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ORIGINAL ARTICLE

Evolution of diagnostic criteria for acute kidney injury in patients with decompensated cirrhosis: A prospective study in a tertiary university hospital

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KEYWORDS
Cirrhosis;
Acute kidney injury;
ICA-AKI criteria;
Mortality

Summary
Background: Recently, changes in acute kidney injury (AKI) diagnostic criteria have been proposed (ICA-AKI criteria). However, in Brazil there is a paucity of data and analyses that evaluate AKI in patients with cirrhosis and determine the impact of the implemented AKI criteria changes. Therefore, this study sought to evaluate the incidence of AKI in patients with cirrhosis; to evaluate the agreement between traditional and ICA-AKI criteria; and to assess its clinical and laboratory characteristics, etiologies, risk factors and outcomes.
Methods: This is a prospective cohort study in hospitalized patients with cirrhosis and acute decompensation. The total number of hospitalizations was evaluated using the PWP statistical model for recurring events; *P* values < 0.05 were considered significant.
Results: A total of 154 admissions of 75 patients were included in the study. Among the hospitalizations, 89 (57.79%) met the ICA-AKI criteria. There was substantial agreement between both AKI classifications (Kappa 0.7293). The main etiology of AKI was pre-renal (59.55%), followed by renal (26.96%) and hepatorenal syndrome (10.11%). A multivariate analysis uncovered risk factors for ICA-AKI, including the MELD score ($P = 0.0162$, RR:1.055, 95% CI:1.010–1.101) and the use of furosemide ($P = 0.001$,RR:2.360, 95% CI:1.417-3.931). A univariate analysis found an association between in-hospital mortality and serum creatinine (sCr) ≥ 1.5 mg/dL($P = 0.0373$), MELD ($P = 0.0296$), bilirubin ($P = 0.0064$), and infection ($P = 0.0045$), while in the multivariate

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analysis, the bilirubin levels ($P = 0.0030$, RR:1.077, 95% CI: 1.025—1.130) and the presence of shock ($P = 0.0002$, RR:8.511, 95% CI: 2.746—26.377) were associated with in-hospital mortality. Among the hospitalizations with AKI, death was significantly associated with non-response to treatment and dialysis. Initial stage 1A-AKI had lower in-hospital mortality than stage 1B-AKI.
Conclusions: AKI incidence was high in this cohort of patients with decompensated cirrhosis, and substantial agreement between AKI definitions was observed. In-hospital mortality was associated with worse liver function, AKI, infection and the presence of shock. Also, sCr > 1,5 mg/dL remained an important prognostic factor.

Introduction

Acute kidney injury (AKI) is a common complication of cirrhosis. It has an incidence of 20% in hospitalized patients and is associated with a poor prognosis [1—5]. The traditional AKI diagnostic criterion was defined as an increased serum creatinine (sCr) > 50% from the baseline to a final value ≥ 1.5 mg/dL (133 ≥ μmol/L) [6,7]. However, sCr is considered a non-ideal marker for renal function, because it is influenced by body weight, nutritional status, race, age and gender [8]. Moreover, in cirrhosis, sCr is also affected by decreased creatine formation in muscles, which is secondary to malnutrition and sarcopenia, increased renal tubular secretion of creatinine, increased volume of distribution in cirrhosis that can dilute sCr, and the interference of its values by elevated bilirubin [8,9].

In recent years, changes have been proposed in the diagnostic criteria for AKI [10—12]. The change in the AKI definition has been evaluated in the context of cirrhosis, and the use of dynamic changes in sCr has become the main parameter in the definition of the diagnosis of AKI in patients with cirrhosis. According to the 2015 International Club of Ascites Meeting, AKI was defined as a sCr ≥ 0.3 mg/dL increase within 48 hours or a 50% increase in the known or presumed baseline sCr (ICA-AKI criteria), and it has three severity stages [13]. A cut-off value of sCr of 1.5 mg/dL should still be considered, since it is associated with meaningful clinical outcomes, such as in-hospital mortality [14]. However, there is a lack of studies that evaluate the application of ICA-AKI criteria in hospitalized Brazilian patients with cirrhosis.

Therefore, this study sought to evaluate the incidence of AKI in patients with cirrhosis; to evaluate the agreement between traditional and ICA-AKI criteria in the diagnosis of AKI; and to assess its clinical and laboratory characteristics, etiologies, risk factors, response to treatment, progression for liver transplantation, and mortality.

Materials and methods

Clinical design and Patient selection

The present study was a prospective cohort study that included patients with cirrhosis non-electively admitted from October 2016 to August 2017 at the Clinics Hospital of the University of Campinas (UNICAMP), Campinas, Brazil. The diagnosis of cirrhosis was performed by biopsy or by a combination of clinical, radiological, laboratory, and/or endoscopic findings. Inclusion criteria were patients with cirrhosis ≥ 18 years of age undergoing non-elective hospitalization. Exclusion criteria were hepatocellular carcinoma (HCC) beyond the Milan criteria [15] or any extra-hepatic neoplasia; pre-known chronic renal failure (glomerular filtration rate (GFR) < 60 mL/min/1.73m^2 per period ≥ 3 months) with proteinuria greater than 500 mg/24 hours, or morphological alterations compatible with chronic nephropathy on the ultrasound exam, or patients on dialysis prior to inclusion in the study; previous liver transplantation; presence of severe comorbidities; or lack of informed consent.

This evaluation occurred in the first 24 hours of hospital admission with clinical and laboratory data collected according to the institutional care routines. Follow-up was performed throughout the hospitalization until hospital discharge or until the evolution to liver transplantation or death. During follow-up, only the first episode of AKI was considered during each hospitalization. However, patients who were discharged and subsequently readmitted during the study period were included again, and each hospitalization was evaluated separately. After hospital discharge, patients were continued to be monitored for mortality at 30 and 90 days.

Variables evaluated

Demographic and anthropometric data were obtained, as well as the etiology of cirrhosis, comorbidities, previous liver complications [ascites, spontaneous bacterial peritonitis (SBP), esophageal varices, portal hypertensive bleeding, hepatic encephalopathy and HCC] and previous renal dysfunction. Serum biochemistry included albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin and fractions, international normalized ratio (INR), urea, creatinine, sodium, potassium, leukogram, total platelet count and C-reactive protein. Child-Turcotte-Pugh and MELD score were also evaluated [16,17].

Renal dysfunction evaluation

The traditional AKI diagnostic criterion was defined as an increased sCr > 50% from the baseline to a final value ≥ 1.5 mg/dL [6,7]. ICA-AKI criteria were defined as an increase of sCr ≥ 0.3 mg/dL within 48 hours or a 50% increase in the known or presumed baseline sCr [13]. Precipitating factors of renal dysfunction were evaluated, such as the use of nephrotoxic drugs in the last 30 days;

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conditions associated with hypovolemia and shock; the use of vasoactive drugs; previous use of diuretic medications; large volume paracentesis ($\geq$ 5 L) without albumin infusion in the last 30 days; infection within seven days prior to worsening renal function; recent portal hypertensive bleeding; acute portal vein thrombosis and surgery or trauma. Shock was defined according to the American College of Chest Physicians report [18].

The etiology of AKI was classified as pre-renal, hepatorenal syndrome (HRS, according to ICA-AKI criteria)[13], renal, and post-renal. Renal AKI were defined as evidence of structural renal disease [proteinuria > 500 mg/day, haematuria > 50 cells per high power field, abnormal ultrasonographic findings, urinary sodium excretion fraction > 1% (in the absence of use of diuretics)] and/or AKI immediately after shock or AKI during or after treatment with known nephrotoxic drugs with no other cause for renal dysfunction.

Baseline sCr was defined as the sCr of the last 7 days or, in case of absence, the sCr obtained in the previous 3 months, when available. In subjects without a previous sCr, the sCr on admission was used as the baseline [13]. The sCr upon hospital admission and at the time of diagnosis of AKI (ICA-AKI) as well as and the maximum sCr reached during evaluation were also measured. sCr measurement was performed by the non-compensated, colorimetric kinetic Jaffé method (Roche Diagnóstica Brasil Ltd.).

Three AKI stages were defined as follows: Stage 1: increase in sCr $\geq$ 0.3 mg/dL or an increase in sCr $\geq$ 1.5-fold to 2-fold from baseline (1A: peak level of sCr < 1.5 mg/dL, 1B: peak level of sCr $\geq$ 1.5 mg/dL); Stage 2: increase in sCr > 2-fold to 3-fold from baseline; Stage 3: increase of sCr > 3-fold from baseline or sCr $\geq$ 4.0 mg/dLwith an acute increase $\geq$ 0.3 mg/dL or initiation of renal replacement therapy [13].

The approach of AKI in patients with cirrhosis was made according to current international guidelines recommendations [13]. Initially, the use of diuretics was suspended, and venous hydration was performed as needed, associated with volume expansion with albumin (at a dose of 1 g/kg, maximum of 100 g/day, for two consecutive days). The AKI etiological investigation was also performed and included evaluation of the use of nephrotoxic drugs and/or iodinated radiological contrasts, investigation of infectious foci, performance of urine analysis, and ultrasound of the kidneys and urinary tract. Patients who did not respond to 48 hours of volume expansion with albumin and met the criteria for HRS were submitted to terlipressin (whenever possible) or noradrenaline in combination with 20% human albumin (20—40 g/day) until the sCr dropped below 1.5 mg/dL or baseline sCr values, with reevaluations every 2 days of treatment, up to a maximum of 14 days of treatment.

ICA-AKI response to treatment (resolution) was classified was either complete, partial or no resolution. A complete response was defined as the regression of the ICA-AKI stage at the endpoint, in relation to the ICA-AKI inclusion in the study, associated with a reduction in sCr levels below baseline or up to 0.2 mg/dL above baseline. Partial response was defined as the regression of the ICA-AKI stage with a reduction of sCr to $\geq$ 0.3 mg/dL above the baseline value. No resolution was defined when no ICA-AKI regression in the outcome was observed. Death was not considered as a progression of the ICA-AKI.

Ethical considerations

The Ethics Committees of the University of Campinas approved this study (number 2.040.432) and the study followed the 1975 Declaration of Helsinki. Informed consent was obtained from participants.

Statistical analysis

Frequency tables of the categorical variables with absolute frequency (*n*) and percentage (%) values, and descriptive statistics of the numerical variables with mean values, standard deviation (SD), minimum, maximum and median values were reported. The agreement between the two diagnostic criteria for AKI was assessed using the Kappa coefficient. To evaluate the factors associated with death, sCr $\geq$ 1.5 mg/dL, and ICA-AKI, the Prentice, Williams, and Peterson (PWP) model for recurrent events was used [19]. This statistical tool was necessary to allow the inclusion of more than one hospitalization per patient throughout the study. It also allowed weighting each variable in subjects with multiple admissions. Univariate and multivariate logistic regressions were performed where appropriate. In the multivariate logistic regression analysis, the variable selection criterion used was stepwise. The same model was used to compare death and non-death groups within the AKI group. The relative risk (RR) values and their 95% confidence intervals (95% CIs) were described. For the definition of risk factors for ICA-AKI in the first admission of each patient, the odds ratio (OR) was also described. A two-tailed probability value of < 0.05 was considered statistically significant. The SAS (Statistical Analysis System) for Windows, version 9.4 (SAS Institute Inc, 2002-2008, Cary, NC, USA) software package was used for the statistical analyses and was undertaken by biomedical statisticians from the Statistics Service at School of Medical Sciences of the University of Campinas.

Results

Study population

During the study period, 235 hospitalizations corresponding to 148 patients were evaluated. Of these, 39 hospitalizations (34 patients) were from non-cirrhotic patients and were excluded from the study. Of the remaining 196 hospitalizations (114 patients), 42 hospitalizations (39 patients) had at least one of the exclusion criteria. Thus, 154 hospitalizations (75 patients) met the criteria and became the study population. Fig. 1 shows the flowchart of the study and the population evaluated, according to the inclusion and exclusion criteria.

Characteristics of patients and hospitalizations

Of the 75 included patients, the mean age was 56.49 years (SD $\pm$ 9.65), and the majority were male (60%, 45 patients). The main etiology of cirrhosis was alcohol, either alone (36%, 27 patients) or in association with viral etiologies (56%, 42 patients). The vast majority of patients had already presented some complication of cirrhosis

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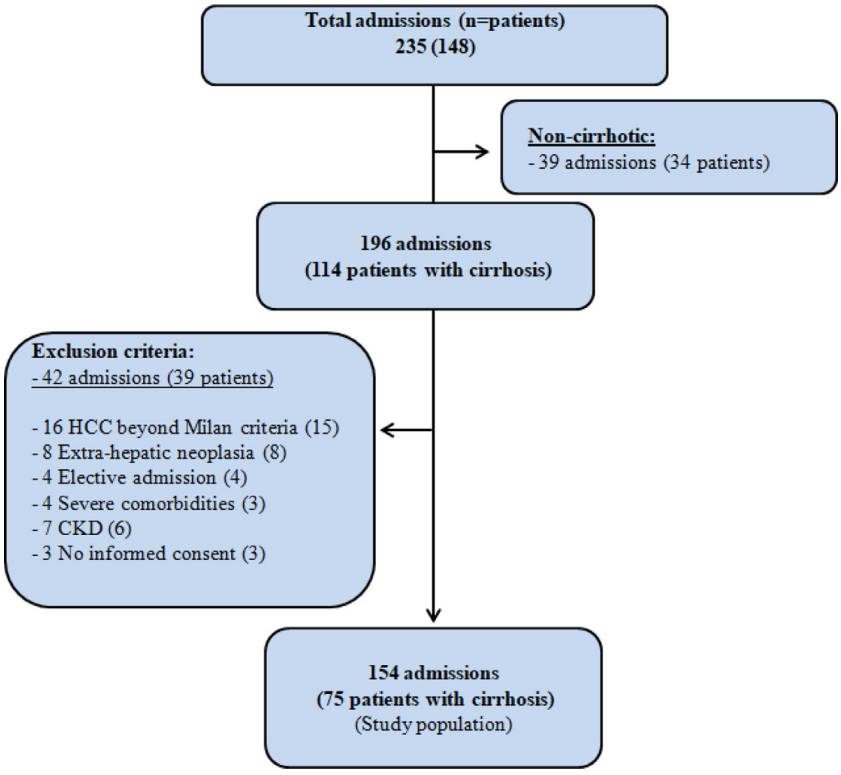

Figure 1 Flowchart of the study. HCC: hepatocellular carcinoma; CKD: chronic kidney disease.

before hospitalization. Ascites and esophageal varices were reported in 64 patients (87.67%). Twenty-four patients (32.88%) had already presented with renal dysfunction prior to enrollment in the study. Regarding liver prognostic scores, 30 patients were Child-Pugh B (40.5%), and 43 patients were Child-Pugh C (58.1%). Only one patient was Child-Pugh A, who was admitted for acute pancreatitis. The mean MELD score of hospitalized patients was 18.15. The main cause of hospitalization was large volume ascites, followed by SBP and hepatic encephalopathy. Table 1 shows the clinical characteristics of the 75 included patients and the mean laboratory data from all admissions.

AKI incidence and etiologies

Of the 154 hospitalizations evaluated, 89 (57.79%) had AKI according to the ICA-AKI criteria. When considering only the first hospitalization of each patient in the analysis, 41 of 75 patients presented AKI, resulting in an incidence of 54.67%. The main etiology was pre-renal, which was observed in 62 of the 89 admissions (69.66%), followed by renal, occurring in 24 hospitalizations (26.96%). Post-renal AKI was observed in 3.37% of those who had AKI. Analyzing the pre-renal AKI, 85.48% (53/62) were responsive to volume, while 14.51% (9/62) met HRS criteria (10.11% of all admissions with AKI). The mean albumin dose/kg/day for volume expansion in responders and non-responders was 0.94 ± 0.21 g and 0.90 ± 0.21 g, respectively. The mean changes in sCr after volume expansion with albumin were -0.56 ± 0.74 mg/dL for the responders and 0.51 ± 1.09 mg/dL for the non-responders (Fig. 2). Fig. 3 shows the incidence and etiology of AKI in this cohort. Regarding the traditional AKI diagnostic criterion, 71 hospitalizations (46.1%) had renal dysfunction.

Agreement between AKI diagnostic criteria

In the evaluation of agreement between the two AKI criteria, the ICA-AKI criteria and the traditional SCr criterion, the Kappa concordance value was 0.7293 (0.6237—0.8349), which represents a substantial concordance.

Factors associated with AKI occurrence

Among the analyzed variables in all admissions (obtained upon arrival of the patient or during hospitalization before AKI occurrence), those who had statistical significance in the PWP model in the univariate analysis as risk factors for AKI occurrence were: higher MELD score (20.0 ± 6.0 vs 14.5 ± 3.6, $P = 0.0301$, RR: 1.044, 95% CI: 1.004—1.085); lower serum sodium levels (132.5 ± 5.6 vs 134.1 ± 4.7 mEq/L, $P = 0.0087$, RR: 0.956, 95% CI: 0.924—0.989); use of furosemide ($P = 0.0053$, RR: 1.977, 95% CI: 1.224—3.193); use of spironolactone ($P = 0.0154$, RR: 1.831, 95% CI: 1.122—2.987); and non-alcoholic etiology of cirrhosis ($P = 0.0357$, RR: 1.670, 95% CI: 1.035—2.694), as shown in Table 2. In the multivariate analysis, the MELD score ($P = 0.0162$, RR: 1.055, 95% CI: 1.010—1.101) and the use of furosemide ($P = 0.001$, RR: 2.360, 95% CI: 1.417—3.931) were significantly associated with the occurrence of AKI by the ICA-AKI criteria. The admissions at higher risk of AKI occurrence were those whose patients had high MELD values and made use of furosemide. When only the first

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Table 1 Clinical characteristics of included patients and laboratory data of admissions.

Variables	Total of patients (75)
Age, years (mean ± SD)	56.49 ± 9.65
Gender (%)	
Male	45 (60%)
Female	30 (40%)
Etiology of cirrhosis (%)	
Alcohol	27 (36%)
Alcohol + HCV	13 (17.33%)
Alcohol + HBV	2 (2.67%)
HCV	12 (16.00%)
HBV	1 (1.33%)
Cryptogenic	13 (17.33%)
Others	7 (9.33%)
Previous complications of cirrhosis (%)	(73)
Ascites	64 (87.67%)
SBP	10 (13.70%)
EV	64 (87.67%)
PHB	33 (45.21%)
HE	37 (50.68%)
HCC	10 (13.70%)
Previous renal dysfunction	24 (32.88%)
Number of hospitalizations in 6 m (median CI)	3 (0—6)
Child-Pugh classification (%)	(74)
A	1 (1.35%)
B	30 (40.54%)
C	44 (59. 45%)
Child-Pugh Score (mean ± SD)	9.82 ± 1.63
Meld Score (mean ± SD)	18.15 ± 6.47
Meld-Na Score (mean ± SD)	20.63 ± 6.68
Comorbidities (%)	
Hypertension	23 (30.67%)
Diabetes	27 (36%)
Diuretics (%)	
Furosemide	45 (60%)
Spironolactone	47 (62.67%)
Beta-blocker (%)	34 (45.33%)

Variables	Total of Admissions (154)
Laboratory (mean ± SD)	
Albumin (g/dL)	2.63 ± 0.52
Total bilirubin (mg/dL)	3.93 ± 6.40
INR	1.56 ± 0.29
Urea (mg/dL)	60.35 ± 37.08
Sodium (mEq/L)	133.00 ± 5.31
Potassium (mEq/L)	4.53 ± 0.75
Leucocytes × 10^3	6.66 ± 4.01
Platelets × 10^3	109.50 ± 80.40
AST (U/L)	49.91 ± 36.26
ALT (U/L)	29.12 ± 28.60
C-reative protein (mg/dL)	34.70 ± 28.80

SD: standard deviation; HCV: hepatitis C virus; HBV: hepatitis B virus; SBP: spontaneous bacterial peritonitis; EV: esophageal varices; PHB: portal hypertensive bleeding; HE: hepatic encephalopathy; HCC: hepatocellular carcinoma; CI: confidence interval; m: months; Na: sodium; INR: international normalized ratio; AST: aspartate aminotransferase; ALT: alanine aminotransferase.

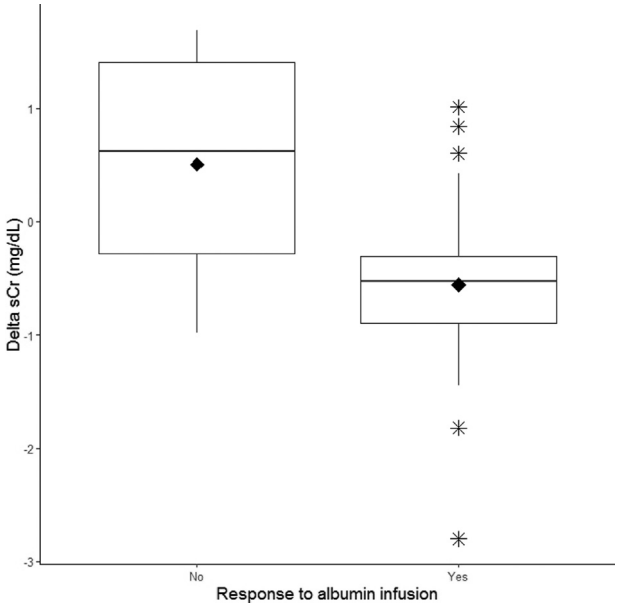

Figure 2 Delta serum creatinine after albumin expansion in responders and non-responders. sCr: serum creatinine.

admission of each patient was considered, in the univariate analysis, the risk factors for the occurrence of AKI by the ICA-AKI criteria were: higher MELD score ($P = <.0001$, OR: 1.307, 95% CI: 1.143—1.495), higher Child-Pugh classification ($P = 0.005$, OR: 4.142, 95% CI: 1.537—11.164) and lower albumin levels ($P = 0.0119$, OR: 0.288, 95% CI: 0.109—0.760), as shown in Table 3. In the multivariate analysis, only the MELD score ($P = 0.0001$, OR: 1.303, 95% CI: 1.139—1.490) was significantly associated with the occurrence of AKI.

Evolution of acute kidney injury (ICA-AKI)

Of the 89 hospitalizations with ICA-AKI, 69 (77.52%) occurred on admission, and the remaining 20 occurred during hospitalization. Fifty-nine (66.29%) hospitalizations with ICA—AKI at admission or during in-hospital stay were initially stage 1 (stage 1A: 22.47%; stage 1B: 43.82%), twenty-two (24.72%) were stage 2, and eight (8.98%) were stage 3. In 29.21% (26), there was stage progression. Of the initially stage 1 patients, 37.28% (22) progressed the renal dysfunction compared with 13.63% (3) of those initially at stage 2. When substratifying stage 1 admissions, 90% of those initially classified as S1A did not show renal dysfunction worsening, while in 53.8% admissions with S1B AKI stage progression took place (Fig. 4). When classified by etiology, 61.53% (16) of ICA-AKI stage progression cases corresponded to renal etiology. There was no progression of AKI stage in cases of post-renal etiology. The maximum ICA-AKI of hospitalizations was 41.57% (37) in stage 1, 31.46% (28) in stage 2, and 26.95% (24) in stage 3 (S3). Two-thirds of the cases of ICA-AKI maximum S3 corresponded to renal etiology.

Regarding the response to treatment, 46.6% (41) had complete resolution of the ICA-AKI, 24.72% (22) had partial response, and in 29.21% (26), there was no regression of the AKI stage. Of hospitalizations with a complete response to treatment, 87.8% (36) were classified as pre-renal, and 80.76% (21) of those without treatment response

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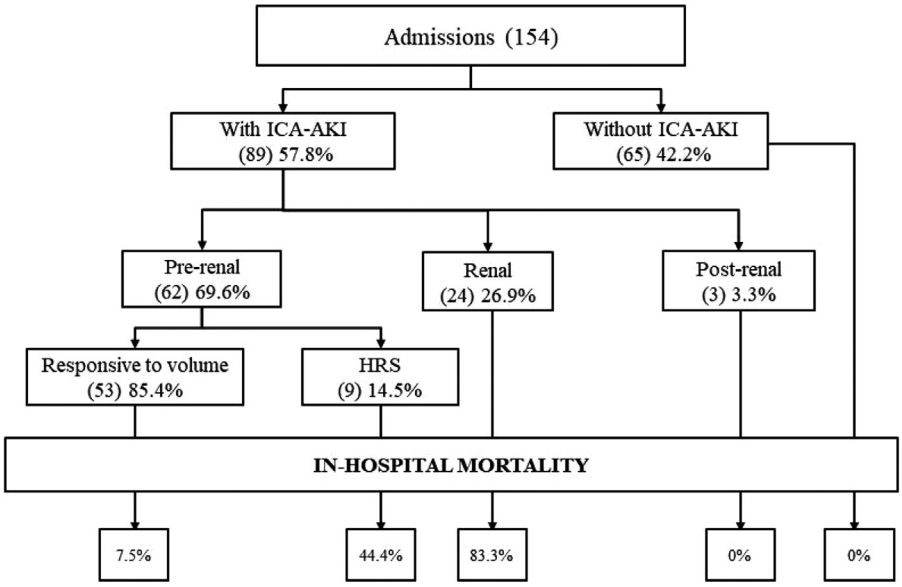

Figure 3 Incidence of acute kidney injury, etiologies and in-hospital mortality. ICA-AKI: International Club of Ascites - Acute Kidney Injury; HRS: hepatorenal syndrome.

corresponded to renal etiology. Of the 89 admissions with ICA-AKI, nine (10.22%) met HRS criteria. Six of these occurrences started treatment with 1 mg intravenous terlipressin in bolus every 6 hours. Two of them were switched to noradrenalin in the first day of treatment (one due to allergic reaction and the other because of the onset of dynamic ST-segment change on electrocardiogram). In the remaining three hospitalizations with HRS, vasoconstrictors (terlipressin or noradrenaline) were not administered. The mean terlipressin dose was 4 mg/day, the mean albumin dose was 40 g/day, and the mean treatment period was 9.5 days (3 to 14 days). In five cases (55.5%), there was response to treatment, but only one of these cases had sCr values that returned to baseline levels. All nine cases of HRS had already presented prior admission with volume responsive ICA-AKI. During the study period, eleven patients were submitted to renal replacement therapy, and all were at S3 at the time of indication. Nine (81.81%) corresponded to renal etiology and two cases were HRS not responsive to therapy.

Outcome: hospital discharge, liver transplantation, and death

In the follow-up of hospitalizations of this cohort, 124 of them (80.51%) resulted in patient hospital discharge, and two of them (1.29%) had patients transplanted during hospitalization. In total, seven patients underwent liver transplant up to 90 days of hospitalization. Of the nine HRS cases, four evolved to death (44%), and four (44%) were transplanted within 30 days of hospitalization.

During the evaluation period, 28 patients (18.18%) evolved with in-hospital death, all with some degree of AKI. Of these, twenty-six (92.85%) had sCr $\geq$ 1.5 mg/dL (P = 0.0373, RR: 4.754, 95% CI: 1.096—20.610). Along with sCr $\geq$ 1.5 mg/dL in the univariate analysis, among the admissions, the MELD score (P = 0.0296, RR 1.076, 95% CI: 1.007—1.149), the total bilirubin values (P = 0.0064, RR: 1.053, 95% CI: 1.015—1.093), and the presence of infection (P = 0.0045, RR: 2.139, 95% CI: 1.266-3.612) were associated with in-hospital death (Table 4). In the multivariate analysis, the variables independently associated with the risk of in-hospital death were the bilirubin levels (P = 0.0030, RR: 1.077, 95% CI: 1.025—1.130) and the presence of shock (P = 0.0002, RR: 8.511, 95% CI: 2.746—26.377). In the evaluation of mortality at 30 days and up to 90 days of hospitalization, 89.47% (34/38) and 82.35% (42/51) presented sCr $\geq$ 1.5 mg/dL, respectively.

Renal variables and association with in-hospital mortality

In the analysis of the individuals who had AKI, the variables that had a significant association with in-hospital mortality were the non-complete resolution of ICA-AKI (P = 0.0130), the partial non-resolution of AKI by ICA-AKI (P = 0.0004), and the need for renal replacement therapy (P = 0.0044). In fact, all patients who underwent dialysis during hospitalization evolved to death (11 patients). When stratifying renal dysfunction in only three stages (S1, S2 and S3), the maximum ICA-AKI stage 3 was nearly significant for mortality in patients with AKI (P = 0.0519). Table 5 shows the comparison between death and non-death among patients with AKI.

Twenty-six cases had progression of the AKI stage during hospitalization. Of these, 18 died, accounting for 64.28% of deaths. In 92.85% (26) of the deaths, sCr was $\geq$ 1.5 mg/dL. Table 6 presents a descriptive analysis of the renal variables associated with in-hospital mortality (total deaths). Since all cases of in-hospital death had AKI, it was not possible to calculate the P-value of these renal variables.

In the descriptive analysis, the etiology of AKI and ICA-AKI stage, especially if there was progression of AKI, showed higher in-hospital mortality. Fig. 3 illustrates in-hospital mortality according to the etiology of AKI, and Fig. 4 shows the in-hospital mortality according to the progression of AKI.

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Table 2 Risk factors for ICA-AKI development (total admissions).

	Without AKI (65)	With AKI (89)	*P*-value	RR	95% CI
Age (years) (mean ± SD)	57.7 ± 9.6	57.7 ± 8.5	0.7597	1.004	0.979—1.030
Gender, Male/Female (%)	40(61.5%)/25 (38.5%)	47(52.8%)/42(47.2%)	0.0904	0.670	0.422—1.065
Etiology, *n* (%)					
Non-alcoholic	**30 (46.15%)**	**45 (50.56%)**	**0.0357***	**1.670**	**1.035—2.694**
HCV	22 (33.84%)	16 (17.97%)	0.7834	1.085	0.607—1.939
HBV	8 (12.3%)	5 (5.61%)	0.7371	0.811	0.238—2.764
Cryptogenic	15 (23.07%)	24 (26.96%)	0.4765	1.221	0.704—2.117
Previous complications of cirrhosis, *n* (%) 65	65	87			
Ascites	62 (95.38%)	79 (90.80%)	0.0625	2.475	0.954—6.423
SBP	21 (32.3%)	22 (25.28%)	0.1858	1.568	0.805—3.051
EV	59 (90.76%)	80 (91.95%)	0.8413	0.921	0.412—2.058
PHB	33 (50.76%)	43 (49.42%)	0.9138	1.025	0.651—1.614
HE	32 (49.23%)	53 (60.91%):	0.6556	1.112	0.697—1.775
HCC	12 (18.46%)	16 (18.39%)	0.7327	1.112	0.605—2.044
Previous renal dysfunction, *n* (%)	36 (55.38%)	52 (59.77%)	0.2896	1.334	0.783—2.272
Child-Pugh classification, *n* (%)	65	87			
A	0	1 (1.14%)			
B	38 (58.46%)	36 (41.37%)			
C	27 (41.53%)	51 (58.62%)	0.6043	0.882	0.549—1.417
Child-Pugh Score (mean ± SD)	9.4 ± 1.4	10.0 ± 1.6	0.9058	1.009	0.870—1.171
Meld Score (mean ± SD)	**14.5 ± 3.6**	**20.0 ± 6.0**	**0.0301***	**1.044**	**1.004—1.085**
Comorbidities (%)					
Hypertension	12 (18.46%)	34 (38.2%)	0.1670	1.389	0.872—2.215
Diabetes	29 (44.61%)	45 (50.56%)	0.3730	1.246	0.768—2.022
Diuretics (%)					
Furosemide	**39 (60%)**	**51 (57.3%)**	**0.0053***	**1.977**	**1.224—3.193**
Spironolactone	**41 (63.07%)**	**54 (60.67%)**	**0.0154***	**1.831**	**1.122—2.987**
Beta-blocker (%)	33 (50.76%)	43 (48.31%)	0.5873	1.132	0.723—1.774
Nephrotoxic drugs (%)	13 (20%)	18 (20.22%)	0.0603	0.540	0.283—1.027
Surgery/Trauma (%)	2 (3.07%)	3 (3.37%)	0.4472	0.453	0.059—3.496
Albumin, g/dL (mean ± SD)	2.8 ± 0.5	2.5 ± 0.5	0.9787	1.006	0.643—1.574
INR (mean ± SD)	1.5 ± 0.3	1.6 ± 0.3	0.5096	0.744	0.309—1.791
Total bilirubin, mg/dL(mean ± SD)	2.6 ± 1.7	4.9 ± 8.2	0.1326	1.022	0.993—1.052
Sodium, mEq/L (mean ± SD)	**134.1 ± 4.7**	**132.5 ± 5.6**	**0.0087***	**0.956**	**0.924—0.989**
Urea, mg/dL (mean ± SD)	**43.7 ± 16.8**	**72.3 ± 42.7**	**0.0004***	**1.009**	**1.004—1.014**

PWP model — Univariate analysis; ***P* < 0.05**; AKI: Acute kidney injury; ICA-AKI: International Club of Ascites—Acute Kidney Injury; RR: relative risk; SD: standard deviation; HCV: Hepatitis C virus; HBV: Hepatitis B virus; SBP: spontaneous bacterial peritonitis; EV: esophageal varices; PHB: portal hypertensive bleeding; HE: hepatic encephalopathy; HCC: hepatocellular carcinoma; CI: confidence interval; INR: international normalized ratio.

Discussion

The present study described a high incidence of AKI, both designated by conventional criteria and by the ICA-AKI criteria. Moreover, a substantial correlation between the two criteria in the diagnosis of AKI was observed, that is, the majority of the AKI patients had sCr ≥ 1.5 mg/dL. The main etiologies of AKI were pre-renal responsive to volume, followed by renal and HRS. In the analysis of the risk factors associated with ICA-AKI, non-alcoholic etiology of cirrhosis, higher MELD scores, lower levels of serum sodium, and the use of diuretics were associated with its occurrence. The MELD score and the use of furosemide were independent variables for ICA-AKI occurrence. When analyzing only the first admission of each patient, the MELD score remained independently associated with ICA-AKI occurrence. The MELD score, the presence of infection, high bilirubin values, and sCr ≥ 1.5 mg/dL were associated with mortality. High bilirubin values and the presence of shock were also associated with death in the multivariate analysis. In patients who had AKI, significant association with in-hospital mortality was the progression of AKI despite the implemented therapies, including renal replacement therapy.

When considering only the first admission, ICA-AKI incidence was 54.67%. Taking into account the total number of hospitalizations, the incidence was 57.79%. These results are greater than those described in most studies using traditional AKI criteria [1—4]. Differently from our study, which also found a high incidence of AKI evaluated by the traditional criteria, other studies have shown that the application of newer AKI criteria increases the occurrence of this condition in hospitalized patients with cirrhosis [20]. Indeed,

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Table 3 Risk factors for ICA-AKI development (first admission).

	Without AKI (34)	With AKI (41)	*P*-value	OR	95% CI
Age (years) (mean ± SD)	56.1 ± 10.6	56.8 ± 8.9	0.7758	1.007	0.960–1.056
Gender, Male/Female (%)	21(61.8%)/13 (38.2%)	24(58.5%)/17(41.5%)	0.7764	0.874	0.345–2.215
Etiology, *n* (%)					
Non-alcoholic	14 (41.2%)	19 (46.3%)	0.6539	0.811	0.324–2.030
HCV	13 (38.2%)	12 (29.3%)	0.4132	0.668	0.255–1.754
HBV	2 (5.9%)	1 (2,4%)	0.4627	0.400	0.035–4.613
Cryptogenic	6 (17.6%)	7 (17.1%)	0.9478	0.961	0.289–3.189
Previous complications of cirrhosis, *n* (%)	34	39			
Ascites	31 (91.2%)	33 (84,6%)	0.4005	0.532	0.122–2.315
SBP	6 (17.6%)	4 (10.3%)	0.3647	0.533	0.137–2.076
EV	29 (85.3%)	35 (89.7%)	0.5659	1.509	0.371–6.142
PHB	17 (50%)	16 (41%)	0.4428	0.696	0.275–1.758
HE	18 (52.9%)	19 (48.7%)	0.7189	0.844	0.336–2.121
HCC	5 (14.7%)	5 (12.8%)	0.8149	0.853	0.224–3.240
Previous renal dysfunction, *n* (%)	9 (26.5%)	15 (38.5%)	0.2788	1.736	0.640–7.711
Child-Pugh classification, *n* (%)	**34**	**39**			
B	**20 (58.8%)**	**10 (25.6%)**			
C	**14 (41.2%)**	**29 (74.4%)**	**0.0050***	**4.142**	**1.537–11.164**
Meld Score (mean ± SD)	**14.5 ± 3.6**	**21.1 ± 6.8**	**< .0001***	**1.307**	**1.143–1.495**
Comorbidities (%)					
Hypertension	8 (23.5%)	15 (36.6%)	0.2252	1.875	0.679–5.178
Diabetes	12 (35.3%)	15 (36.6%)	0.9077	1.058	0.410–2.729
Diuretics (%)					
Furosemide	18 (52.9%)	27 (65.9%)	0.2574	1.714	0.674–4.357
Spironolactone	19 (55.9%)	28 (68.3%)	0.2703	1.700	0.662–4.370
Beta-blocker (%)	15 (44.1%)	19 (46.3%)	0.8474	1.094	0.439–2.728
Nephrotoxic drugs (%)	8 (23.5%)	8 (19.5%)	0.6728	0.788	0.261–2.383
Albumin, g/dL (mean ± SD)	**2.8 ± 0.5**	**2.4 ± 0.5**	**0.0119***	**0.288**	**0.109–0.760**
INR (mean ± SD)	1.5 ± 0.3	1.6 ± 0.3	0.0666	4.803	0.898–25.676
Total bilirubin, mg/dL(mean ± SD)	2.8 ± 1.8	7.4 ± 11.3	0.0673	1.185	0.988–1.422
Sodium,mEq/L (mean ± SD)	134.3 ± 4.9	132.7 ± 6.1	0.2098	0.945	0.865–1.032
Urea, mg/dL (mean ± SD)	**40.4 ± 15.8**	**69.3 ± 48**	**0.0025***	**1.038**	**1.013–1.063**

Logistic regression – Univariate analysis; ***P* < 0.05**; AKI: Acute kidney injury; ICA-AKI: International Club of Ascites–Acute Kidney Injury; OR: odds ratio; SD: standard deviation; HCV: Hepatitis C virus; HBV: Hepatitis B virus; SBP: spontaneous bacterial peritonitis; EV: esophageal varices; PHB: portal hypertensive bleeding; HE: hepatic encephalopathy; HCC: hepatocellular carcinoma; CI: confidence interval; INR: international normalized ratio.

Piano et al. (2013) have demonstrated that changing AKI criteria increases the rate of AKI detection in hospitalized patients with cirrhosis [14]. Wong et al. (2017) evaluated AKI in this context and found an incidence of 47%, while Huelin et al. (2017) followed 547 hospitalized patients with cirrhosis and described ICA-AKI in 53% of the population either at admission or during hospitalization [21,22]. Recently, Bansho et al. (2018) in a Brazilian cohort of decompensated patients with cirrhosis reported a lower prevalence of ICA-AKI (37%), but they only performed an admission evaluation, whereas the present study assessed AKI occurrence throughout the hospitalization period [23]. On the other hand, when evaluating patients with cirrhosis admitted to the intensive care unit, the occurrence of AKI according to ICA-AKI criteria rises to 73.0%, as recently reported by Xiong et al. (2018) [24].

The use of diuretics spironolactone and furosemide were risk factors for the onset of AKI in our population, and these findings are in agreement with previously published studies [25,26]. Despite the use of diuretics (based on percentages of all admissions) was higher in total admissions without AKI, their use was associated with AKI occurrence. The explanation for this is that the PWP methodology is not modeled by percentages. When we analyzed successive hospitalizations, the use of diuretics (spironolactone and furosemide) was more prevalent in the first admissions with AKI (data not shown). In the last hospitalizations, however, an absence of diuretics in admissions with AKI predominated (since the diuretics had already been withdrawn from patients who had AKI in previous admissions). Therefore, diuretics were associated with the occurrence of AKI (furosemide remained significant in the multivariate analysis), despite the seemingly contradictory results in Table 2. However, when taking into account only the first admission, AKI occurrence was associated only with worse liver function (Table 3). Martin-Llahi et al. (2011) showed that the most frequent causes of AKI in the population with cirrhosis were infections, followed by volume depletion, which was responsible for two thirds of the cases [27]. We also found the association of

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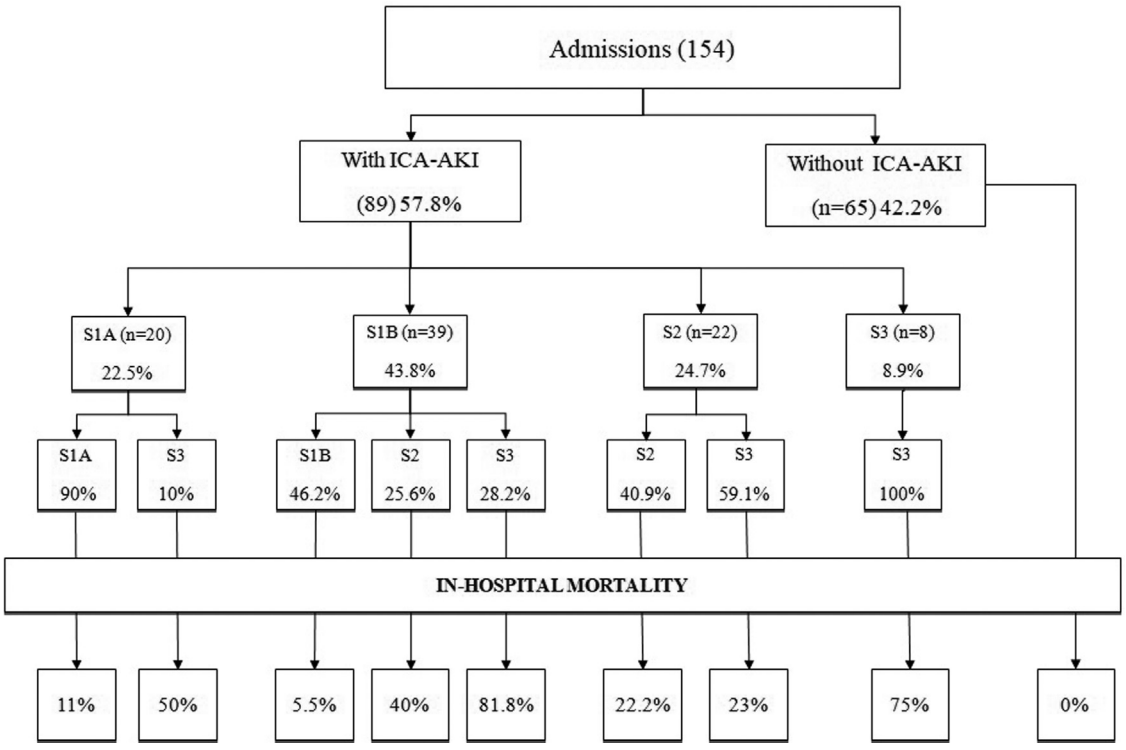

Figure 4 Staging/Progression of ICA-AKI versus Mortality. ICA-AKI: International Club of Ascites - Acute Kidney Injury; S: stage.

hyponatremia with ICA-AKI, probably reflecting the consequences of portal hypertension and bacterial translocation in advanced cirrhosis [28–30].

Regarding the etiology of renal injury in this study, the pre-renal type was the most prevalent (present in two thirds of cases), followed by renal etiology, HRS, and finally post-renal, (26.96%, 10.11%, and 3.37%, respectively). These data are in consonance with other reports and confirm that post-renal etiology is uncommon in this setting [31,32]. AKI was related to in-hospital mortality, especially when evaluating the etiology. The etiology of better prognosis was pre-renal, with 8% mortality, as opposed to renal etiology, with an in-hospital mortality rate of 83%. Allegretti et al. (2015) evaluated causes of AKI with mortality up to 90 days, and the pre-renal etiology was associated with lower mortality when compared to renal and HRS etiologies, the latter with no differences between them [33]. Martin-Llahi et al. (2011) showed divergent data: 3-month patient survival of 73% in parenchymal nephropathy, and 46%, 31%, and 15% survival ratein those with pre-renal AKI, AKI associated with infections, and HRS, respectively [27]. What may account for this difference is the fact that the authors classified AKI into four groups by adding an etiology of AKI associated with infection, which may have underestimated the mortality of the renal etiology group. In our cohort, infection was also associated with mortality. However, we did not evaluate the impact of the association of etiology with the presence or absence of infection and mortality.

Fagundes et al. (2013), in a prospective study involving 375 hospitalized patients with cirrhosis, evaluated the presence of AKI and mortality for up to 90 days [34]. Stage 1 patients were subdivided into two groups with markedly different prognoses: those with sCr < 1.5 mg/dL had similar survival to patients without AKI, and the subgroup with sCr peak ≥ 1.5 mg/dL, which had an intermediate survival between patients without AKI and patients with AKI Stage 2. Other studies have also associated the AKI stage with prognosis and survival [14,22,35,36]. In our study, when we addressed stage 1A and 1B, we also observed different mortality rates. Admissions with initial AKI stage 1A had 7.14% of non-survivor patients, while in those with AKI stage 1B, the rate of non-survivors was 53.57%. We also noted that the absence of resolution of AKI and the need for dialysis were associated with mortality. In fact, all of our patients who required renal replacement therapy died. It is noteworthy that AKI requiring dialysis seems to be increasing in hospitalized patients with cirrhosis [37]. Recent studies have shown that patients with advanced cirrhosis requiring renal replacement therapy present high mortality [38,39].

The baseline sCr variation of >0.3 mg/dL, while maintaining the sCr < 1.5 mg/dL, does not appear to be completely benign. It has a better response to treatment when early implemented and has lower rates of AKI progression and better prognosis. Thus, it is suggested to use the two parameters, that is, the ICA-AKI criteria and the cut-off value of 1.5 mg/dL, and/or AKI stage progression in order to titrate the intensity of AKI treatment in patients with cirrhosis. The recent EASL guideline reserves albumin expansion in those subjects with AKI stage > 1A or in those who had progressed the renal dysfunction and, similarly, indicates the treatment with vasoconstrictors in those who meet HRS criteria and have AKI stage >1A [30].

The present study has some limitations. Although hospitalized patients with cirrhosis had undergone specific

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Table 4 Risk factors for death (total admissions).

	Survivors (126)	Non-survivors (28)	*P*-value	RR	95% CI
Age, years (mean ± SD)	57.6 ± 9.0	58.3 ± 8.8	0.7575	1.007	0.963–1.052
Gender, Male/female	71(56.3%)/54(43.7%)	16 (57.1%)/13(42.9%)	0.2344	0.605	0.264–1.386
Previous complications of cirrhosis, *n* (%)	126	26			
Ascites	119 (94.44%)	22 (84.61%)	0.6704	1.291	0.398–4.191
SBP	41 (32.53%)	2 (7.69%)	0.9991	0.999	0.188–5.312
EV	118 (93.65%)	21 (80.76%)	0.0852	0.393	0.135–1.138
PHB	64 (50.79%)	12 (46.15%)	0.8017	0.899	0.392–2.063
HE	72 (57.14%)	13 (50%)	0.3918	0.692	0.297–1.609
HCC	23 (18.25%)	5 (19.23%)	0.2839	1.777	0.621–5.084
Previous renal dysfunction, *n* (%)	75 (59.52%)	13 (50%)	0.9774	0.986	0.373–2.606
Child-Pugh Score (mean ± SD)	9.6 ± 1.5	10.1 ± 1.8	0.5734	1.080	0.826–1.411
MELD Score (mean ± SD)	**16.9 ± 5.2**	**21.2 ± 7.0**	**0.0296***	**1.076**	**1.007–1.149**
Comorbidities (%)					
Hypertension	37 (29.36%)	9 (32.14%)	0.7863	0.886	0.370–2.123
Diabetes	62 (49.2%)	12 (42.85%)	0.5351	0.744	0.292–1.895
Diuretics (%)					
Furosemide	77 (61.11%)	13 (46.42%)	0.8630	1.075	0.472–2.450
Spironolactone	81 (64.28%)	14 (50%)	0.9206	0.959	0.423–2.174
Beta-blocker (%)	65 (51.58%)	11 (39.28%)	0.6104	0.811	0.361–1.818
Infection (%)	**49 (38.89%)**	**24 (85.71%)**	**0.0045***	**2.139**	**1.266–3.612**
Hypovolemia/Dehydration (%)	29 (23.01%)	13 (46.42%)	0.8480	1.048	0.646–1.701
Shock (%)	5 (3.96%)	20 (71.42%)	0.6243	0.876	0.517–1.486
Paracentesis (%)	69 (54.76%)	14 (50%)	0.3751	1.271	0.748–2.159
Nephrotoxic drugs (%)	23 (18.25%)	8 (28.57%)	0.0603	0.540	0.283–1.027
Creatinine ≥ 1.5 mg/dL (%)	**47 (37.3%)**	**26 (92.85%)**	**0.0373***	**4.754**	**1.096–20.610**
Peak ICA-AKI (65) (%)					
Stage 1A	16 (12.7%)	2 (7.1%)			
Stage 1B	17 (13.5%)	1 (3.6%)	0.4779	0.414	0.036–4.724
Stage 2	23 (18.3%)	6 (21.4%)	0.7992	0.798	0.141–4.524
Stage 3	5 (4%)	19 (67.9%)	0.2923	2.252	0.497–10.202
INR (mean ± SD)	1.6 ± 0.3	1.6 ± 0.3	0.8068	0.812	0.154–4.292
Total Bilirrubin, mg/dL (mean ± SD)	**3.1 ± 3.7**	**7.7 ± 12.2**	**0.0064***	**1.053**	**1.015–1.093**
Sodium, mEq/L (mean ± SD)	133.4 ± 4.9	132.0 ± 6.7	0.0949	0.955	0.905–1.008

PWP model – Univariate analysis; ***P* < 0.05**; AKI: Acute kidney injury; ICA-AKI: International Club of Ascites–Acute Kidney Injury; RR: relative risk; SD: standard deviation; HCV: Hepatitis C virus; HBV: Hepatitis B virus; SBP: spontaneous bacterial peritonitis; EV: esophageal varices; PHB: portal hypertensive bleeding; HE: hepatic encephalopathy; HCC: hepatocellular carcinoma; CI: confidence interval; INR: international normalized ratio.

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Table 5 Factors associated with mortality in patients with AKI ($n = 89$ admissions).

	Survivors ($n = 61$)	Non-survivors ($n = 28$)	*P*-value
Serum Creatinine mg/dL (mean ± SD)			
Baseline sCr	1.0 ± 0.3	1.0 ± 0.3	0.8834
Admission sCr	1.7 ± 0.8	1.7 ± 1.0	0.3619
Peak sCr	2.1 ± 0.8	3.3 ± 1.2	0.1004
Admission ICA-AKI (%)			
Stage 1A	17 (27.9%)	3 (10.7%)	
Stage 1B	25 (41%)	14 (50%)	0.8429
Stage 2	17 (27.9%)	5 (17.9%)	0.7984
Stage 3	2 (3.3%)	6 (21.4%)	0.2233
Peak ICA-AKI (%)			
Stage 1A	16 (26.2%)	2 (7.1%)	
Stage 1B	17 (27.9%)	1 (3.6%)	0.4781
Stage 2	23 (37.7%)	6 (21.4%)	0.7992
Stage 3	5 (8.2%)	19 (67.9%)	0.2923
Complete Resolution ICA-AKI (%)			
No	**23 (37.7%)**	**25 (89.3%)**	**0.0130***
Partial Resolution ICA-AKI (%)			
No	**3 (4.9%)**	**22 (81.5%)**	**0.0004***
Dialysis (%)	**0 (0%)**	**11 (39.3%)**	**0.0044***

***P* < 0.05**; AKI: Acute Kidney Injury; SD: standard deviation; sCr: serum creatinine; ICA-AKI: International Club of Ascites—Acute Kidney Injury.

Table 6 Renal variables and association with in-hospital mortality (total admissions).

Variable (n = admissions)	Total (n)	Survivors (126)	Non-survivors (28)
ICA-AKI, $n = 154$ (%)			
No	65 (42.21%)	65 (51.58%)	0
Yes	89 (57.79%)	61 (48.41%)	28 (100%)
Initial ICA-AKI, $n = 89$ (%)			
Stage1	59 (66.29%)	42 (33.33%)	17 (60.71%)
Stage 1A	18 (30.5%)	16 (38.09%)	2 (7.14%)
Stage 1B	41 (69.49%)	26 (61.9%)	15 (53.57%)
Stage 2	22 (24.72%)	17 (13.49%)	5 (17.85%)
Stage 3	8 (8.98%)	2 (1.58%)	6 (21.42%)
Progression of AKI, $n = 89$ (%)	26 (29.21%)	8 (6.34%)	18 (64.28%)
Resolution			
Complete	41 (46.06%)	38 (30.15%)	3 (10.71%)
Partial	22 (24.71%)	20 (15.87%)	2 (7.14%)
No Resolution	26 (29.21%)	3 (2.38%)	23 (82.14%)
Etiology of AKI, $n = 89$ (%)			
Pre-renal	53 (59.55%)	49 (38.89%)	4 (14.28%)
Renal	24 (26.96%)	4 (3.17%)	20 (71.42%)
HRS	9 (10.11%)	5 (3.96%)	4 (14.28%)
Post-renal	3 (3.37%)	3 (2.38%)	0 (0%)

ICA-AKI: International Club of Ascites—Acute Kidney Injury; HRS: hepatorenal syndrome.

nutritional assessment, such information was not systematically collected, and it was not possible to evaluate the role of malnutrition/sarcopenia on sCr assessment or even on outcomes [8,40]. Another caveat was that the quantification of diuresis was performed in an irregular manner, and there were missing data in the first 24 hours of admission. These difficulties in obtaining this parameter have already been described elsewhere [13,30]. The use of urinary biomarkers could also aid in the diagnosis of the etiology of AKI [41,42].

Finally, in clinical practice, it is noteworthy that patients with advanced cirrhosis are prone to AKI, with increased severity in subsequent admissions, especially with regard to HRS etiology. This led us to evaluate all hospitalizations during the study period, and not only the first hospitalization of each subject. Of the nine cases of HRS, all had previous admissions with volume responsive ICA-AKI. Therefore, the PWP model for recurrent events was adopted, which allowed weighting each variable in subjects with multiple admissions

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[19]. Interestingly, the mean number of non-elective hospitalizations per patient in the last six months was three, reflecting the severity of our cohort, which was also evidenced by the mean MELD score of 18.15. Nevertheless, the inclusion of only 75 patients was a limitation of the study.

Through this prospective cohort of patients with decompensated cirrhosis, it was possible to obtain the landscape of AKI in different stages and etiologies as well as its evolution and impact on mortality.

Conclusion

AKI incidence was high in this cohort of patients with decompensated cirrhosis, and substantial agreement between AKI definitions was observed. In-hospital mortality was associated with worse liver function, AKI, infection, and the presence of shock, and sCr > 1,5 mg/dL remained an important prognostic factor.

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Disclosure of interest

The authors declare that they have no competing interest.

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