A Dynamic Definition of Acute Kidney Injury Does not Improve Prognosis Assessment in Acutely Decompensated Patients with Cirrhosis

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Background/objectives: to compare the prognostic accuracy for 28 and 90-day transplant-free mortality of a modified CLIF-SOFA score (including a dynamic definition of acute kidney injury) with that of the classic CLIF-SOFA score and KDIGO score for acute kidney injury in patients with acute decompensation of cirrhosis. **Methods:** A retrospective analysis of all admissions of acutely decompensated patients with cirrhosis was carried out from January 2012 to December 2014. Classic and modified CLIF-SOFA scores were analyzed, as well as acute kidney injury diagnosis using the KDIGO score regarding their accuracy for 28- and 90-day transplant free mortality prediction. **Results:** 108 admissions were analyzed. Acute kidney injury diagnosis was met in 37 (34%) patients. Acute-on-chronic liver failure was diagnosed in 59 (55%) patients using the classic CLIF-SOFA score; and in 64 (59%) patients using the modified CLIF-SOFA score. Both CLIF-SOFA scores were highly effective in predicting 28-day transplant-free mortality (AUCROC 0.93 and 0.92, $p = 0.34$) as well as 90-day transplant-free mortality (AUCROC 0.79 and 0.78, $p = 0.78$). Acute kidney injury diagnosis had significantly lower accuracy in mortality assessment (28 and 90-day transplant free mortality AUCROC 0.67 [$p = 0.002$] and 0.63 [$p = 0.02$]). **Conclusions:** To our knowledge, this is the first evidence of the limited impact of modifying the fixed kidney injury definition currently used for acute-on-chronic liver failure. (J CLIN EXP HEPATOL 2017;7:135–143)

Accurately predicting prognosis in cirrhosis allows improving therapeutic strategies and organ allocation policies in liver transplantation.^{1,2} Recently, acute-on-chronic liver failure has been defined as the development of organ failure(s) in patients with cirrhosis admitted for an acute decompensating event and has been associated with elevated mortality. This syndrome is objectively defined and classified through the development of the CLIF-SOFA score, which assesses organ failure severity and its impact on survival.³ The individual influence of renal failure is remarkable, since it classifies as acute-on-chronic liver failure in absence of other organ dysfunctions when creatinine is equal or higher than 2 mg/dL.⁴

In patients with cirrhosis, renal failure has been defined as an increase in serum creatinine $\geq 50\%$ from baseline, to a final value higher than 1.5 mg/dL.⁵ Lately, this fixed threshold has been disputed, as when present, it is often associated with a severely reduced glomerular filtration rate.⁶ The KDIGO group proposed the term acute kidney injury, and defined this syndrome based on small creatinine changes over time, without a specific cut-off point.^{6–8} However, several prospective studies still highlight the importance of the 1.5 mg/dL serum creatinine threshold in predicting survival in patients with cirrhosis; in the recently published International Club of Ascites recommendations for the diagnosis of acute kidney injury, the authors state the need for additional studies to clarify this creatinine cut-off prognostic value.^{9–11}

The proposal of several acute kidney injury definitions has created confusion; the lack of extensive validation makes their selection difficult for the hepatologist or internal medicine specialist in every day clinical practice. In particular, the influence of dynamic changes of serum creatinine in acutely-ill patients with cirrhosis has not been extensively analyzed. Therefore we aim to evaluate which renal failure criteria shows better accuracy for predicting survival in a cohort of patients with cirrhosis admitted for an acute decompensating event: we will assess the prognostic accuracy of two previously validated scores: the KDIGO AKI score and the CLIF-SOFA score in

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Abbreviations: AUCROC: area under the curve of the receiving operating characteristic; CLIF-SOFA: Chronic Liver Failure-Sequential Organ Failure Assessment; HIV: human immunodeficiency virus; INR: international normalized ratio; KDIGO: Kidney Disease Improving Global Outcome; MELD: model for end stage liver disease

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comparison with a modified CLIF-SOFA score which includes dynamic acute kidney injury definitions.

PATIENTS AND METHODS

Study population. A retrospective clinical record analysis of all consecutive hospital admissions of patients with cirrhosis due to acute decompensating events was carried out. The information was obtained from the electronic clinical records from January 1st 2012 to December 31st 2014 in the Italian Hospital of Buenos Aires, Argentina. All medical care interventions for the beneficiaries are registered centrally in a computerized data repository, with only one electronic health record per person. Patient information from admission until discharge, transplant, death or end of study was obtained. For mortality prognostic accuracy the first hospitalization episode was considered; a latter episode was only considered if it occurred 90 days after the first enrollment. This was done to diminish the possibility of overestimating mortality of a repeated hospitalization episode occurring in a shorter period of time. The Clinical Research Committee of the aforementioned hospital approved the study, in accordance with the 1975 Declaration of Helsinki.

Inclusion Criteria

Inclusion criteria referred to patients older than 18 years with previous diagnosis of cirrhosis, based on liver biopsy, or a composite of clinical signs and findings provided by laboratory test, endoscopy and radiologic imaging. Patients hospitalized for at least one day who had an acute decompensating event of cirrhosis were included. Acute decompensating event were defined with the same criteria as used by the CANONIC group for the CLIF-SOFA score development, and were as follows: acute development of large ascites (grade II–III according to the International Ascites Club definitions) within less than two weeks (first or later episode, excluding patients with refractory ascites), acute encephalopathy (defined as the acute development of a change in mental status in a patient with previous normal consciousness and without evidence of acute neurologic disease, including patients with a first or new episode of encephalopathy but excluding those patients with chronic hepatic encephalopathy), gastrointestinal bleeding (upper and or lower gastrointestinal bleeding of any etiology), bacterial infections, or any combination of these events.³

Exclusion Criteria

Patients were excluded if they were pregnant, were admitted to the hospital for a scheduled procedure such as variceal endoscopic ligation, or surgical or percutaneous procedures (transjugular intrahepatic portosystemic shunt, therapeutic paracentesis for refractory ascites, etc.), patients

undergoing post-operative acute decompensation, had hepatocellular carcinoma outside Milan criteria or had human immunodeficiency virus (HIV) infection. Additionally, if a patient was admitted more than once, only the first hospitalization (or latter episode occurring ≥ 90 days from the initial enrollment date) was considered.

Baseline Evaluation

Demographic information, cirrhosis etiology, diagnosis of hepatocellular carcinoma, and the acute decompensating event responsible for hospital admission were recorded in every episode; laboratory data including complete blood counts and international normalization ratio (INR), serum creatinine, serum sodium, bilirubin and albumin values were obtained at admission, as well as clinical data referred to neurological, respiratory and cardiovascular function; including the need for mechanical respiratory assistance, vasopressors use or hemodialysis. Standard clinical prognostic scores (MELD and Child–Pugh score) were calculated at admission.

Follow-up Evaluation and Outcome

Information regarding patient evolution in every hospitalization episode was obtained. Possible outcomes considered were discharge, transplant or death; the considered follow up periods were 28 and 90 days from hospital admission. The worst clinical and biochemical parameters observed during the hospitalization period were documented, including laboratory tests, worse stage of hepatic encephalopathy according to the West Haven scale, need for mechanical respiratory assistance, vasopressors use or hemodialysis.

Prognostic Scores and Acute Kidney Injury Definitions

The following definition of acute kidney injury was considered:

- **KDIGO acute kidney injury definition:** Increase in serum creatinine by ≥ 0.3 mg/dL within 48 h; or increase in serum creatinine to ≥ 1.5 times from baseline, which is known or presumed to have occurred within the prior 7 days. The acute kidney injury criterion for decline in urine output was not used, as it was felt to be unreliable in patients with ascites and without a bladder catheter (in accordance with Revised consensus recommendations of the International Club of Ascites). In this definition, the following groups were considered:

No acute kidney injury: Patients who do not reach serum creatinine thresholds mentioned below, at admission or during the hospitalization episode.

Stage 1: serum creatinine increase 1.5–1.9 times from baseline values; or serum creatinine increase ≥ 0.3 mg/dL.

Stage 2: serum creatinine increase 2–2.9 times from baseline values.

Stage 3: serum creatinine increase 3 times from baseline values; or serum creatinine increase to ≥ 4.0 mg/dL; or initiation of renal replacement therapy.

The diagnosis of acute kidney injury by this score was performed at admission (if a serum creatinine value ≤ 7 day was available)

and/or in the initial 48 h of hospitalization (comparing with a serum creatinine value obtained at admission). Patients were classified in a categorical manner (KDIGO acute kidney injury grade 0-III at admission or in the initial 48 h).

The following prognostic scores were considered:

- **Classic CLIF-SOFA score:** The CLIF-SOFA score for acute-on-chronic liver failure diagnosis is detailed in the supplementary material (published online, Table S1). The following acute-on-chronic liver failure grades are considered:

No acute-on-chronic liver failure: No organ failure, or single-organ failure (liver, coagulation, circulation, respiratory) in patients with serum creatinine <1.5 mg/dL and no hepatic encephalopathy; or single cerebral failure in patients with serum creatinine levels <1.5 mg/dL.

Classic acute-on-chronic liver failure I: Single renal failure (sCr $\geq$ 2.0 mg/dL); or single-organ failure (liver, coagulation, circulation, respiratory) in patients with sCr levels ranging from 1.5–1.9 mg/dL and/or grades I-II hepatic encephalopathy; or single cerebral failure in patients with sCr levels ranging from 1.5–1.9 mg/dL.

Classic acute-on-chronic liver failure II: Patient fulfilling criteria for two organ failures (detailed in Table S1).

Classic acute-on-chronic liver failure III: Patient fulfilling criteria for three organ failures (detailed in Table S1).

Patients were classified in a categorical variable if they developed acute-on-chronic liver failure according to the classic CLIF SOFA criteria during the hospitalization period. Additionally, the most severe stage of acute-on-chronic liver failure at any point of the admission was registered.

- **Modified CLIF-SOFA score:** In this score the definition of renal failure used in classic CLIF-SOFA score is replaced by the KDIGO definition, including the 1.5 mg/dL serum creatinine cut-off point (supplementary material, Table S2). The following acute-on-chronic liver failure grades are considered:

No acute-on-chronic liver failure (modified score): No organ failure, or single-organ failure (liver, coagulation, circulation, respiratory) in patients without KDIGO criteria for acute kidney injury stage 1 and no hepatic encephalopathy; or single cerebral failure in patients without KDIGO criteria for acute kidney injury 1.

Modified acute-on-chronic liver failure I: Single kidney failure (AKI 1 + sCr $\geq$ 1.5 mg/dL); or single-organ failure (liver, coagulation, circulation, lungs) in patients with KDIGO AKI 1 + sCr < 1.5 mg/dL and/or grades 1–2 hepatic encephalopathy; or patients with single cerebral failure and KDIGO AKI 1 + sCr < 1.5 mg/dL.

Modified acute-on-chronic liver failure II: Patient fulfilling criteria for two organ failures (detailed in Table S2).

Modified acute-on-chronic liver failure III: Patient fulfilling criteria for three organ failures (detailed in Table S2).

Patients were classified in a categorical variable if they developed acute-on-chronic liver failure according to the modified CLIF-SOFA criteria during the hospitalization period; additionally, the most severe stage of acute-on-chronic liver failure at any point of the admission was registered.

Prognostic Accuracy

In order to compare the prognostic accuracy for 28-day and 90-day transplant-free mortality assessment of the classic and the modified CLIF-SOFA scores, both scores were calculated using the worst clinical and biochemical parameters observed during each admission, whereas for

the KDIGO criteria, the worst grade registered in the first 48 h of admission was considered.

Statistical Analysis

Data was collected using a standardized case report form. Results are showed in percentages, mean and standard deviation for normally distributed data and in median and interquartile range for non-normal distributed data. Bivariate analysis was performed with chi-square or Fisher's test (if any group had <5 patients), *t* Student's test or ANOVA for parametric data and for non-parametric test Mann-Whitney or Kruskal Wallis were used depending on the number of groups evaluated. Transplant-free mortality was assessed at a 28-day and 90-day intervals. The accuracy of the classic CLIF-SOFA score, modified CLIF-SOFA score and KDIGO criteria were evaluated estimating the area under the curve of the receiving operating characteristic (AUCROC). Every statistical test performed will consider a two-tail test and a *p* value below 0.05 for significance.

RESULTS

Study Population

During the study period, 148 admissions of patients with cirrhosis due to an acute decompensating event were recorded. Since several patients were admitted more than once, only the first hospitalization (or latter episode occurring $\geq$ 90 days from the initial enrollment date) was considered. Thus, 108 admissions in 104 patients were analyzed. For survival assessment only 93 admissions were considered, since 15 patients underwent liver transplantation during 90-days of follow-up and were subsequently excluded (patient distribution is shown in Figure 1).

Overall Patient Characteristics

The demographic and clinical characteristics of all patients are described in Table 1, as well as laboratory and clinical scores of each admission. The majority of patients were men (59%) and middle-aged (median 61 years old). Cirrhosis etiology distribution was broad, with similar percentages for hepatitis C, alcohol, cholestatic and cryptogenic cirrhosis. Regarding cirrhosis severity, most patients had advanced disease, with high baseline prognostic scores: median MELD score 18 (IQR 14.5–23) and median Child-Pugh score 11 (IQR 9–12). Prior acute decompensating events were present in 92% of the study cohort. When evaluating the 108 hospitalizations included, the most common cause for admission was hepatic encephalopathy.

Evolution and Outcome

Overall, there were 20 deaths during the study period; 11 occurred during the initial 28-days of follow-up and the remaining 9 during the period comprised between 29–90 days from enrollment. Regarding liver transplantation,

Figure 1 Distribution of patients with cirrhosis's admissions for acute decompensating events according to their inclusion criteria for 28-days and 90-days mortality analysis.

there were a total of 15; 8 were performed during the first 28-days from enrollment and 7 during the 29–90 following days.

Frequency and Characteristics of Patients with Acute Kidney Injury Determined by the KDIGO Criteria

Acute kidney injury diagnosis was met either at enrolment or during the first 48 h in 37 (34%) of the 108 hospitalizations: 27 (73%) classified as grade 1, 8 (22%) as grade 2 and the remaining 2 (5%) as grade 3. There were no significant differences regarding age, gender, cirrhosis etiology or acute decompensating event between patients who developed acute kidney injury and those without this diagnosis. However, patients with acute kidney injury had significantly lower values of albumin (2.4 g/dL [IQR 2–2.8] versus 2.8 g/dL [IQR 2.3–3]; $p = 0.03$) and serum sodium (131 mg/dL [IQR 129–135] versus 135 mg/dL [IQR 131–138];

$p = 0.01$) when compared to patients who did not developed acute kidney injury.

Frequency and Characteristics of Patients with Acute-on-Chronic Liver Failure Determined by the Classic and Modified CLIF-SOFA Score

When assessing acute-on-chronic liver failure using the classic CLIF-SOFA score, 59 patients (55%) were identified: 29 (49%) classified as grade I, 11 (19%) as grade II and the remaining 19 (32%) as grade III. The comparison of baseline characteristics and biochemical features of patients with and without acute-on-chronic liver failure according to the classic CLIF-SOFA are detailed in Table 2. Age and gender distribution was similar between both groups. There were no significant differences regarding the type of acute decompensating event that motivated hospital admission. However, hepatitis C was significantly more frequent in patients without ACLF. Regarding biochemical features,

Table 1 Baseline Characteristics of Patients with Cirrhosis Admitted to the Hospital due to an Acute Decompensating Event (*n* = 104).

Variable	Results
Patients (<i>n</i> = 104)	
Age (years) -median (IQR).	61.5 (50.5–67.5)
Sex (male) - no. (%)	62 (59.6%)
Cirrhosis etiology	
Hepatitis C- no. (%)	24 (23%)
Alcohol- no. (%)	20 (19.2%)
Cholestatic liver disease- no. (%)	19 (18.3%)
Cryptogenic- no. (%)	18 (17.3%)
Autoimmune hepatitis- no. (%)	14 (13.5%)
Other	9 (8.7%)
Hepatocellular carcinoma- no. (%)	7 (6.7%)
Admission episodes (<i>n</i> = 108)	
Cause of admission	
Hepatic encephalopathy - no. (%)	45 (41.7%)
Bacterial Infection- no. (%)	24 (22.2%)
GI hemorrhage - no. (%)	21 (19.4%)
Ascites- no. (%)	18 (16.7%)
Laboratory at admission	
Platelet count ($\times 10^9/L$)-median (IQR).	50.4 (31.7–73.8)
Serum bilirubin (mg/dL)-median (IQR).	3.05 (1.85–6.2)
Serum albumin (gr/dL)-median (IQR).	2.7 (2.2–2.9)
INR-median (IQR)	1.66 (1.47–1.97)
Serum creatinine (mg/dL)-median (IQR).	0.98 (0.73–1.47)
Serum sodium (mEq/L)-median (IQR).	134 (130–137)
Child–Pugh score -median (IQR)	11 (9–12)
MELD score -median (IQR)	18 (14.5–23)

Note: GI: gastro-intestinal.

patients with ACLF had significantly lower serum albumin levels and higher serum creatinine levels at admission.

Using the modified CLIF-SOFA score, 64 (59%) patients met criteria for acute-on-chronic liver failure: 30 (47%) classified as grade I, 15 (23%) as grade II and the remaining 19 (30%) as grade III. As reported with the classic CLIF-SOFA score, no significant differences were observed in demographic features or decompensating events that motivated hospital admission. Patients with ACLF according to the modified CLIF-SOFA criteria had also lower serum albumin levels and higher serum creatinine in comparison with patients without acute-on-chronic liver failure.

Outcome According to Acute Kidney Injury and Acute-on-Chronic Liver Failure Diagnosis

The 28 and 90-day mortality rates are shown in Table 3. Patients with acute-on-chronic liver failure diagnosed by

either score had significantly higher 28-day and 90-day mortality rates in comparison to patients who did not developed this syndrome. Noteworthy, patients with acute kidney injury had higher mortality than those without renal failure, with even superior rates to those described in patients with acute-on-chronic liver failure.

Prognosis Assessment: CLIF-SOFA Score versus Modified CLIF-SOFA Score

As previously stated, when assessing acute-on-chronic liver failure using the modified CLIF-SOFA score, 64 (59%) patients were identified in comparison to 59 (55%) patients classified as acute-on-chronic liver failure with the classic CLIF-SOFA score. The modified score thus identified 5 additional patients with acute-on-chronic liver failure. All these newly diagnosed patients were classified as grade 1. Moreover, 4 patients classified as acute-on-chronic liver

Table 2 Characteristics of Patients According to Acute-on-Chronic Liver Failure Diagnosis by Classic CLIF-SOFA Score (n = 108).

Hospital admissions (n = 108)	Acute-on-chronic liver failure (n = 59)	No acute-on-chronic liver failure (n = 49)	p value
Age (years)	61 (50–68)	63 (51–67)	1
Sex (male)	33 (55.9%)	31 (63.3%)	0.44
Cirrhosis etiology*			
Hepatitis C	8 (14.5%)	16 (32.7%)	0.02
Alcohol	13 (23.7%)	7 (14.3%)	0.30
Cholestatic liver disease	10 (18.2%)	9 (18.4%)	0.98
Autoimmune hepatitis	10 (18.2%)	4 (8.1%)	0.13
Cryptogenic	9 (16.4%)	9 (18.4%)	0.78
Other	5 (9%)	4 (8.1%)	0.86
Acute decompensating event			
Hepatic encephalopathy	24 (40.7%)	21 (42.9%)	0.81
Bacterial infection	13 (22%)	11 (22.4%)	0.95
Ascites	8 (13.6%)	10 (20.4%)	0.34
GI hemorrhage	14 (23.7%)	7 (14.3%)	0.21
Laboratory parameters			
Platelet count ($\times 10^9/L$)	77 (48–112)	78 (52–114)	0.86
Serum bilirubin (mg/dL)	3.1 (1.6–6.4)	3 (2.1–4.7)	0.62
Serum albumin (gr/dL)	2.4 (2–2.9)	2.8 (2.4–3)	0.01
INR	1.8 (1.5–2.1)	1.6 (1.45–1.94)	0.13
Creatinine (mg/dL)	1.16 (0.76–2.04)	0.9 (0.72–1.22)	0.006
Serum sodium (mEq/L)	134 (129–138)	133 (130–137)	0.98

Notes: * Considering 104 patients. **Laboratory parameters obtained at admission. GI: gastro-intestinal.

failure grade 1 by the classic CLIF-SOFA score were reclassified to grade 2 when applying the modified CLIF-SOFA score. The frequency and grades of acute-on-chronic liver failure in all admissions considering both scoring systems are shown in Table 4, highlighting newly diagnosed and re-classified patients with acute-on-chronic liver failure.

The accuracy of KDIGO acute kidney injury criteria and both classic and modified CLIF-SOFA scores for predicting 28-day and 90-day transplant-free mortality were estimated and compared by their areas under the curve of

the receiving operating characteristic (AUCROC). The results are shown in Table 5 and graphed in Figures 2 and 3. Both classic and modified CLIF-SOFA scores were highly effective in predicting 28-day transplant-free mortality (AUCROC 0.93 and 0.92 respectively), as well as 90-day transplant-free mortality (AUCROC 0.79 and 0.78 respectively). However, there were no differences observed in their prognostic accuracy.

The KDIGO criteria for acute kidney injury had a significantly lower prognostic accuracy at predicting

Table 3 Mortality Rates According to AKI Diagnosis by the KDIGO Criteria and ACLF Diagnosis by the CLIF-SOFA and Modified CLIF-SOFA Score.

Admissions (n = 108)	28-day mortality rate*	p	90-day mortality rate**	p
No acute kidney injury (n = 71)	4 (5.9%)	0.03	10 (15.1%)	0.02
Acute kidney injury (n = 37)	7 (21.9%)		10 (37%)	
No acute-on-chronic liver failure (n = 59) (Classic CLIF-SOFA)	0	0.002	4 (9.5%)	0.01
Acute-on-chronic liver failure (n = 49) (Classic CLIF-SOFA)	11 (19.6%)		16 (31.4%)	
No acute-on-chronic liver failure (n = 44) (Modified CLIF-SOFA)	0	0.005	4 (10.8%)	0.04
Acute-on-chronic liver failure (n = 64) (Modified CLIF-SOFA)	11 (18%)		16 (28.6%)	

Note: * Considering 100 patients; 8 patients were transplanted ≤ 28 days after enrollment. ** Considering 93 patients; 7 patients were transplanted during the 29–90 day period after enrollment.

Table 4 Hospitalization Episode Distribution According to ACLF Grades by the CLIF-SOFA and Modified CLIF-SOFA Score.

CLIF-SOFA score	Modified CLIF-SOFA score			
	No ACLF	ACLF Grade I	ACLF Grade II	ACLF Grade III
No ACLF	44	5*	0	0
ACLF Grade I	0	25	4**	0
ACLF Grade II	0	0	11	0
ACLF Grade III	0	0	0	19

Note: * 5 of the patients that were classified as No-ACLF by the CLIF-SOFA score, were classified and as grade I ACLF by the modified CLIF-SOFA score.

** 4 of the patients that were classified as grade I ACLF by the CLIF-SOFA score, were re-classified as grade II ACLF by the modified CLIF-SOFA score.

Table 5 Comparison of KDIGO-AKI Criteria, Classic and Modified CLIF-SOFA Scores for predicting 28-day and 90-day Free-transplant Mortality.

AUCROC	Classic CLIF-SOFA score	Modified CLIF-SOFA score	p value	KDIGO-AKI score	p value*
28-day free transplant mortality (n = 100)	0.93 (0.86–0.99)	0.92 (0.85–0.99)	0.34	0.68 (0.52–0.85)	0.002
90-day free transplant mortality (n = 93)	0.78 (0.65–0.91)	0.78 (0.64–0.92)	0.78	0.65 (0.52–0.77)	0.02

Note: *KDIGO AKI criteria showed a significantly lower AUCROC compared with both CLIF-SOFA scores.

28-day transplant free-mortality (AUCROC 0.67, $p = 0.002$) and 90-day transplant-free mortality (AUCROC 0.63, $p = 0.02$) when compared to either CLIF-SOFA scores.

DISCUSSION

In the present study, we found that the modified CLIF-SOFA, a prognostic score for acute-on-chronic liver failure

which includes a dynamic definition of acute kidney injury, has similar accuracy to predict both 28-day and 90-day transplant-free mortality when compared to the classic CLIF-SOFA score. These findings may seem negative, since mortality prediction was not optimized; however, this is the first evidence of the limited impact of modifying the fixed kidney injury definition currently used for acute-on-chronic liver failure assessment.

Figure 2 Area under the operating receiving curve for 28-day transplant-free mortality prediction according to the KDIGO AKI criteria, classic and modified CLIF-SOFA score.

Note: the area under the curve of the receiving operating characteristic (AUCROC) of the classic and modified CLIF-SOFA scores are 0.9270 (95% CI 0.86–0.99) and 0.9224 (95% CI 0.85–0.99; $p = 0.34$), respectively for 28-day transplant-free mortality prediction. The AUCROC of the KDIGO criteria is 0.6721 (95% CI 0.51–0.82; $p = 0.002$ in comparison with both CLIF-SOFA scores). The diagonal reference line indicates no discrimination.

Figure 3 Area under the operating receiving curve for 90-day transplant-free mortality prediction according to the KDIGO AKI score, classic and modified CLIF-SOFA score.

Note: the area under the curve of the receiving operating characteristic (AUCROC) of the classic and modified CLIF-SOFA scores are 0.7863 (95% CI 0.65–0.91) and 0.7829 (95% CI 0.64–0.92; $p = 0.78$), respectively for 90-day transplant-free mortality prediction. The AUCROC of the KDIGO criteria is 0.6267 (95% CI 0.52–0.77; $p = 0.02$ in comparison with both CLIF-SOFA scores). The diagonal reference line indicates no discrimination.

This study was inspired on the findings of prospective studies that suggest the kinetics of serum creatinine has a strong impact in survival of hospitalized patients with cirrhosis. These studies also proved that adding a 1.5 mg/dL serum creatinine cut-off point to the dynamic definition proposed by the KDIGO criteria may result in better risk stratification.^{9,10} The currently accepted acute-on-chronic liver failure definition is based on an ad hoc scoring system – the CLIF-SOFA score – using fixed serum creatinine values.^{3,12} Similarly, latter scores designed to assess prognosis in these patients (such as the CLIF-C ACLF score) also considered specific creatinine cut-off points.¹³ Based on the lack of data regarding the impact of creatinine changes in this setting, we designed a modified acute-on-chronic liver failure score that included a dynamic acute kidney injury definition combined with a 1.5 mg/dL serum creatinine cut-off point.

Both the classic and the modified CLIF-SOFA scores showed remarkably high accuracy in 28-days transplant free-mortality assessment (AUCROC above 0.9) with lower efficacy for 90-days mortality prediction (AUCROC 0.78). These findings are similar to those described by Angeli et al.⁶ The slightly higher accuracy found in our study is probably related to the fact that the worst stage of ACLF during each admission was considered. The lack of improvement in mortality assessment of the modified CLIF-SOFA score suggests that despite that a dynamic definition of acute kidney injury is useful for an earlier diagnosis and initiation of potentially effective treatment for this syndrome; it probably does not have enough strength by itself to improve the mortality prediction of a complex multi-organ failure prognostic score.

However, using a lower threshold for acute-on-chronic liver failure severity classification, such as implemented in the modified CLIF-SOFA score, resulted in 5 newly diagnosed patients and 4 re-classified patients to a more severe stage. Whether this redefinition could result in earlier and more rational application of therapeutic resources cannot be evaluated in this retrospective cohort, but should be considered for larger prospective studies.

The value of acute kidney injury as a sole prognostic marker in hospitalized patients with cirrhosis had been previously established; acute kidney injury diagnosis and its progression has shown correlation with survival in these of patients.¹⁴ This is why we compared the prognostic accuracy of acute kidney injury and acute-on-chronic liver failure scores. Despite the fact that in our study acute kidney injury diagnosis portrayed an even higher 28 and 90-days mortality rates than those observed in ACLF patients, it ultimately had worse prognostic accuracy for mortality than both CLIF-SOFA scores

These findings are most likely based on the fact that both acute-on-chronic liver failure scores evaluate not only kidney function, but also include respiratory, cardiovascular, cerebral and liver failure assessment, all which have

been thoroughly associated with poor prognosis in critically ill patients with cirrhosis.¹⁵ In a recently published paper by Angeli et al., acute-on-chronic liver failure stratification by the CLIF-SOFA score was found to be more accurate than KDIGO acute kidney injury stratification for mortality prediction⁶; our findings agree with these results, thus providing external validation.

We found that the prevalence of acute-on-chronic liver failure in patients with cirrhosis admitted for an acute decompensating event was 55–59%, quite higher than previously reported.^{3,16} This is probably due to the fact that in our protocol design we considered the worst clinical and biochemical parameters registered in each hospitalization, thus allowing us to analyze not only patients with acute-on-chronic liver failure at admission but also those who developed this syndrome during their hospital stay. Moreover, the study was performed in a liver transplant center, where patients are known to be sicker than in other institutions. In concordance, acute kidney injury diagnosis reached 34%, a higher proportion than reported by other authors.⁶

The present study had several limitations due to its retrospective design, which precluded from analyzing additional clinical and biochemical data in an orderly fashion; furthermore, the small proportion of events (deaths) did not allowed us to perform transplant-free survival curves. The utility of this new proposed score and its influence in hospitalized patient outcome thus needs to be analyzed in a prospective fashion.

CONCLUSIONS

A dynamic evaluation of acute kidney injury has recently been adopted due to its improvement in prognosis assessment in patients with acutely decompensated cirrhosis. However, in our cohort of acutely decompensated patients with cirrhosis, the addition of this dynamic evaluation of serum creatinine to the classic CLIF-SOFA score offered no advantage in prognosis assessment. Yet, it allowed detecting several additional patients with acute-on-chronic liver failure and re-classifying others in a more severe stage; whether this staging system could improve timing and thus treatment results should be prospectively evaluated.

AUTHOR CONTRIBUTIONS

Marciano S. and Mauro E. contributed equally to this study; they designed the study protocol, performed the research/collected research data, corrected the manuscript and provided analytical oversight. Dirchwolf, M collected research data, drafted the manuscript and provided analytical oversight. Debernardi ME performed the research/collected data and corrected the manuscript draft. Giunta D; Pagotto V. and Rojas L. revised and corrected the study

protocol, performed the statistical analysis and revised the manuscript for intellectual content. Gadano A. supervised the manuscript, corrected the study protocol, provided analytical oversight and revised the manuscript intellectual content. All authors have read and approved the final version.

CONFLICTS OF INTEREST

The authors have none to declare.

FUNDING/SUPPORT STATEMENT

None to declare.

Appendix A. SUPPLEMENTARY DATA

Supplementary material related to this article can be found, in the online version, at [doi:10.1016/j.jceh.2017.03.004](https://doi.org/10.1016/j.jceh.2017.03.004).

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