Research Article

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

A modified acute kidney injury classification for diagnosis and risk stratification of impairment of kidney function in cirrhosis

Claudia Fagundes[1,2,3,4,†], Rogelio Barreto[1,2,3,4,†], Mónica Guevara[1,2,3,4], Elisabet Garcia[2], Elsa Solà[1,2,3,4], Ezequiel Rodríguez[1,2,3,4], Isabel Graupera[1,2,3,4], Xavier Ariza[1,2,3,4], Gustavo Pereira[1,2,3,4], Ignacio Alfaro[1], Andrés Cárdenas[5], Javier Fernández[1,2,3,4], Esteban Poch[2,6], Pere Ginès[1,2,3,4,*]

[1]*Liver Unit, Hospital Clínic, University of Barcelona, Barcelona, Catalunya, Spain;* [2]*Institut d'Investigacions Biomèdiques August-Pi-Sunyer (IDIBAPS), Spain;* [3]*Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHED), Spain;* [4]*Instituto Reina Sofía de Investigación Nefrológica, Spain;* [5]*Gastroenterology Unit, Hospital Clínic, University of Barcelona, Spain;* [6]*Nephrology Unit, Hospital Clínic, University of Barcelona, Spain*

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Background & Aims: The Acute Kidney Injury Network (AKIN) criteria are widely used in nephrology, but information on cirrhosis is limited. We aimed at evaluating the AKIN criteria and their relationship with the cause of kidney impairment and survival.
Methods: We performed a prospective study of 375 consecutive patients hospitalized for complications of cirrhosis. One-hundred and seventy-seven (47%) patients fulfilled the criteria of Acute Kidney Injury (AKI) during hospitalization, the causes being hypovolemia, infections, hepatorenal syndrome (HRS), nephrotoxicity, and miscellaneous (62, 54, 32, 8, and 21 cases, respectively).
Results: At diagnosis, most patients had AKI stage 1 (77%). Both the occurrence of AKI and its stage were associated with 3-month survival. However, survival difference between stages 2 and 3 was not statistically significant. Moreover, if stage 1 patients were categorized into 2 groups according to the level of serum creatinine used in the classical definition of kidney impairment (1.5 mg/dl), the two groups had a significantly different outcome. Combining AKIN criteria and maximum serum creatinine, 3 risk groups were identified: (A) patients with AKI stage 1 with peak creatinine ⩽1.5 mg/dl; (B) patients with stage 1 with peak creatinine >1.5 mg/dl; and (C) patients with stages 2–3 (survival 84%, 68%, and 36%, respectively; p <0.001). Survival was independently related to the cause of kidney impairment, patients with HRS or infection-related having the worst prognosis.
Conclusions: A classification that combines the AKIN criteria and classical criteria of kidney failure in cirrhosis provides a better risk stratification than AKIN criteria alone. The cause of impairment in kidney function is key in assessing prognosis in cirrhosis.

Introduction

Since the pioneer studies of Sherlock and Schroeder, it has been known that impairment of kidney function is a common event in the natural history of cirrhosis and is associated with poor prognosis [1,2]. These as well as other studies reported a unique form of kidney failure that occurs in patients with cirrhosis due to severe hypoperfusion of the kidney related to an impairment in the systemic arterial circulation, with marked splanchnic arterial vasodilation leading to arterial hypotension [3]. Since then, this characteristic form of kidney failure has been known as hepatorenal syndrome [4–6]. On the other hand, a large number of subsequent studies have reported that patients with cirrhosis in addition to HRS may develop impairment of kidney function due to a variety of other causes, particularly volume depletion, bacterial infections, administration of nephrotoxic agents, and chronic kidney diseases, or a combination thereof [7–13].

The diagnosis of HRS is currently based on reaching a serum creatinine concentration above 1.5 mg/dl, together with the exclusion of other causes of kidney impairment [14,15]. By extension, the same cut-off level of serum creatinine has been used for the diagnosis of impairment of kidney function due to

Keywords: Cirrhosis; Ascites; Acute kidney injury; Kidney failure; Hepatorenal syndrome.
Received 7 December 2012; received in revised form 20 March 2013; accepted 18 April 2013; available online 10 May 2013
☆ DOI of original article: http://dx.doi.org/10.1016/j.jhep.2013.05.035.
* Corresponding author. Address: Liver Unit, Hospital Clínic, Villarroel, 170, 08036 Barcelona, Catalonia, Spain.
E-mail address: pgines@clinic.ub.es (P. Ginès).
† These authors contributed equally to this work.
Abbreviations: AKIN, Acute Kidney Injury Network; AKI, Acute Kidney Injury; HRS, hepatorenal syndrome; GFR, glomerular filtration rate; ICU, intensive care unit; CRP, C-reactive protein; SIRS, systemic inflammatory response syndrome; MELD, Model for End-Stage Liver Disease.

Table 1. Baseline demographic and clinical data, liver, kidney and circulatory function in the 375 patients included in the study.

Demographics	
Age, yr	61 ± 12 (25-91)
Sex, male	232 (62%)
Medical history	
Diabetes	110 (29%)
Hypertension	85 (23%)
Chronic kidney impairment*	46 (12%)
Preadmission serum creatinine (mg/dl)**	1.0 ± 0.4 (0.3-3.6)
Treatment with beta-blockers	79 (21%)
Etiology of cirrhosis	
Alcoholic	153 (41%)
Hepatitis C	130 (35%)
Alcoholic + hepatitis C or B	42 (11%)
Other	50 (14%)
Cause of admission	
Infection***	130 (35%)
Gastrointestinal bleeding	91 (24%)
Ascites	66 (17%)
Hepatic encephalopathy	36 (10%)
Other causes	52 (14%)
Admission at intensive care unit	72 (19%)
Variables of kidney, liver and circulatory function	
Serum bilirubin (mg/dl)	5.0 ± 6.5 (0.2-36.3)
Serum albumin (g/L)	28 ± 5 (15-41)
INR	1.5 ± 0.5 (1.0-5.4)
MELD score	18 ± 7 (6-40)
Child-Pugh score A/B/C	9 ± 2 (5-14) 10%/49%/41%
Serum creatinine (mg/dl)	1.3 ± 0.8 (0.3-6.5)
Glomerular filtration rate (ml/min/1.73 m^2)****	66 ± 35 (7-225)
Serum sodium (mEq/L)	134 ± 6 (111-153)
Serum potassium (mEq/L)	4.3 ± 0.8 (2.2-7.1)
Ascites at admission	253 (68%)
Encephalopathy at admission	143 (38%)
Mean arterial pressure (mmHg)	83 ± 16 (37-135)
Heart rate (bpm)	93 ± 21 (48-150)
Leukocyte count (10^9 cells/L)	7.5 ± 4.6 (0.9-30)
C-reactive protein (mg/dl)	3.9 ± 5.0 (0.02-27.7)
Presence of SIRS*****	110 (29%)
Shock	61 (16%)

Values are given as mean ± SD (range) or number and percentage.
*HRS type 2 in 10, intrinsic nephropathy in 27, unknown in 9.
**See definition in Patients and methods. Available in 335 patients.
***Non-spontaneous bacterial peritonitis infection in 109 patients (urinary tract infection in 36, spontaneous bacteremia in 19, pneumonia in 16, soft tissue and skin infection in 9, others in 29) spontaneous bacterial peritonitis in 21 patients.
****Estimated by MDRD.
*****SIRS (systemic inflammatory response syndrome) was available in 308 patients.

causes other than HRS. This criterium of diagnosis has high specificity but low sensitivity, because in cirrhosis a serum creatinine of 1.5 mg/dl indicates a marked reduction in glomerular filtration rate (GFR) [16,17]. Some studies have used criteria based on an increase in serum creatinine with respect to baseline (usually 25% or 50%), together with a peak value above 1.5 mg/dl.

In nephrology, the diagnosis of acute impairment of kidney function has been an area of great controversy. Recently, the Acute Kidney Injury Network (AKIN) proposed new diagnostic criteria for acute impairment in kidney function, known as Acute Kidney Injury (AKI) [18]. The AKIN criteria are based on changes in serum creatinine in the short-term and are accurate in early detection of impairment of kidney function in the general population of hospitalized patients and also in predicting prognosis. For this reason, these criteria are being used extensively in the nephrology and intensive care fields. However, information on the AKIN criteria in patients with cirrhosis is still very limited [19,20]. Therefore, these criteria require validation in large series of patients. On the other hand, despite their potential usefulness, these criteria do not provide information on the different causes of impairment of kidney function in cirrhosis. This distinction is important because the outcome and management differ depending on the cause of kidney impairment [3,13]. Based on this, the current study was designed to evaluate prospectively the AKIN criteria and their relationship with the cause of impairment in kidney function and survival in a large series of consecutive patients hospitalized for complications of cirrhosis.

Patients and methods

Study population

Three hundred and seventy-five consecutive patients with cirrhosis hospitalized from July 2009 to August 2011 were included in a prospective study. Both patients admitted to the regular ward (303 patients, 80.8%) or ICU (72 patients, 19.2%) were included. Patients admitted for diagnostic procedures or elective therapeutic interventions (i.e., large-volume paracentesis, variceal band ligation, percutaneous tumor ablation) were not included. Other exclusion criteria were: (1) hepatocellular carcinoma outside Milan criteria or advanced non-hepatic neoplasia; (2) previous liver or kidney transplantation; and (3) chronic kidney disease under hemodialysis treatment before admission.

Study design

At admission, liver, kidney, and circulatory function were assessed in all patients. Previous complications of cirrhosis as well as the presence of chronic diseases, such as diabetes mellitus, arterial hypertension, and chronic impairment of kidney function were recorded. Kidney function was assessed by measuring serum creatinine concentration at regular intervals during hospitalization. Special emphasis was made on the identification of causes potentially related to development of kidney impairment, particularly loss of extracellular fluid, gastrointestinal bleeding, treatment with potentially nephrotoxic agents, and bacterial infections. The study was approved by the Institutional Review Board and all patients provided written informed consent to participate.

Definitions

Impairment of kidney function

Impairment of kidney function was defined using the AKIN criteria and graded in stage 1, 2, and 3 [18]. If a particular patient developed two episodes of AKI during hospitalization, only the first episode was considered.

Using the AKIN criteria, AKI in hospitalized patients is defined whenever there is an increase in serum creatinine $\geqslant$0.3 mg/dl or $\geqslant$50% in two measurements 48 h apart. The development of AKI is estimated by comparing serum creatinine at admission with that obtained 48 h later. Subsequently, the development of AKI is evaluated at 48-h intervals, in which the baseline is the serum creatinine value at the beginning of the period and the end value is that of the end of the period.