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

Sebastián Marciano [*,†], Ezequiel Mauro [*], Melisa Dirchwolf [*], María Emilia Debernardi [‡], Diego Giunta [†], Vanina Pagotto [†], Liliana Rojas [†], Adrián Gadano [*,†]

[*]Liver Unit, Hospital Italiano, Buenos Aires, PC 1181, Argentina, [†]Department of Research, Hospital Italiano, Buenos Aires, PC 1181, Argentina and [‡]Internal Medicine, Centro de Educación Médica e Investigaciones Clínicas Norberto Quirno "CEMIC", Buenos Aires, PC 1431, Argentina

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)**

Acute Kidney Injury

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 ≥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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Address for correspondence: Sección Hepatología, Hospital Italiano de Buenos Aires, Juan Domingo Perón 4190 - PC: 1181ACH - Ciudad Autónoma de Buenos Aires, Argentina.
E-mail: sebastian.marciano@hospitalitaliano.org.ar
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 radio; 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 o 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)