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New consensus definition for acute kidney injury accurately predicts 30-day mortality in cirrhosis with infection

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Abstract

Background & Aims—A consensus conference proposed that cirrhosis-associated acute kidney injury (AKI) be defined as an increase in serum creatinine by >50% from the stable baseline value in <6 months or by 0.3mg/dL in <48 hrs. We prospectively evaluated the ability of these criteria to predict mortality within 30 days among hospitalized patients with cirrhosis and infection.

Methods—337 patients with cirrhosis admitted with or developed an infection in hospital (56% men; 56±10 y old; model for end-stage liver disease score, 20±8) were followed. We compared data on 30-day mortality, hospital length-of-stay, and organ failure between patients with and without AKI.

Results—166 (49%) developed AKI during hospitalization, based on the consensus criteria. Patients who developed AKI had higher admission Child-Pugh (11.0±2.1 vs 9.6±2.1; $P<.0001$), and MELD scores (23±8 vs 17±7; $P<.0001$), and lower mean arterial pressure (81±16mmHg vs 85±15mmHg; $P<.01$) than those who did not. Also higher amongst patients with AKI were mortality in 30 days (34% vs 7%), intensive care unit transfer (46% vs 20%), ventilation requirement (27% vs 6%), and shock (31% vs 8%); AKI patients also had longer hospital stays (17.8±19.8 days vs 13.3±31.8 days) (all $P<.001$). 56% of AKI episodes were transient, 28% persistent, and 16% resulted in dialysis. Mortality was 80% among those without renal recovery, higher compared to partial (40%) or complete recovery (15%), or AKI-free patients (7%; $P<.0001$).

Conclusions—30-day mortality is 10-fold higher among infected hospitalized cirrhotic patients with irreversible AKI than those without AKI. The consensus definition of AKI accurately predicts 30-day mortality, length of hospital stay, and organ failure.

Keywords

bacterial infection; liver fibrosis; hepatorenal syndrome; MELD; NACSELD

Renal dysfunction is a common complication of liver cirrhosis, occurring in approximately 20% of all hospitalized patients with cirrhosis¹. At one end of the spectrum of renal dysfunction is type 1 hepatorenal syndrome (HRS), which is an acute form of renal failure associated with significant morbidity and mortality². Because of the rigid diagnostic criteria of type 1 HRS, which requires a serum creatinine of >2.5mg/dL (233μmol/L) for its diagnosis³, patients with lesser degrees of renal dysfunction are less likely to be treated. However, there is emerging evidence suggesting that even milder degrees of renal dysfunction in cirrhosis are associated with a poor prognosis^{4–6}. Furthermore, serum creatinine, the most widely accepted measure of renal function, does not accurately reflect renal function in advanced cirrhosis, especially in those with muscle wasting⁷. Therefore, in decompensated cirrhosis, patients with normal serum creatinine may already have significant renal dysfunction⁸. The International Ascites Club and the Acute Dialysis Quality Initiative (ADQI) group recently proposed that acute renal injury (AKI) in cirrhosis should be re-defined as a rise in serum creatinine of 0.3mg/dL (26.4μmol/L) in less than 48 hours or a 50% increase in serum creatinine from a stable baseline reading within the previous 6 months, irrespective of the final serum creatinine level⁹. This definition, although similar to the definition of AKI in non-cirrhotic patients by the Acute Kidney Injury

Network (AKIN)¹⁰, involves no stages of AKI. Such acute small increases in serum creatinine have been shown to be clinically significant in cirrhotic patients in intensive care unit^{11,12}, and in cirrhotic patients in an ambulatory setting⁴.

Although AKI in cirrhosis can occur spontaneously, it is frequently precipitated by an acute event². The most common precipitant of renal failure in patients with cirrhosis is bacterial infection^{13,14}. Both spontaneous bacterial peritonitis (SBP)^{15,16} and other bacterial infections are recognized to be associated with a high incidence of renal failure in cirrhosis^{14,17}. Once renal failure develops in infected patients, the probability of survival is significantly reduced to 31% at 3 months, comparable to patients with HRS¹⁴. In fact, renal dysfunction is the most significant independent predictor of death in patients with cirrhosis and SBP¹⁸. However, all of the studies that reported poor survival in patients with infection-associated renal failure have defined renal failure as a serum creatinine of >1.5mg/dL (133μmol/L). This led us to speculate that the new AKI definition of 0.3mg/dL (26.4μmol/L) increase in serum creatinine in 48 hours or a doubling of serum creatinine from a stable baseline reading in the previous 6 months irrespective of the final serum creatinine level⁸ may be associated with better outcome prediction. Therefore, an aim of this prospective study was to evaluate the new AKI definition as set out by the International Ascites Club and ADQI⁹ in the prediction of mortality within 30 days in a multi-center cohort of cirrhotic patients hospitalized with various bacterial infections. We have chosen to study a population of cirrhotic patients with infections as they are more likely to develop AKI as a complication of their infection with a more severe outcome, and therefore potentially have the most to gain from an earlier diagnosis.

Methods

The study was approved by the respective Institutional Review Boards of the participating centers in NACSELD (North American Consortium for the Study of End-Stage Liver Disease). Data were managed using REDCap (Research Electronic Data Capture) tools located at Virginia Commonwealth University¹⁹. REDCap is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

Patients with cirrhosis who were either admitted with or developed an infection during their hospitalization were approached for informed consent. The patients enrolled were not consecutive patients who had infection at the 12 participating centers; rather, each center enrolled all eligible patients whenever the principal investigators were on inpatient service. Because each principal investigator joined the consortium at different time points, the number of patients enrolled by each center varied. Each center contributed 5–15% of the enrolled patients. Cirrhosis was diagnosed with a combination of biochemical, radiological and endoscopic findings if liver biopsy confirmation was not available. Infections from all body sites as defined below were included. Patients who had infections but did not require hospital admission were excluded, as were patients who were admitted but did not develop an infection as inpatients. Other exclusion criteria included immuno-compromised patients

with human immunodeficiency virus infection, prior organ transplant, and disseminated malignancies.

Once informed consent was obtained, data collection began with patient demographics, vital signs, baseline full blood count, biochemistry, liver and renal function, and details of the infection including antibiotic treatment as well as the development of a second infection. Serum creatinine levels 3 months before the admission were collected wherever available. Baseline creatinine values were used from these three-month pre-admission periods if elevated to $>1.5\text{mg/dL}$ ($133\mu\text{mol/L}$) on admission; admission values were used if they were normal or if pre-hospitalization baselines were not available. Patients were then monitored daily until discharge for the development of AKI, defined by the International Ascites Club and ADQI⁹. Patients who developed AKI had further data collection with respect to the AKI episodes, and these included the precipitating event, treatment given (midodrine, octreotide, albumin) and whether the AKI episodes were transient, persistent, or progressive (see definitions below). Terlipressin was not part of the treatment regimen as it is not available in North America. Data regarding intensive care unit admissions, organ failure, liver transplantation, and length of hospital stay were also collected. Patients who were discharged alive were followed regularly as part of their standard of care, and contacted at 30 days post-enrolment to determine survival. Every enrolled patient was counted at day 30 as either dead or alive to determine the 30-day mortality.

We defined infections according to standard criteria²⁰: (a) spontaneous bacteremia: positive blood cultures without a source of infection; (b) SBP: ascitic fluid polymorphonuclear cells $>250/\mu\text{L}$; (c) lower respiratory tract infections: new pulmonary infiltrate in the presence of: (i) at least one respiratory symptom (cough, sputum production, dyspnea, pleuritic pain) with (ii) at least one finding on auscultation (rales or crepitation) or one sign of infection (core body temperature $>38^{\circ}\text{C}$ or less than 36°C , shivering or leucocyte count $>10,000/\text{mm}^3$ or $<4,000/\text{mm}^3$) in the absence of antibiotics; (d) *Clostridium difficile* Infection: diarrhea with a positive *C. difficile* assay; (e) bacterial entero-colitis: diarrhea or dysentery with a positive stool culture for *Salmonella*, *Shigella*, *Yersinia*, *Campylobacter*, or pathogenic *E. coli*; (f) soft-tissue/skin Infection: fever with cellulitis; (g) urinary tract infection (UTI): urine white blood cell $>15/\text{high power field}$ with either positive urine gram stain or culture; (h) intra-abdominal infections: diverticulitis, appendicitis, cholangitis; (i) other infections not covered above, and (j) fungal infections as a special category.

AKI outcomes¹⁵ were defined on the basis of baseline creatinine (admission creatinine or creatinine within 3 months prior to hospitalization in whom the admission creatinine was $>1.5\text{mg/dL}$) as (a) transient AKI: serum creatinine returning to pre-AKI levels at the end of the AKI episode, (b) persistent AKI: persistent increase in serum creatinine $>0.3\text{mg/dL}$ within 48 hours or $>50\%$ increase from baseline not requiring dialysis, and (c) progressive AKI: increase in serum creatinine $>0.3\text{mg/dL}$ in 48 hours or $>50\%$ increase from baseline despite control of infection or increase that required renal replacement therapy.

Statistical Analysis

Categorical data are presented as a percentage as well as the actual numbers used to calculate the percentages. Continuous data are presented as mean $\pm$ standard deviation while

discrete data are presented as median with the accompanying inter-quartile range. Group comparisons for categorical variables were done using the χ^2 test with the corresponding degrees of freedom while group comparisons for continuous variables were done with either a two-sample t-test or a one-way ANOVA if more than three groups were compared. Group comparisons for discrete data were done using a non-parametric Wilcoxon Rank-Sum test (Mann-Whitney U test) for two groups or the Kruskal-Wallis for more than two groups. For all analyses, a p value <0.05 was considered to be statistically significant.

The determinants of the development of AKI and of mortality were calculated using a logistic regression model. A multivariate logistic regression model, with backward elimination, was used to arrive at a parsimonious model to determine predictors of AKI. The variables analyzed were etiology of cirrhosis, various parameters at admission including mean arterial pressure (MAP), heart rate, international normalized ratio, bilirubin, white blood cell count, sodium, baseline creatinine, second infection and SBP. The resulting model was then pared down by eliminating, one by one, covariates that were not significant at the 0.05 level, and the final model where all covariates significant at the 0.05 level were identified. Similarly, a multivariate logistic regression model, with backward elimination, was used to arrive at a parsimonious model to determine predictors of death. The variables analyzed were the same as those used for the prediction of AKI with the addition of MELD, number of organ failures, and AKI outcome (No AKI, transient, persistent or progressive).

Results

A total of 337 inpatients with cirrhosis and infection were enrolled in 12 centers in North America between December 2010 and November 2012. There were 187 males with a mean age of 55.9 ± 9.7 years. Patient demographics, vital signs and laboratory findings at the time of enrolment are included in Table 1. Two hundred and eighty-seven patients were admitted with an infection, while 50 patients developed an infection after admission. All patients who developed nosocomial infections were admitted for other complications of cirrhosis, such as hepatic encephalopathy, variceal bleeding and ascites management. Culture results were available in 309 patients. The leading infections were UTI in 92 (27%), SBP in 71 (21%), skin infection in 47 (14%), pneumonia in 35 (10%), and spontaneous bacteremia not associated with any other infections in 31 (9%) patients (Table 2a). Empirical antibiotics were commenced in 95% of cases before culture results were available. The majority of infectious isolates were gram-positive bacteria (37%), followed by gram-negative bacteria (30%) and fungi (5%). A large proportion of infections yielded no growth on culture (26%). In the case of culture negative episodes, antibiotics were continued for 5 days. The index infection was nosocomial in 50 (15%) patients and 76 (23%) patients went on to develop a second infection while hospitalized. The type of infection and the organisms involved in the second infection are shown in Table 2b, as are the risk factors for the development of a second infection (Table 2c). There was no difference in the severity of liver dysfunction as indicated by MELD score between those patients who developed nosocomial infection or not (Table 3a), nor was there any difference between those patients who developed second infection or not.

One hundred and sixty-six patients (49%) developed a mean of 1.2 ± 0.5 episodes of AKI during their hospitalization. Their mean admission creatinine was 1.28 ± 0.63 mg/dL. Of these, 73 had elevated creatinine on admission (2.32 ± 1.12 mg/dL), therefore their pre-admission baseline (1.01 ± 0.39 mg/dL) creatinine anytime within the previous 3 months was used to determine occurrence of AKI (table 1). The time lapse between the baseline serum creatinine and the admission creatinine in these 73 patients was approximately 2 weeks. The remaining 93 patients had a creatinine < 1.5 mg/dL on admission and therefore this was used to determine whether an episode of AKI occurred or not. The mean creatinine peak value was 2.65 ± 1.42 mg/dL for all patients with AKI. The majority of patients (57%) had a serum creatinine increase between 0.3–0.5 mg/dL, while 19%, 10% and 14% of patients had a serum creatinine increase of 0.6–1.0 mg/dL, 1.1–1.5 mg/dL and > 1.5 mg/dL respectively, and their complete renal recovery rates were 59%, 74%, 43% 29% respectively. There was no difference in age, gender, etiology, admission creatinine levels, severity of liver disease, or other laboratory parameters between the patients who had the various categories of AKI severity. The most common precipitating infection for AKI was UTI, followed by SBP and skin infections. Sixty-four percent (64%; 32/50) of patients with a nosocomial infection had an AKI compared to 46% (129/280) of patients without a nosocomial infection; this difference was statistically significant ($p=0.0195$; OR=2.08, 95% confidence interval (CI) [1.12, 3.88]). Sixty-eight percent (52/76) of patients with a second infection had an AKI compared to 44% (114/260) of patients without a second infection; this difference was also statistically significant ($p=0.0002$; OR=2.77, 95% CI [1.61, 4.77]).

Patients who had an episode of AKI had a significantly lower admission MAP, higher admission serum creatinine but similar baseline serum creatinine values compared to those who did not develop AKI (Table 1). There was a further drop in the MAP in the AKI group at the peak of the AKI episode (from 83 ± 13 mmHg to 76 ± 14 mmHg, $p < 0.001$), which recovered upon resolution of the AKI (82 ± 13 mmHg). A significant negative correlation was observed between the admission MAP and the admission serum creatinine (data not shown) in patients who had an episode of AKI, but not in those who did not.

Twenty of the 166 patients (12%) did not receive any treatment for their AKI, 59 (36%) received albumin infusions only, while the remaining 87 patients (52%) received midodrine and octreotide (pharmacotherapy) in addition to albumin. Overall, the patients who developed nosocomial infections had a worse outcome compared with those who were admitted with an infection (Table 3a). However, those patients who already had AKI on admission fared just as bad as those who developed their AKI during their hospital admission (Table 3b). Despite being the commonest precipitating infection, there was no difference in terms of clinical outcomes between those who had UTI versus other infections as the precipitating event (data not shown).

Despite treatment given to the majority of patients with AKI, there were significantly more patients with AKI who were transferred to intensive care units, who required mechanical ventilation, who developed complications such as hepatic encephalopathy, shock and organ failure compared to patients who did not develop AKI (Table 4a). Therefore, there were significantly more deaths and longer hospital stays in those who developed AKI versus those who did not (Table 4a). Overall, there were 56 deaths in the AKI group and 12 deaths in the

non-AKI group. All patients died from multi-organ failure. There was no difference in patient outcome when comparing those who received albumin alone, versus those who received albumin + midodrine + octreotide (Table 4b).

Renal outcome was available only in 153 of 166 patients with AKI. The AKI was transient in 82 (52%), persistent in 38 (25%) and progressive in 14 (9%) patients. Nineteen patients (12%) were started on dialysis. Apart from a significantly lower platelet count amongst patients commenced on dialysis, there were no other differences among patients with various renal outcomes. Ultimately, 86 (56%) of the 153 patients had a complete renal recovery, 42 (28%) had a partial recovery, while 25 (16%) did not recover from their AKI episode (Table 4c). Of the patients with complete renal recovery, 3% received no specific AKI treatment, 36% received albumin only while 60% received pharmacotherapy in addition to albumin. The respective percentages were 7%, 43% and 50% in patients with partial renal recovery. Of the 25 patients who did not have a renal recovery, pharmacotherapy was given to 14 patients (56%). Patients who had no renal recovery had a significantly lower serum sodium concentration ($128 \pm 6 \text{ mmol/L}$) compared to those with partial ($132 \pm 7 \text{ mmol/L}$) or a complete recovery ($131 \pm 6 \text{ mmol/L}$) ($p=0.01$). Patients without renal recovery had a longer length of stay (LOS), more often needed intensive care unit admission, developed shock, organ failure, and/or required mechanical ventilation (Table 4c). As a result, the 30-day mortality rate was significantly higher in those who developed AKI (34%) versus those who did not (7%) ($p<0.0001$). 30-day mortality was the highest amongst patients who did not recover from their AKI (80%), compared to those with partial (40%) or complete (15%) renal recovery. Even in those patients with complete recovery of their AKI, the 30-day mortality was still higher compared to patients without AKI (7%).

Table 5 presents the multivariable analyses of factors associated with AKI occurrence and death. From the univariate analyses of parameters presented in Tables 1 and 4, the independent factors associated with an increased risk of AKI occurrence were the development of a second infection and MELD score. The factors associated with an increased risk of death within 30 days were AKI outcome (transient, persistent, or progressive), number of organ failures, MELD score, admission mean arterial pressure and SBP as the precipitating infection.

Table 6 represents the sensitivity and specificity of AKI diagnosed with the new criteria in the prediction of 30-day mortality in cirrhotic patients hospitalized with infection. The positive predictive value of these new AKI diagnostic criteria for death is 34%, while the negative predictive value is 93%.

Discussion

This study demonstrates that AKI, as defined by the ADQI and International Ascites Club⁹ is a common occurrence in hospitalized cirrhotic patients, whether admitted with an infection or developed an infection as inpatients, and this definition accurately predicts the development of adverse outcomes in this patient population. This ability to predict an adverse outcome is relevant irrespective of whether the AKI is diagnosed as an acute rise in serum creatinine in <48 hours, or as a 50% increase in serum creatinine from a stable

baseline value taken within the previous 3 months. Although AKI development was transient in most cases, a significant proportion of patients went on to develop progressive renal failure. Unfortunately, patients who experienced AKI had more complications, longer LOS and higher 30-day mortality. Interestingly, even patients who completely recovered their renal function after an episode of AKI had a significantly higher 30-day mortality compared to those who never developed AKI.

Bacterial infections have been known to be associated with a high risk of renal failure in cirrhosis^{14–17}, and this was once again confirmed in our cohort of patients. Our patients demonstrated that UTI was by far the most common cause of AKI, in contrast to previous publications, which identified gastrointestinal infections and SBP as the most common precipitants of AKI¹³. This may be related to our definition of AKI, which uses a lower threshold for the diagnosis for renal failure. This also underscores the importance of preventing UTI in hospitalized cirrhotic patients, which usually is a nosocomial infection, associated with insertion of a urinary catheter, often for unclear reasons. Spontaneous bacterial peritonitis and spontaneous bacteremia were also important causes of AKI in our patients. Although prophylactic measures are in place for prevention of recurrent SBP²¹, primary prevention of both SBP and spontaneous bacteremia is not the usual standard of care. Research efforts are needed to better identify a subset of cirrhotic patients that may benefit from primary prophylactic measures against these infections²².

Forty-nine percent of the hospitalized cirrhotic patients with infections developed AKI. This incidence is higher than previously reported using traditional criteria^{15,17}, likely related to the use of the expanded definition of AKI⁹. A similar incidence of AKI development complicating infections in cirrhosis has been reported when the expanded AKI diagnostic criteria were applied²³. Interestingly, none of the specific infection types and rates were different between those who did or did not develop AKI, although SBP was independently associated with 30-day mortality compared to non-SBP infections. The patients who developed AKI had more advanced liver disease as indicated by the higher Child-Pugh and MELD scores. These patients may also have had a more severe infection as shown by their significantly higher white cell counts and more severe hemodynamic instability as evidenced by a significantly lower MAP. Ruiz-del-Arbol et al demonstrated that patients with SBP who developed renal failure had a significantly lower MAP at the start of their infection and this fell even further at infection resolution, associated with higher neurohormonal levels, suggesting an additional reduction in the effective arterial blood volume related to the infection-induced arterial vasodilatation²⁴. Our patients who developed AKI mirrored these pathophysiological changes by demonstrating a lower serum sodium concentration and higher serum creatinine levels on admission. Furthermore, the MAP fell further with increasing serum creatinine at the peak of the AKI episode, suggesting that progression of unstable hemodynamics, contributing to worsening renal function. Therefore, every effort should be made to improve the effective arterial blood volume in order to reduce the risk for the development of AKI. This is already standard of care for SBP¹⁶ and has shown a trend towards AKI improvement in non-SBP infections²⁵.

It is interesting to note that the development of a second infection in hospital is also strongly predictive of AKI development, even after controlling for hospital LOS. This could be due

to a second insult, i.e. a second infection further complicating the already impaired hemodynamics, compounding the neuro-hormonal imbalance and leading to multiple organ failure and death. Second infections are common in hospitalized cirrhotic patients, occurring in at least 24% of patients²⁶. These are largely preventable infections, consisting of aspiration pneumonia, catheter-associated UTI, *C. difficile* and fungal infections, the latter often related to antibiotic use. Therefore, preventing second infections, as a means to prevent AKI, is critical to improve outcomes in hospitalized cirrhotic patients.

More than half of the AKI episodes only had minor increases in the serum creatinine levels of between 0.3 to 0.5mg/dL, not sufficient to reach the diagnostic criteria for type 1 HRS³. This would also explain why almost half of these patients either did not receive any treatment for their AKI, or only received albumin. It appears that the addition of midodrine and octreotide to albumin as a treatment for these cases of AKI, many of whom had only minor increases of serum creatinine, did not influence the clinical outcome. However, their clinical course was not benign. Significantly more patients were transferred to intensive care unit, required mechanical ventilation, and developed organ failure compared to those who did not develop AKI. The negative impact of AKI on the natural history of cirrhosis is well described^{5,6}, with the incidence of cirrhotic complications increasing in parallel with the severity of the AKI⁵. It is therefore not surprising that the most severe form of AKI is associated with such negative outcomes²⁷. It is interesting to note that irrespective of whether the patient presents with AKI on admission, or develops it while an inpatient, the outcome is equally unfavorable. It then follows that treatment for AKI should begin well before the stringent diagnostic criteria of type 1 HRS are reached, since even the most effective therapy of vasoconstrictor and albumin for type 1 HRS is only effective in <40% of patients²⁸. Towards this goal, the recent proposal to define renal dysfunction based on criteria of the AKIN modified for the cirrhotic population⁹ will help to identify patients at an earlier stage of renal dysfunction, when a better response could be expected from pharmacotherapy and albumin.

Once AKI was established, the clinical course was quite varied, ranging from complete to partial to no recovery. In our cohort of patients, we were unable to identify any factor that predicted the clinical course of AKI, once it was established. However, persistent or progressive renal dysfunction was associated with worse survival despite resolution of the infection. The risk of 30-day mortality appears to increase exponentially when those with complete renal recovery are compared to those with partial or no recovery; 80% of patients without renal recovery died within 30 days, a 10-fold increase compared to those without AKI. This finding is similar to what was reported by Belcher et al⁵, who described an in-hospital mortality rate of 71% for their cirrhotic patients who experienced progression of their AKI. This is astounding considering that AKI in decompensated cirrhosis is potentially a preventable condition^{16,22,29,30}. Also striking is the doubling of 30-day mortality even in those patients who experienced a complete AKI recovery compared to those who never developed AKI, which could indicate that reaching the AKI threshold itself may be an important endpoint in addition to its reversal or progression. These findings underscore the critical need for instituting measures to prevent AKI, or at least initiating treatment sooner than the current convention. Therapy could be potentially guided by clinical criteria such as

the ones identified in this study: the development of a second infection, or a high MELD score. While these factors are also predictive of type 1 HRS, the rigidity of those criteria used as benchmarks to initiate therapy means that many patients may have reached a “point of no return”.

One of the strengths of this study of AKI in hospitalized infected cirrhotic patients is that it is the largest prospective study on this topic to date. We have focused on AKI related to infection alone, but the same outcomes may also be found in patients with AKI related to other precipitating factors, but this will have to await future studies for confirmation. The drawback of this study may be that the AKI diagnosis was largely based on further increases of the serum creatinine using the admission or baseline 21 creatinine as the starting point, but the baseline creatinine may not always be available. Therefore, we could have potentially under-diagnosed the incidence of AKI. Despite this drawback, the study confirms the utility of the diagnostic criteria for AKI in cirrhosis as proposed by the International Ascites Club and ADQI⁸. Although the positive predictive value of the AKI diagnosis for mortality is not particularly high, and this may have been affected by treatment provided to the patients, it is important to note that most of the patients who died had AKI. Furthermore, if the patient did not develop AKI, the patient would most likely survive till 30 days. In addition, these diagnostic criteria have clinical relevance for this population of patients, as they also predict organ failure, hospital LOS. The results suggest that future studies should target preventive measures for AKI according to these new criteria, especially since the development of AKI is associated with negative impact on patient outcomes even in those who survive the initial episode of AKI and infection³¹.

In conclusion, the diagnostic criteria of AKI as defined by ADQI and the International Ascites Club⁹ are useful in predicting outcome for the hospitalized cirrhotic population with infection. AKI is common in this population of patients, associated with significant morbidity and mortality. Therefore, it is imperative that clinicians taking care of cirrhotic patients admitted into hospital with infection treat the infection promptly, and institute measures to prevent the development of a nosocomial or second infection during hospitalization.

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Abbreviations

ADQI	Acute Dialysis Quality Initiative
AKI	acute kidney injury
AKIN	Acute Kidney Injury Network
C.difficile	Clostridium difficile
HRS	hepatorenal syndrome

LOS	length of stay
MAP	mean arterial pressure
MELD	model for end-stage liver disease
NACSELD	North American Consortium for the Study of End-Stage Liver Disease
REDCap	Research Electronic Data Capture
SBP	spontaneous bacterial peritonitis
UTI	urinary tract infection

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Table 1

Baseline patient demographics, vital signs and laboratory findings

	All patients	AKI+	AKI-	P value
n	337	166	171	
Age	55.91 ± 9.66	55.54 ± 8.95	56.26 ± 10.31	0.4942 ¹
Gender				
Male	187 (56%)	90 (55%)	97 (57%)	0.6433 ²
Female	148 (44%)	75 (45%)	73 (43%)	
Etiology of liver cirrhosis				
: alcohol	105 (31%)	51 (31%)	54 (32%)	0.9936 ²
: viral	87 (26%)	42 (25%)	45 (26%)	
: alcohol + viral	49 (14%)	24 (14%)	25 (15%)	
: cholestatic	56 (17%)	28 (17%)	28 (16%)	
: others	40 (12%)	21 (13%)	19 (11%)	
MAP (mmHg)	83±16	81±16	85±15	0.0355 ¹
Heart rate (beats/minute)	88±17	88±16	88±17	0.9168 ¹
Bilirubin (mg/dL)	5.6±6.0	6.6±6.9	4.6±4.8	0.0021 ¹
Albumin (gm/dL)	2.7±0.7	2.6±0.7	2.8±0.7	0.0026 ¹
WBC (X10 ⁹ /L)	8.65±7.25	9.78±8.31	7.56±5.85	0.0048 ¹
Platelet count (X10 ⁹ /L)	31±65	41±77	21±49	0.0046 ¹
INR	1.81±1.15	1.91±0.84	1.71±1.38	0.1094 ¹
Serum Na (mmol/L)	132±7	131±7	134±6	0.0016 ¹
Serum creatinine (admission) (mg/dL)	1.52±1.15	1.90±1.19	1.15±0.99	<0.0001 ¹
Serum creatinine (baseline) (mg/dL)	1.24±0.95	1.32±0.90	1.15±0.98	0.104 ¹
CP score	10.3±2.2	11.0±2.1	9.6±2.1	<0.0001 ¹
CP class (A/B/C)				
A	10 (4%)	2 (2%)	8 (6%)	<0.0001 ²
B	95 (34%)	33 (23%)	62 (45%)	
C	174 (62%)	107 (75%)	67 (49%)	
MELD score	20±8	23±8	17±7	<0.0001 ¹

Notes:

¹Two-sample t-test

² χ^2 test

AKI+: with acute kidney injury; AKI-: without acute kidney injury; CP score: Child Pugh score; CP class: Child Pugh class; INR: International normalized ratio; MAP: mean arterial pressure; MELD: Model for End-stage Liver Disease; Na: sodium; WBC: white blood cell count; admission serum creatinine is the value on the day of admission for all patients; baseline creatinine is admission creatinine except for those who had elevated creatinine on admission (n=73), then baseline reading within the 3 month pre-hospitalization period was used.

P value refers to AKI+ compared to AKI-.

Table 2a

Type of index infection and culture results

	All patients	AKI+	AKI–
n	337	166	171
Site of infection:			
UTI	92 (27%)	49 (29%)	43 (26%)
SBP	71 (21%)	35 (21%)	36 (22%)
Spontaneous bacteremia	31 (9%)	19 (11%)	12 (7%)
Respiratory tract infection	35 (10%)	16 (10%)	19 (11%)
Skin	47 (14%)	21 (12%)	26 (16%)
Clostridium Difficile	17 (5%)	9 (5%)	8 (5%)
Bacterial enterocolitis	2 (1%)	2 (1%)	0 (0%)
Intra-abdominal infection	11 (3%)	4 (2%)	7 (4%)
Fungal	5 (2%)	3 (1%)	2 (1%)
Secondary bacterial peritonitis	4 (1%)	2 (1%)	2 (1%)
Procedure related infection	1 (1%)	0 (0%)	1 (1%)
Other	21 (6%)	12 (7%)	9 (6%)
Nosocomial index infection	50 (15%)	32 (19.2%)	18 (10.5%) ^{#I}
Developed second infection	76 (23%)	52(31.3%)	24 (14.0%) ^{*I}
Organisms Involved:			
Gram positive	114 (37%)	60 (38%)	54 (36%)
Gram negative	94 (30%)	53 (34%)	41 (27%)
Fungus	15 (5%)	10 (6%)	5 (3%)
No organism identified	80 (26%)	32 (20%)	48 (32%)
Other organism	6 (2%)	3(2%)	3 (2%)

[#]
p=0.03;^{*}
p<0.01

Notes:

^I
 χ^2 test

Table 2b

Type of second infection and culture results

Site of infection	n=76	Type of organism	n=76
UTI	20 (26%)	Gram positive	33 (43%)
Respiratory Tract infection	21 (28%)	Gram negative	29 (38%)
C. Difficile colitis	13 (17%)	No organisms	7 (9%)
Fungal	7 (9%)	Fungus	7 (9%)
Others	15 (20%)	Other organisms	0 (0%)

Table 2c

Risk factors for the development of second infection

Effect	Estimate	OR (95% CI)	Standard Error	Wald χ^2	p-value
MAP on admission	0.02	1.02 (1.00, 1.04)	0.01	3.97	0.0462
INR	0.25	1.29 (1.02, 1.61)	0.12	4.68	0.0306
Bilirubin	0.05	1.05 (1.01, 1.09)	0.02	5.41	0.0200

AKI+: with acute kidney injury; AKI-: without acute kidney injury; SBP: spontaneous bacterial peritonitis; UTI: urinary tract infection

Table 3**Patient Outcome According to Presenting Features**

a) Comparing patients who did or did not develop nosocomial infection				
	All Patients	Yes Nosocomial Inf	No Nosocomial Inf	P-value
n	330/337	50	280	
Number of Deaths	66/330 (20%)	16/50 (32%)	50/280 (18%)	0.0213 ¹
Transferred to ICU	107/329 (33%)	27/50 (54%)	80/279 (29%)	0.0004 ¹
Developed AKI	161/330 (49%)	32/50 (64%)	129/280 (46%)	0.0195 ¹
Length of hospital stay (days)	15.65 ± 26.84	19.96 ± 13.01	14.87 ± 28.58	0.0450 ²
MELD	20.13 ± 7.96	21.72 ± 7.71	19.85 ± 7.99	0.1270 ²
Complications:				
Mechanical ventilation	51/325 (16%)	12/48 (25%)	39/277 (14%)	0.0548 ¹
HE	192/327 (59%)	37/50 (74%)	155/277 (56%)	0.0171 ¹
Shock	62/326 (19%)	14/48 (29%)	48/278 (17%)	0.0524 ¹
Any new organ failure	202/330 (61%)	39/50 (78%)	163/280 (58%)	0.0082 ¹
Number of organ failures/patient (Median, IQR)	1.0 (0.0, 1.0)	1.0 (1.0, 2.0)	1.0 (0.0, 1.0)	0.0030 ³

b) Comparing patients with AKI at admission to those without AKI at admission				
	All Patients	AKI + at Admission	AKI – at Admission	P-value
n	166	73	93	
Number of Deaths	56/166 (34%)	25/73 (34%)	31/93 (33%)	0.9017 ¹
Transferred to ICU	76/165 (46%)	36/72 (50%)	43/93 (43%)	0.3717 ¹
Length of hospital stay (days)	17.78 ± 19.81	15.57 ± 14.18	19.53 ± 23.26	0.1800 ²
MELD	23.41 ± 7.80	26.42 ± 6.98	21.04 ± 7.61	< 0.0001 ²
Complications:				
Mechanical ventilation	43/162 (27%)	18/69 (26%)	25/93 (27%)	0.9098 ¹
HE	119/163 (73%)	54/72 (75%)	65/91 (71%)	0.6100 ¹
Shock	51/163 (31%)	22/72 (31%)	29/91 (32%)	0.8576 ¹
Any new organ failure	127/166 (77%)	58/73 (79%)	69/93 (74%)	0.4277 ¹
Number of organ failures/patient (Median, IQR)	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)	1.0 (0.0, 2.0)	0.8771 ³

Notes:

¹ Chi-square test, 1 d.f.

²Two sample t-test

³Wilcoxon Rank-sum test

AKI+: with acute kidney injury; AKI-: without acute kidney injury; HE: hepatic encephalopathy; ICU: intensive care unit; Inf: infection; MELD: Model for End-stage Liver Disease; IQR: Interquartile range

Table 4

Patient Outcome According to Renal Status and According to Treatment

a) Comparison of patients who did or did not develop acute kidney injury				
	All Patients	AKI+	AKI-	P-value Adjusted for MELD^d
n	337	166	171	
Number of Deaths	68 (20%)	56 (34%)	12 (7%)	<0.0001
Transferred to ICU	111/336 (33%)	76/165 (46%)	35 (20%)	0.0015
Length of hospital stay (days)	15.5±26.6	17.8±19.8	13.3±31.8	<0.0001
Complications:				
Mechanical ventilation	53/331 (16%)	43/162 (27%)	10/169 (6%)	0.0008
HE	196/334 (59%)	119/163 (73%)	77/171 (45%)	0.0023
Shock	64/333 (19%)	51/163 (31%)	13/170 (8%)	0.0002
Any new organ failure	206/337 (61%)	127/166 (77%)	79/171 (46%)	0.0003
Number of organ failures/patient (Median, IQR)	1 (0,1)	1 (1, 2)	0 (0, 1)	<0.0001

b) Comparison of patients with different types of treatment for AKI			
	Albumin Alone (n=59)	Albumin + midodrine + octreotide (n=87)	p-value
Number of Deaths	27.1% 16/59	34.5% (30/87)	0.3472 ^I
Transferred to ICU	44.1% (26/59)	42.5% (37/87)	0.8538 ^I
Length of hospital stay (days)	15.14 ± 14.03	18.86 ± 23.80	0.2386 ^I
MELD	23.44 ± 6.67	22.98 ± 8.49	0.7251 ^I
Complications:			
Mechanical ventilation	25.0% (14/56)	23.0% (20/87)	0.7827 ^I
HE	72.4% (42/58)	74.4% (64/87)	0.7889 ^I
Shock	36.8% (21/57)	25.3% (22/87)	0.1384 ^I
Any new organ failure	78.0% (46/59)	77.0% (67/87)	0.8924 ^I
Number of organ failures/patient	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)	0.6189 ²

c) Comparison of patients with and without renal recovery				
Renal Recovery	Complete	Partial	None	P-value
n	86	42	25	
Number of Deaths	13 (15%)	17 (40%)	20 (80%)	< 0.0001 ^I
Transferred to ICU	34 (40%)	19 (45%)	17 (68%)	0.0422 ^I
Length of hospital stay (days)	18.4±23.9	13.2±8.4	25.0±20.5	0.0696 ²

c) Comparison of patients with and without renal recovery				
Renal Recovery	Complete	Partial	None	P-value
MELD	23.3 ± 7.8	23.1 ± 8.1	23.8 ± 7.0	0.9446 ²
Complications:				
Mechanical ventilation	14/84 (17%)	13/41 (32%)	13/25 (52%)	0.0015 ¹
HE	58/84 (69%)	30/42 (71%)	23/25 (92%)	0.0692 ¹
Shock	21/86 (24%)	14/41 (34%)	14/25 (56%)	0.0115 ¹
Any new organ failure	64/86 (74%)	31/42 (74%)	24/25 (96%)	0.0565 ¹
Number of organ failures/patient (Median, IQR)	1 (0, 1)	1 (0, 3)	2 (1, 3)	0.0006 ³

Notes:

¹ χ^2 test

² Two-sample t-test

³ Wilcoxon Rank-sum test

⁴ The adjusted P-value was derived using an ANCOVA model with either a binomial logistic regression model, a linear regression model using ranks (LOS) or an ordinal logistic regression model (Number of Organ Failures)

HE: hepatic encephalopathy; ICU: intensive care unit; IQR: interquartile range

Table 5

Independent factors associated with a) the development of acute kidney injury, and b) 30-day mortality in a multi-variate logistic regression analysis

a)						
Effect	Estimate	OR (95% CI)	Standard Error	Wald χ^2	d.f.	p-value
WBC/1000	0.03	1.03 (0.99, 1.07)	0.02	2.43	1	0.1192
Na	-0.03	0.97 (0.94, 1.01)	0.02	2.03	1	0.1541
Second Infection (Yes)	0.75	2.12 (1.17, 3.83)	0.30	6.15	1	0.0131
MELD	0.11	1.12 (1.08, 1.16)	0.02	35.49	1	<0.0001
Age	0.01	1.01 (0.98, 1.04)	0.01	0.43	1	0.5122

b)						
Effect	Estimate	OR (95% CI)	Standard Error	Wald χ^2	d.f.	p-value
MAP at Admission	0.04	1.04 (1.01, 1.06)	0.01	7.65	1	0.0057
MELD	0.10	1.10 (1.04, 1.17)	0.03	11.01	1	0.0009
SBP Infection	0.94	2.56 (1.06, 6.20)	0.45	4.33	1	0.0375
Number of Organ Failures	1.29	3.64 (2.37, 5.61)	0.22	34.61	1	<0.0001
AKI Outcome				22.39	2	<0.0001
No AKI vs. Persistent/Progressive	-0.56	0.16 (0.07, 0.40)	0.28			
Transient vs. Persistent/Progressive	-0.72	0.14 (0.05, 0.36)	0.29			
Age	0.01	1.01 (0.97, 1.05)	0.02	0.21	1	0.6472

Table 6

Utility of Acute Kidney Injury in Predicting Mortality in Cirrhotic Patients Hospitalized with Infections

	Death	Survival	TOTAL
AKI +	56	110	166
AKI –	12	159	171
TOTAL	68	269	337

Sensitivity = $56/68 = 0.8235$

Specificity = $159/269 = 0.5911$

Positive Predictive Value = $56/166 = 0.3373$ (Type I error rate, α)

Negative Predictive Value = $159/171 = 0.9298$ (Type II error rate, β)