimated by the Logistic Regression Model (N = 198)

Acute Kidney Injury by AKIN	Child Score at Hospital Admission	Hepatic Encephalopathy	Infection	Predicted Probability (%)
No	Child B	No	No	2.1
			Yes	7.4
		Yes	No	14.1
			Yes	38.3
	Child C	No	No	8.0
			Yes	24.7
		Yes	No	40.3
			Yes	71.8
Yes	Child B	No	No	6.9
			Yes	21.9
		Yes	No	36.7
			Yes	68.5
	Child C	No	No	23.4
			Yes	53.5
		Yes	No	70.4
			Yes	89.9

AKIN indicates Acute Kidney Injury Network.

When comparing patients with and without AKI, there was no difference in frequency of hypertension and diabetes, although these are comorbidities usually associated to chronic loss of renal function.[24] In a study, which evaluated risk factors for AKI postorthotopic liver transplantation adopting AKIN definition, there was also no difference in groups with or without AKI in relation to diabetes or hypertension.[25] Mean serum sodium at admission was not significantly different between these groups either, whereas the same parameter was significantly lower in nonsurvivors. Hyponatremia has been identified as a prognostic factor in patients awaiting liver transplantation.[26–28]

Patients with AKI at hospital admission in this study had significantly higher hospital mortality when compared with those without renal impairment. Patients with more severe stages of AKIN (AKIN 2 and 3) seem to have a higher risk of mortality when compared with AKIN 1. However, the small number of patients classified in stages 2 and 3 compromises the statistical analysis of this difference. Association of renal impairment and mortality in cirrhotic patients had been shown in previous studies in clinical contexts such as spontaneous bacterial peritonitis,[19,21] gastrointestinal bleeding,[22] and sepsis unrelated to spontaneous bacterial peritonitis.[20] Studies addressing critically ill cirrhotic patients had also found that AKI was independently associated to mortality.[29,30] An important point to notice in this study is the fact that the variation in creatinine values with greater sensitivity and specificity in relation to hospital mortality in ROC curve analysis was 0.3 mg/dL, which is the 1 proposed by AKIN criteria. These data reinforce the applicability of these criteria when evaluating cirrhotic patients.

Overall mortality in this study was relatively high (40.4%). Mortality in other studies had varied from 9% in a study including gastrointestinal bleeding to 81.1% in a study with critically ill cirrhotic patients.[19,20,22,31] Some factors might have contributed to the high mortality rate in this study. First of all, the study selected cirrhotic patients with ascites, which represent decompensated cirrhosis and thus a more advanced stage of the disease.[32] Second, patients were either of Child-Pugh B or C scores and had relatively high MELD scores, which represent more severe

TABLE 6. Coordinates of the ROC Curve Analysis Using Different Creatinine Variation Values in Respect to Hospital Mortality (AUC = 0.652)

Creatinine Variation (mg/dL)	Sensitivity (%)	Specificity (%)
−1	100	0
0.05	97.5	8.5
0.09	97.5	9.3
0.10	87.5	25.4
0.15	77.5	34.7
0.19	76.3	34.7
0.20	70.0	46.6
0.25	63.8	58.5
0.29	60.0	59.3
0.30	**60.0**	**63.6**
0.35	47.5	72.9
0.39	46.3	72.9
0.40	43.8	80.5
0.45	41.3	87.3
0.49	40.0	87.3
0.50	40.0	88.1
0.55	36.3	90.7
0.60	33.8	91.5
0.65	30.0	91.5
0.69	27.5	92.4
0.70	23.8	92.4
0.75	21.3	92.4
0.79	21.3	92.4
0.80	18.8	93.2
0.85	17.5	93.2
0.90	16.3	94.1
0.95	16.3	94.9
0.99	15.0	94.9
1.00	15.0	94.9
1.05	13.8	95.8
1.15	12.5	95.8
1.20	12.5	96.6
1.25	11.3	96.6
1.35	8.8	96.6
1.40	7.5	96.6
1.45	6.3	96.6
1.55	6.3	97.5
1.65	5.0	97.5
1.70	3.8	97.5
1.80	3.8	98.3
1.95	2.5	98.3
2.15	1.3	99.2
2.45	0	99.2
3.60	0	100

AUC indicates area under curve; ROC, receiver operating characteristic.
The numbers in bold indicates the variation in creatinine with best sensitivity and specificity.

liver dysfunction and therefore higher mortality.[33] Another possible explanation for the mortality value in this study would be a higher frequency of hepatorrenal syndrome among patients with AKI. Hepatorenal syndrome, mainly type 1, seems to have a worse prognosis than other causes of AKI in cirrhosis.[5,34] Unfortunately, it was not possible to define precisely the prevalence of hepatorenal syndrome among cases of AKI due to the retrospective nature of the study.

Besides higher mortality and MELD score, patients who fullfilled AKIN criteria had also greater frequency of sepsis. Among nonsurvivors not only sepsis but also the diagnosis of infection was more frequent when compared with survivors. In fact, cirrhotic patients are prone to infectious complications due to facilitating mechanisms such as changes in intestinal flora intestinal barrier and defects in innate immune and reticuloendothelial system for instance.[35–37] A national database survey in the United States evaluated hospital discharges and found that cirrhotic patients are more likely to die while hospitalized, to have sepsis during hospitalization and to die from sepsis.[38] Renal failure is recognized as a frequent complication associated to infection in cirrhosis.[39] This has been confirmed in spontaneous bacterial peritonitis[19,21] and sepsis not related to spontaneous bacterial peritonitis.[20]

In the final model in logistic regression, AKI, hepatic encephalopathy, Child-Pugh score, and infection were independently associated to hospital mortality. In a systematic review regarding natural history and prognostic indicators of survival in cirrhosis,[32] Child-Pugh score was the most common independent predictor of death in the studies analyzed. In a Danish population-based cohort study including patients with alcoholic cirrhosis, 1-year mortality among patients with hepatic encephalopathy was 64% and the median survival time after the development of this complication was 2.4 months.[40] The relationship between infection in cirrhotics and prognosis has already been discussed. Table 5 puts in evidence the impact of acute renal failure on mortality, as AKI accounts for higher probabilities of death in patients with the same distribution of other variables associated to hospital mortality in logistic regression.

In summary, a variation in serum creatinine of at least 0.3 mg/dL (as defined by AKIN criteria) in the first 48 hours of hospitalization identified a group of cirrhotic patients who has a greater risk of hospital mortality. Although more studies are necessary to validate the applicability of AKIN criteria in cirrhotic patients, the results strongly suggest that the variation in serum creatinine proposed is useful to the early detection of patients with worse prognosis.

REFERENCES

1. Arroyo V, Gines P, Gerbes AL, et al. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis: International Ascites Club. *Hepatology*. 1996;23:164–176.
2. Moreau R, Lebrec D. Acute renal failure in patients with cirrhosis: perspectives in the age of MELD. *Hepatology*. 2003;37:233–243.
3. Garcia-Tsao G, Parikh CR, Viola A. Acute kidney injury in cirrhosis. *Hepatology*. 2008;48:2064–2077.
4. Salerno F, Gerbes A, Gines P, et al. Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. *Gut*. 2007;56:1310–1318.
5. Schepke M, Appenrodt B, Heller J, et al. Prognostic factors for patients with cirrhosis and kidney dysfunction in the era of MELD: results of a prospective study. *Liver Int*. 2006;26:834–839.
6. Hampel H, Bynum GD, Zamora E, et al. Risk factors for the development of renal dysfunction in hospitalized patients with cirrhosis. *Am J Gastroenterol*. 2001;96:2206–2210.
7. Sherman DS, Fish DN, Teitelbaum I. Assessing renal function in cirrhotic patients: problems and pitfalls. *Am J Kidney Dis*. 2003;41:269–278.
8. Mehta RL, Kellum JA, Shah SV, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care*. 2007;11:R31.

9. Chertow GM, Burdick E, Honour M, et al. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. *J Am Soc Nephrol*. 2005;16:3365–3370.
10. Praught ML, Shlipak MG. Are small changes in serum creatinine an important risk factor? *Curr Opin Nephrol Hypertens*. 2005;14:265–270.
11. Levy MM, Macias WL, Vincent JL, et al. Early changes in organ function predict eventual survival in severe sepsis. *Crit Care Med*. 2005;33:2194–2201.
12. Coca SG, Peixoto AJ, Garg AX, et al. The prognostic importance of a small acute decrement in kidney function in hospitalized patients: a systematic review and meta-analysis. *Am J Kidney Dis*. 2007;50:712–720.
13. Gines P, Schrier RW. Renal failure in cirrhosis. *N Engl J Med*. 2009;361:1279–1290.
14. Wong F, Nadim MK, Kellum JA, et al. Working Party proposal for a revised classification system of renal dysfunction in patients with cirrhosis. *Gut*. 2011;60:702–709.
15. Bellomo R, Kellum J, Ronco C. Acute renal failure: time for consensus. *Intensive Care Med*. 2001;27:1685–1688.
16. Kellum JA, Levin N, Bouman C, et al. Developing a consensus classification system for acute renal failure. *Curr Opin Crit Care*. 2002;8:509–514.
17. Davis CL. What's in a name, AKI? *Liver Transpl*. 2009;15:455–456.
18. Bellomo R, Kellum JA, Ronco C. Defining acute renal failure: physiological principles. *Intensive Care Med*. 2004;30:33–37.
19. 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; 20:1495–1501.
20. 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;129:1944–1953.
21. Sort P, Navasa M, Arroyo V, et al. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. *N Engl J Med*. 1999;341:403–409.
22. Cardenas A, Gines P, Uriz J, et al. Renal failure after upper gastrointestinal bleeding in cirrhosis: incidence, clinical course, predictive factors, and short-term prognosis. *Hepatology*. 2001;34(4 Pt 1):671–676.
23. Barri YM, Sanchez EQ, Jennings LW, et al. Acute kidney injury following liver transplantation: definition and outcome. *Liver Transpl*. 2009;15:475–483.
24. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis*. 2002;39(2 Suppl 1): S1–266.
25. Iglesias JI, DePalma JA, Levine JS, Risk factors for acute kidney injury following orthotopic liver transplantation: the impact of changes in renal function while patients await transplantation. *BMC Nephrol*. 2010;11:30.
26. Ruf AE, Kremers WK, Chavez LL, et al. Addition of serum sodium into the MELD score predicts waiting list mortality better than MELD alone. *Liver Transpl*. 2005;11:336–343.
27. Heuman DM, Abou-Assi SG, Habib A, et al. Persistent ascites and low serum sodium identify patients with cirrhosis and low MELD scores who are at high risk for early death. *Hepatology*. 2004;40:802–810.
28. Kim WR, Biggins SW, Kremers WK, et al. Hyponatremia and mortality among patients on the liver-transplant waiting list. *N Engl J Med*. 2008;359:1018–1026.
29. du Cheyron D, Bouchet B, Parienti JJ, et al. The attributable mortality of acute renal failure in critically ill patients with liver cirrhosis. *Intensive Care Med*. 2005;31:1693–1699.
30. Jenq CC, Tsai MH, Tian YC, et al. RIFLE classification can predict short-term prognosis in critically ill cirrhotic patients. *Intensive Care Med*. 2007;33:1921–1930.
31. Fang JT, Tsai MH, Tian YC, et al. Outcome predictors and new score of critically ill cirrhotic patients with acute renal failure. *Nephrol Dial Transplant*. 2008;23:1961–1969.
32. 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;44:217–231.
33. Durand F, Valla D. Assessment of prognosis of cirrhosis. *Semin Liver Dis*. 2008;28:110–122.
34. Alessandria C, Ozdogan O, Guevara M, et al. MELD score and clinical type predict prognosis in hepatorenal syndrome: relevance to liver transplantation. *Hepatology*. 2005;41:1282–1289.
35. Wong F, Bernardi M, Balk R, et al. Sepsis in cirrhosis report on the 7th meeting of the International Ascites Club. *Gut*. 2005;54:718–725.
36. Navasa M, Rodes J. Bacterial infections in cirrhosis. *Liver Int*. 2004;24:277–280.
37. Yoneyama K, Miyagishi K, Kiuchi Y, et al. Risk factors for infections in cirrhotic patients with and without hepatocellular carcinoma. *J Gastroenterology*. 2002;37:1028–1034.
38. Foreman MG, Mannino DM, Moss M. Cirrhosis as a risk factor for sepsis and death: analysis of the National Hospital Discharge Survey. *Chest*. 2003;124:1016–1020.
39. Fasolato S, Angeli P, Dallagnese L, et al. Renal failure and bacterial infections in patients with cirrhosis: epidemiology and clinical features. *Hepatology*. 2007;45:223–229.
40. Jepsen P, Ott P, Andersen PK, et al. Clinical course of alcoholic liver cirrhosis: a Danish population-based cohort study. *Hepatology*. 2010;51:1675–1682.