Research Article
Cirrhosis and Liver Failure

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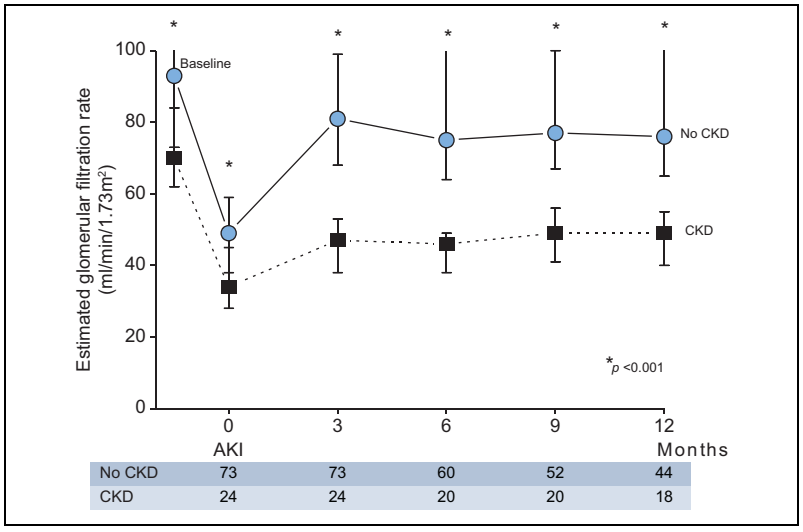
Development of chronic kidney disease after acute kidney injury in patients with cirrhosis is common and impairs clinical outcomes

Graphical abstract



Highlights

- Chronic kidney disease develops in up to 25% of patients with cirrhosis who survive an episode of acute kidney injury.
- Risk factors for the development of chronic kidney disease are nosocomial acute kidney injury and increased severity.
- Transition to chronic kidney disease is associated with increased risk of acute kidney injury, cirrhotic complications and hospital re-admissions.

Authors

Octavi Bassegoda, Patricia Huelin, Xavier Ariza, …, Esteban Poch, Elsa Solà, Pere Ginès

Correspondence

pgines@clinic.cat (P. Ginès).

Lay summary

Episodes of acute impairment of kidney function are common in patients with cirrhosis. This study shows that the development of chronic impairment of kidney function is frequent in patients surviving these acute episodes and that it is associated with a higher risk of developing other complications of cirrhosis and to a higher rate of 3-month hospital readmissions.

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Research Article
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Development of chronic kidney disease after acute kidney injury in patients with cirrhosis is common and impairs clinical outcomes ☆

Octavi Bassegoda[1,2,3,†], Patricia Huelin[1,2,3,†], Xavier Ariza[4], Cristina Solé[1,2,3], Adrià Juanola[1,2,3], Jordi Gratacós-Ginès[1,2,3], Marta Carol[2,3,5], Isabel Graupera[1,2,3], Elisa Pose[1,2,3], Laura Napoleone[1,2,3], Sonia Albertos[1,2,3], Gloria de Prada[1,2,3], Marta Cervera[2,3,5], Javier Fernández[1,2,3], Núria Fabrellas[2,3,5], Esteban Poch[5,6], Elsa Solà[1,2,3,5,‡], Pere Ginès[1,2,3,5,*,‡]

[1]*Liver Unit, Hospital Clínic de Barcelona, University of Barcelona, Barcelona, Catalonia, Spain;* [2]*Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Catalonia, Spain;* [3]*Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEReHD), Barcelona, Catalonia, Spain;* [4]*Digestive Diseases Unit, Hospital Moisès Broggi, Sant Joan Despí, Catalonia, Spain;* [5]*Faculty of Medicine and Life Sciences, University of Barcelona, Barcelona, Catalonia, Spain;* [6]*Nephrology Unit, Hospital Clínic, University of Barcelona, Barcelona, Catalonia, Spain*

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Background & Aims: Acute kidney injury (AKI) is common in cirrhosis and is associated with poor prognosis. In patients who survive after AKI, it is not known whether the acute injury leads to chronic impairment of kidney function (chronic kidney disease [CKD]). The aim of the study was to determine the frequency of CKD at 3 months after an AKI episode and its effects on patient outcomes.
Methods: Patients admitted for complications of cirrhosis during a 6.5-year period were evaluated using the same protocol, with assessment of kidney function at regular intervals during and after hospitalization. CKD was defined as estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m^2 at 3 months after AKI.
Results: A total of 409 patients (168 with AKI and 241 without AKI) were included. After 3 months, 97 patients with AKI and 188 patients without AKI had survived. Of the 97 patients with AKI, 24 had developed CKD at 3 months compared to only 2 of the 188 patients without AKI (25% *vs.* 1%, odds ratio 31; p <0.0001). Risk factors independently associated with CKD were nosocomial AKI and severity of AKI (stage ≥1B). At diagnosis of CKD, all patients had stage 3A CKD and one-quarter of them progressed to stages 3B and 4 after 1 year. The transition from AKI to CKD was associated with an increased rate of 3-month hospital readmission, increased frequency of AKI, bacterial infections, ascites, and refractory ascites and a trend towards a higher need for liver transplantation. Transplant-free survival was not impaired.
Conclusions: CKD frequently develops in patients with cirrhosis who survive AKI and has a negative impact on relevant clinical outcomes. The transition from AKI to CKD is common and should be considered a high-risk condition in patients with cirrhosis.

Lay summary: Episodes of acute impairment of kidney function are common in patients with cirrhosis. This study shows that the development of chronic impairment of kidney function is frequent in patients surviving these acute episodes and that it is associated with a higher risk of developing other complications of cirrhosis and to a higher rate of 3-month hospital readmissions.

Introduction

Acute impairment of kidney function occurs very commonly in patients with decompensated cirrhosis and is associated with poor prognosis.[1–4] In recent years, a new definition and diagnostic criteria for acute impairment of kidney function, known as acute kidney injury (AKI), has emerged. The definition of AKI has been validated in patients with cirrhosis and is included in the most recent international guidelines for patients with decompensated cirrhosis.[5,6] The concept of AKI has been a major step forward in the diagnosis of acute impairment of kidney function in clinical practice and has stimulated research in this field. Some important new concepts have emerged from the research on AKI in cirrhosis in recent years, including; i) staging of patients with AKI in 4 different categories (1A, 1B, 2, and 3) that correlates with clinical outcomes;[6,7] ii) relevance of baseline serum creatinine in the prediction of outcomes;[8,9] iii) relevance of urinary output as an important prognostic factor in patients with AKI;[10] iv) outcome of renal replacement therapy in patients with AKI;[11] and v) identification of some kidney biomarkers able to establish with high accuracy the differential diagnosis between hepatorenal syndrome (currently known as HRS-AKI) and acute tubular necrosis (ATN).[12–15]

Despite this important progress, some relevant questions related to AKI in cirrhosis still remain unanswered. One of these questions is the outcome of kidney function of patients who survive an episode of AKI; particularly, whether the recovery of renal function is complete or whether AKI leads to chronic impairment of kidney function. Studies in the general population have shown that CKD may occur after severe AKI and have a negative impact on kidney and patient outcomes.[16,17] The prevalence of CKD is high in

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* Corresponding author. Address: Liver Unit, Hospital Clínic de Barcelona, Barcelona, Catalonia, Spain.
E-mail address: pgines@clinic.cat (P. Ginès).
† Contributed equally as co-first authors.
‡ Co-senior authors.
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patients with cirrhosis, particularly among patients with decompensated cirrhosis.[7] This may be related at least in part to the high prevalence of predisposing factors to CKD, particularly diabetes mellitus and arterial hypertension. However, it is also possible that CKD will have developed as a consequence of an episode of AKI in some patients.

In this context, we aimed to investigate whether CKD occurs after AKI in cirrhosis and has an impact on the evolution of disease and clinical outcomes.

Patients and methods

Study population

From July 2009 to December 2015, all patients with cirrhosis admitted to the Liver Unit of Hospital Clínic of Barcelona for management of decompensated cirrhosis were included in a prospective database aimed at evaluating pathogenic and clinical aspects of impairment of kidney function in cirrhosis. Cirrhosis was diagnosed either by liver biopsy or a combination of clinical, biochemical, ultrasonography, and/or endoscopy findings. Exclusion criteria were: i) age <18 or >85 years, ii) lack of baseline serum creatinine value prior to admission, iii) hepatocellular carcinoma outside Milan criteria, iv) extrahepatic malignancies, v) severe comorbidities, vi) previous kidney or liver transplantation, vii) HIV infection, and viii) lack of written informed consent. Patients admitted for scheduled diagnostic or therapeutic procedures were not included. Patients with CKD before admission were analyzed separately for comparison.

Study design and objectives

Demographic, clinical and analytical data were collected prospectively at admission and during hospitalization. For the purpose of the study, patients were classified into 2 groups according to development of AKI: the AKI group and non-AKI group. AKI could be either present at admission or develop during hospitalization. After discharge from hospital, patients were followed-up in the outpatient clinic for at least 12 months or until transplantation or death. Visits at the clinic were scheduled at regular intervals during follow-up, usually within the first 1–2 weeks after discharge and then at approximately 3-month intervals or more frequently, if needed. Standard follow-up assessment included liver and kidney function tests in each visit. In most patients, serum creatinine was measured at the scheduled time points Table S1). Information about evolution of patients after the index hospital admission was collected retrospectively from the electronic medical record system and was available for most patients (95%).

The primary objective of the study was to determine the frequency of CKD (see definition below) at 3 months after the AKI episode. For comparison, the frequency of CKD in the group of patients without AKI was also assessed at 3 months after the index admission. Secondary objectives were to evaluate the impact of CKD developing after AKI on clinical outcomes, including major complications of cirrhosis (AKI, ascites, refractory ascites, bacterial infections, hepatic encephalopathy, and gastrointestinal bleeding), hospital readmissions at 3 months, liver transplantation, and transplant-free survival.

Definitions

AKI was defined according to the criteria of the International Club of Ascites (ICA) recently adopted by the EASL guidelines, as an increase in serum creatinine ≥0.3 mg/dl at hospital admission or during hospitalization with respect to baseline.[4,6] The baseline serum creatinine used was the most recent stable value available in the previous 3 months before admission. Patients without serum creatinine available within the previous 3 months before admission were excluded. AKI was categorized into 4 stages (1A, 1B, 2, and 3) according to the modified ICA classification.[6,7] AKI was also classified into 4 types: ATN, HRS-AKI, hypovolemia-induced AKI, or miscellaneous causes. Nosocomial AKI was defined as AKI that was not present at the time of hospitalization and developed at least 48 h after admission.

CKD was defined according to the KDIGO guidelines as an estimated glomerular filtration rate (eGFR) below 60 ml/min/1.73m^2 for at least 3 months.[18] This is considered in current guidelines as CKD stages 3A to 5. We used this definition because the risk of clinically relevant events increases when eGFR falls below 60 ml/min/1.73m^2.[18] All eGFR values were calculated using the abbreviated modified diet in renal disease (MDRD-4) equation: eGFR (ml/min/1.73 m^2) = 186 × creatinine$^{-1.154}$ × age$^{-0.203}$ × (0.742 if female) × (1.212 if black).[19] In patients in the AKI group, eGFR was assessed at AKI diagnosis and after 3 months, whereas in patients in the non-AKI group, eGFR was assessed at admission to hospital and 3 months later. Only patients in whom eGFR was lower than 60 ml/min/1.73^2 in all measurements performed were considered to have CKD. This definition is usual practice in the studies from the general population and follows the recommended approach in CKD guidelines.[18,20] CKD was classified into stage 3A (eGFR from 60 to 45 ml/min/1.73^2), stage 3B (from 44 to 30), stage 4 (from 29 to 15), or stage 5 (less than 15).[18,20]

Statistical analysis

Normally distributed continuous variables were reported as mean ± SD and compared by *t* test. Non-normally distributed continuous variables were reported as median and IQR and compared with Mann-Whitney *U* test. Categorical variables were reported as proportions and compared with Chi-squared test. The 12-month survival was estimated by the Kaplan-Meier method and compared by means of log-rank test. Patients transplanted during follow-up were excluded from the survival analysis. A stepwise logistic regression analysis, with backward elimination was used to identify independent predictors of CKD development. The odds ratios (ORs) and their 95% CI were calculated. The 2-tailed significance for all statistical tests was set at 0.05. The statistical analysis was performed using SPSS statistical package, version 20.0. The protocol was approved by the institutional review board of the hospital and all patients provided written informed consent to participate in the study.

Results

Characteristics of the study population

Our cohort included 504 patients admitted to hospital for complications of cirrhosis. Out of the 504 patients, 409 (81%) had a baseline serum creatinine within a 3-month period before admission and constitute the study population. Of the 409 patients included, 168 (41%) had AKI at admission or developed it during hospitalization (AKI group), whereas the remaining 241 (59%) patients did not develop AKI (non-AKI group). Comparison of baseline characteristics of patients from both groups is shown in Table 1. In the AKI group, after 3 months of follow-up, 97 patients were alive, 58 patients had died, 8 had been transplanted, and 5 were lost to follow-up. Corresponding figures at 3 months after admission in the non-AKI group were 188, 26, 9,

Table 1. Characteristics of all patients included categorized according to presence or absence of AKI.

	Patients with AKI (n = 168)	Patients without AKI (n = 241)
Age, years	60 ± 10	60 ±12
Gender, male	136 (81)	147 (61)
Etiology of cirrhosis		
Alcohol	75 (45)	85 (35)
Hepatitis C infection	43 (25)	77 (32)
Others	50 (30)	79 (33)
Diabetes mellitus	49 (29)	67 (28)
Arterial hypertension	46 (26)	50 (21)
Treatment with beta blockers	65 (37)	87 (36)
Bacterial infection at admission	92 (55)	100 (41)
Hepatic encephalopathy at admission	53 (32)	49 (20)
Ascites at admission	134 (80)	124 (51)
Refractory ascites before admission	20 (12)	14 (6)
Gastrointestinal bleeding at admission	24 (14)	39 (16)
Mean arterial pressure (mmHg)	81 ±12	84 ± 12
Serum bilirubin (mg/dl)	2.4 (1.3–5.1)	2.3 (1.2–3.7)
Serum albumin (g/L)	28 (24–32)	29 (25–33)
INR	1.6 (1.4–1.9)	1.4 (1.3–1.6)
Serum creatinine (mg/dl)		
Baseline*	0.9 (0.7–1.1)	0.8 (0.7–0.9)
At admission	1.7 (1.4–2.2)	0.8 (0.6–1.0)
Leucocyte count (cells × 10^3/μL)	6.6 (4.7–10)	4.7 (3.5–7.0)
MELD score	19 ± 6	14 ± 5
Child-Pugh score	9 (8–11)	8 (7–10)
ACLF		
Number of patients	106 (61)	8 (3)
Grade (1/2/3)	47/21/38	1/5/2

Values are number of patients (percentage), or median (IQR), or mean ± SD. Normally distributed continuous variables were compared using *t* test. Non-normally distributed continuous variables were compared using Mann-Whitney *U* test. Categorical variables were reported compared with Chi-squared test.
ACLF, acute-on-chronic liver failure; AKI, acute kidney injury; INR, international normalized ratio; MELD, model for end-stage liver disease.
*Most recent serum creatinine available within the previous 3 months before admission.

and 18, respectively (3-month mortality 35% *vs.* 11% in the AKI and non-AKI group, respectively; p <0.0001). The distribution of patients in the study is shown in Fig. 1.

Development of CKD and risk factors

Twenty-four of the 97 patients (25%) from the AKI group had CKD 3 months after AKI (median eGFR 47 ml/min/1.73m^2; IQR 38–53), whereas the remaining 73 patients did not have CKD (median eGFR 81 ml/min/1.73m^2; IQR 68–99). By contrast, only 2 of the 188 patients (1%) from the non-AKI group developed CKD during the same time frame (OR 31; 95% CI 7-133; p <0.0001) (Fig. 1). Similar results (23% *vs.* 1%, respectively; p <0.001) were found if the whole cohort of 504 patients was analyzed (including the 95 patients who did not have baseline serum creatinine within 3 months of admission).

In univariate analysis, factors at diagnosis of AKI that were associated with development of CKD were age, diabetes mellitus, baseline serum creatinine, serum creatinine at diagnosis of AKI, AKI stage, and nosocomial AKI (Table 2). Interestingly, no relationship was found between the etiology of AKI and the development of CKD. In particular, patients with HRS-AKI had no higher frequency of CKD development compared to other etiologies of AKI (Table 2). Moreover, no relationship was found between the type of precipitating factors of AKI or management of AKI and development of CKD (Table S2). With respect to treatment with albumin for AKI, 15 patients (63%) in the CKD group received i.v. albumin during hospitalization compared to 35 patients (48%) in the no-CKD group (p = 0.216). Moreover, there were no significant differences among groups in the total dose of albumin received (100 g, IQR 60–140 and 100 g, IQR 60–160, respectively; p = 0.295) or in serum albumin levels at the end hospitalization (31 ± 7 *vs.* 30 ± 5 g/L, respectively; p = 0.133). There were no significant differences in urinary biomarker levels at the time of diagnosis of AKI between patients with and without subsequent CKD development (neutrophil gelatinase-associated lipocalin 30 [20–51] *vs.* 47 [20–85] μg/g of creatinine; IL-18: 3 (1–11) *vs.* 10 (2-40) pg/g of creatinine, respectively; p >0.10 for both; available in 54% and 45% of patients, respectively). In multivariate analysis, factors independently associated with the development of CKD were nosocomial AKI and AKI stage (Table 3).

The time-course of changes in eGFR in patients from the AKI group who survived for at least 3 months after AKI is shown in Fig. 2. In the group of patients who did not develop CKD, median eGFR increased markedly after AKI and was persistently elevated for the 12-month follow-up period. By contrast, in patients who developed CKD, eGFR was already slightly lower at the time of AKI, increased barely thereafter, and persisted to be significantly lower for the remaining follow-up period compared to that of patients who did not develop CKD. All patients had stage 3A at diagnosis of CKD. Interestingly, pre-admission eGFR (before the AKI episode) was significantly lower in patients who developed CKD after AKI compared to in patients who did not develop CKD (70 [62–87] ml/min *vs.* 94 [73–113] ml/min, respectively; p = 0.0001) (Fig. 2).

At diagnosis of CKD, median proteinuria was 136 mg/day (IQR 88–320). Abnormalities in kidney morphology, as assessed by ultrasound, were found in only 1 patient. Kidney histology was not available in any of the patients. The impairment of kidney function progressed during the follow-up period in 6 patients (25%), as indicated by an increase in the stage of CKD; 4 patients progressed to stage 3B and 2 to stage 4 (only 1 patient required hemodialysis). eGFR remained stable during follow-up in the remaining patients, except in 1 patient in whom eGFR increased above 60 ml/min/1.73m^2.

Effect of CKD on clinical outcomes

Development of CKD was associated with an increased risk of AKI during follow-up (Table 4). In fact, the number of patients developing new episodes of AKI was significantly higher in the group of patients with CKD compared to those without (75% *vs.* 45%, respectively; p = 0.011) and the mean AKI episodes per patient was also significantly higher. In addition, patients with CKD had a higher frequency of some important complications of cirrhosis, including ascites, refractory ascites, and bacterial infections. As a consequence, the frequency of hospital readmissions at 3 months in patients with CKD was significantly higher (Table 4). There was also a tendency toward a higher frequency of hepatic encephalopathy. By contrast, the frequency of portal hypertensive-related bleeding was similar between the 2 groups. Interestingly, liver transplantation during follow-up

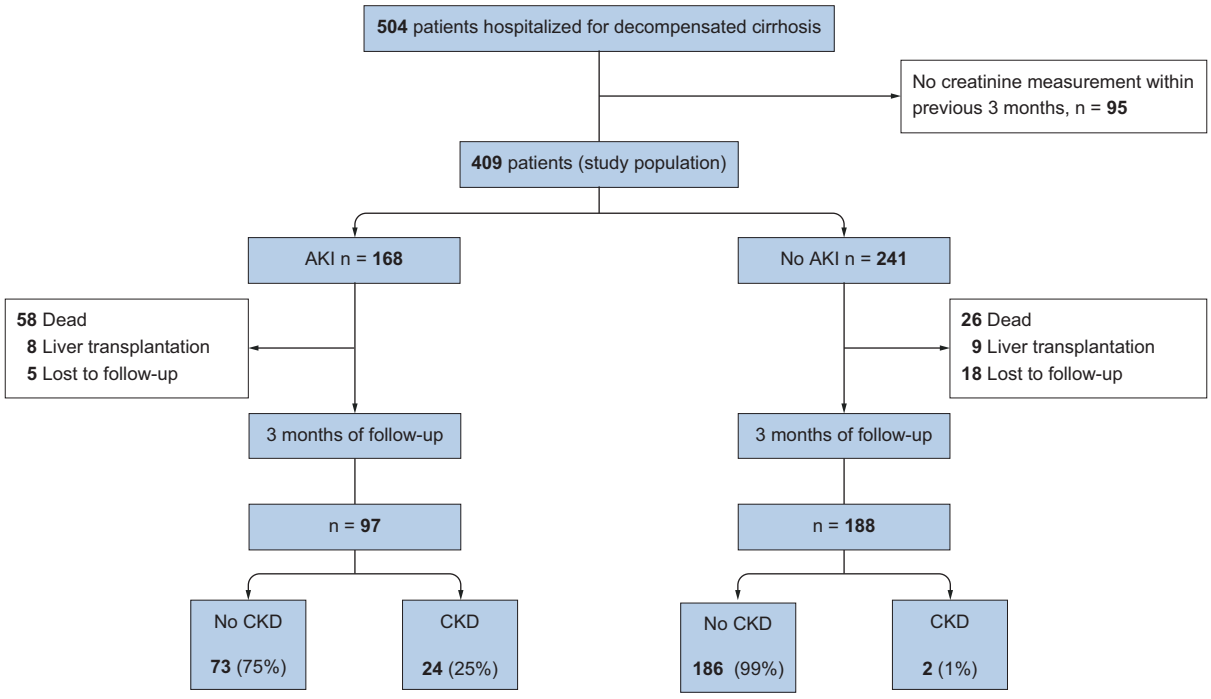

Fig. 1. Flow chart of patients included in the study. AKI, acute kidney injury; CKD, chronic kidney disease.

was more frequent in patients with CKD than in those without, but the difference did not reach statistical significance. Finally, transplant-free survival was similar between the 2 groups (Fig. 3). No patient required combined liver-kidney transplant during follow-up.

Assessment of patients with CKD at time of hospital admission

Patients with previous CKD before admission were not included in the primary analysis of this study because the main objective was to evaluate the potential evolution of AKI to CKD. Therefore, these patients were excluded for obvious reasons. Nevertheless, the subset of patients with previous CKD was analyzed separately to compare their characteristics with those of patients without previous CKD and assess the effect of AKI on survival. During the observation period, 91 patients with CKD were admitted to hospital for complications of cirrhosis, which represents 18% of the overall population. Comparison of baseline characteristics of patients with and without CKD is shown in Table S3. Patients with CKD had a higher frequency of diabetes mellitus, arterial hypertension, ascites at admission, previous refractory ascites, and higher model for end-stage liver disease score. Most importantly, the occurrence of AKI during admission was significantly higher in patients with CKD compared to those without (67% *vs.* 41%, respectively; p <0.0001). Moreover, development of AKI in patients with CKD (so-called acute-on-chronic kidney disease, ACKD) was associated with an impaired prognosis (transplant-free survival at 12 months: 40% *vs.* 72% in patients with and without AKI, respectively; $p = 0.005$). However, compared to patients with AKI without previous CKD, there were no differences in 12-month transplant-free survival (40% *vs.* 40% in patients with AKI with and without previous CKD, respectively; $p = 1.0$). In brief, the presence of CKD is a risk factor for development of AKI and its occurrence is associated with impaired prognosis. Mortality risk after AKI is similar in patients with and without previous CKD.

Discussion

The results of the current study demonstrate that CKD develops frequently in patients with cirrhosis surviving an episode of AKI and that CKD is associated with impaired clinical outcomes, particularly increased risk of hospital readmission within 3 months and increased frequency of episodes of AKI, ascites, refractory ascites, and bacterial infections during follow-up. Interestingly, however, CKD was not associated with impaired 1-year survival.

In the current study, CKD occurred in 25% of patients with decompensated cirrhosis who survived for at least 3 months after an episode of AKI. Analysis of time-course changes of kidney function in these patients showed that eGFR was lower at baseline before admission and at the time of AKI diagnosis, compared to those of patients who did not develop CKD, and did not improve thereafter. It is important to emphasize, however, that none of these patients had CKD before admission. The key pathogenic role of AKI in development of CKD is supported by the observation that the rate of CKD development in patients hospitalized for decompensated cirrhosis without AKI was extremely low (1%). These findings are consistent with those reported from the general population of patients hospitalized with AKI. According to data derived from a recent meta-analysis that included more than 1 million patients from 13 studies the pooled hazard ratio for CKD development among the overall population of hospitalized patients with AKI was 8.8.[17] In the current study, the OR of development of CKD was of 31. This marked difference of risk between the 2 studies raises the possibility that the kidneys of patients with cirrhosis are more susceptible to CKD development than the kidneys of patients without cirrhosis. However, this hypothesis would require

Table 2. Univariate analysis of factors associated with development of CKD in the group of patients with cirrhosis and AKI.

	CKD (n = 24)	No-CKD (n = 73)	*p* value
Age, years	63 ± 8	58 ± 10	**0.047**
Gender, male	17 (71)	59 (81)	0.303
Etiology of cirrhosis			0.595
Alcohol	12 (50)	31 (43)	
Hepatitis C infection	7 (30)	16 (22)	
Others	5 (20)	26 (35)	
Diabetes mellitus	11 (46)	18 (25)	**0.049**
Arterial hypertension	10 (42)	20 (27)	0.189
Treatment with beta blockers	14 (59)	33 (45)	0.264
Bacterial infection at admission	12 (50)	41 (56)	0.599
Hepatic encephalopathy at admission	6 (25)	18 (25)	0.973
Ascites at admission	20 (83)	55 (75)	0,417
Refractory ascites before admission	2 (8)	5 (7)	0.807
Gastrointestinal bleeding at admission	1 (4)	14 (19)	0.078
Mean arterial pressure (mm Hg)	83 ± 14	80 ± 12	0.395
Serum bilirubin (mg/dl)	1.7 (1.2–4.0)	2.2 (1.2–4.0)	0.818
Serum albumin (g/L)	30 ± 6	29 ± 5	0.514
INR	1.4 (1.3–1.8)	1.5 (1.3–1.7)	0.713
Serum creatinine (mg/dl)			
Baseline*	1.0 (0.9–1.2)	0.8 (0.7–1.0)	**<0.0001**
At diagnosis of AKI	1.9 (1.6–2.2)	1.5 (1.3–1.8)	**0.001**
Leucocyte count (cells × 10^3/uL)	5.5 (4.9–10.0)	6.2 (4.2–10.0)	0.904
AKI stage			**0.019**
AKI 1A	4 (17)	35 (48)	
AKI 1B	12 (50)	21 (29)	
AKI 2	7 (29)	10 (14)	
AKI 3	1 (4)	7 (9)	
AKI etiology			0.668
Hypovolemia-induced	13 (54)	30 (41)	
ATN	2 (8)	7 (9)	
HRS-AKI	8 (33)	29 (40)	
Others	1 (4)	7 (10)	
MELD score	21 ± 6	19 ± 7	0.334
Child-Pugh score	8 (7–10)	8 (7–10)	0.793
Nosocomial AKI	12 (50)	15 (21)	**0.005**

Values are number of patients (percentage), or median (IQR), or mean ± SD.
Values in bold denote significance. Normally distributed continuous variables were compared using *t* test. Non-normally distributed continuous variables were compared using Mann-Whitney *U* test. Categorical variables were reported compared with Chi-squared test.
AKI, acute kidney injury; ATN, acute tubular necrosis; CKD, chronic kidney disease; INR, international normalized ratio; HRS-AKI, hepatorenal syndrome; MELD, model for end-stage liver disease.
*Most recent serum creatinine available within the previous 3 months before admission.

Table 3. Independent predictive factors of CKD development in patients with cirrhosis and AKI.

Variable	Odds ratio (95% CI)	*p* value
Nosocomial AKI	5.1 (1.7–15.2)	0.003
AKI stage (1B or greater)	6.0 (1.7–21.2)	0.005

Variables included in the analysis: Diabetes mellitus, AKI stage (1B or greater), nosocomial AKI.
Multivariate analysis was performed using a stepwise logistic regression analysis, with backward elimination, to identify independent predictors of CKD development.
AKI, acute kidney injury; CKD, chronic kidney disease.

confirmation in larger studies. The mechanisms underlying the transition from AKI to CKD remain incompletely understood. It is currently considered that progression of renal damage after AKI is related to a maladaptive repair in the tubular, vascular and interstitial compartments of the kidney that ultimately leads to interstitial fibrosis.[16] Whether the same mechanisms apply to cirrhosis is not known. The possible existence of interstitial fibrosis could not be evaluated because kidney biopsy was not available in the current series.

Factors independently associated with a higher risk of transition to CKD were nosocomial AKI and worse AKI stage. Patients who developed AKI in the hospital had a much higher risk of CKD development compared to those who developed AKI outside the hospital. The reasons for this higher risk of CKD development in nosocomial AKI are unknown and could not be derived from the results of the current study. Likewise, patients with higher AKI stage (1B or greater) had a much greater risk of CKD than those with less severe AKI (stage 1A). Severity of AKI has been shown to be a consistent factor of transition from AKI to CKD in studies in the general population.[21]

Besides the demonstration of transition from AKI to CKD in patients with cirrhosis, the current study showed that CKD was associated with impaired clinical outcomes. One of the most important results was the observation of an increased risk of AKI in patients with CKD. Not only the development of CKD was associated with higher percentage of patients developing AKI during follow-up (75% *vs.* 45% in patients with and without CKD), but also the median number of AKI episodes per patient was significantly higher. AKI and CKD are currently considered interconnected syndromes because AKI predisposes to CKD, while CKD increases the risk of further episodes of AKI.[16] The

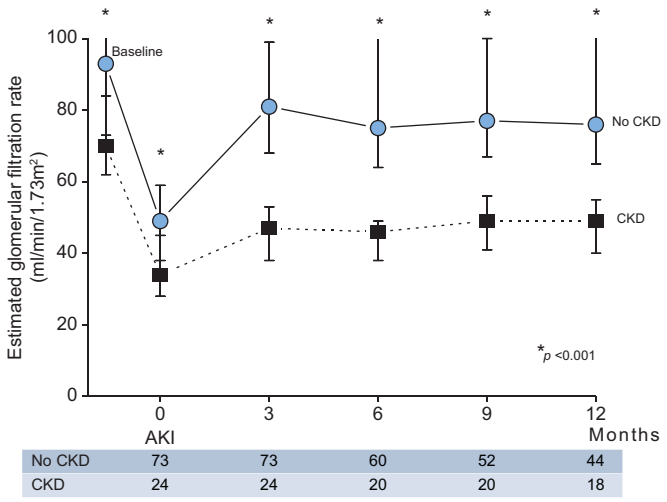

Fig. 2. Time-course of eGFR from before admission (baseline), at time of AKI, and during follow-up in the 97 patients with cirrhosis who survived at least 3 months after AKI categorized according to the development of CKD. Values are median and interquartile range. *p <0.001 with respect to values in CKD group. AKI, acute kidney injury; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

Table 4. Comparison of main clinical outcomes during follow-up in patients with cirrhosis categorized according to the development of CKD after an episode of AKI.

	CKD (n = 24)	No-CKD (n = 73)	p value
Complications of cirrhosis*			
Acute kidney injury			
Patients, n (%)	18 (75)	32 (45)	**0.011**
Episodes per patient	1.5 (0–2)	0 (0–0)	**0.015**
Ascites			
Patients, n (%)	13 (54)	18 (25)	**0.007**
Episodes per patient	1 (0–1)	0 (0–0)	**0.001**
Bacterial infections			
Patients, n (%)	14 (58)	25 (34)	**0.037**
Episodes per patient	1 (0–1.75)	0 (0–1)	**0.019**
Portal hypertension-related bleeding			
Patients, n (%)	4 (17)	7 (10)	0.343
Episodes per patient	0 (0–0)	0 (0–0)	0.294
Hepatic encephalopathy			
Patients, n (%)	9 (38)	14 (19)	0.067
Episodes per patient	0 (0–1)	0 (0–0)	0.117
Development of refractory ascites			
Patients, n (%)	6 (25)	5 (7)	**0.015**
Readmissions at 3 months	16 (67)	27 (37)	**0.011**
Liver transplantation*	6 (25)	7 (10)	0.055
Survival**	17 (71)	54 (74)	0.763

Values are number of patients (percentage), or median (IQR).
Values in bold denote significance.
AKI, acute kidney injury; CKD, chronic kidney disease.
*Evaluated at 12 months
**Number of patients include those transplanted as well as those who died. If patients transplanted were excluded differences were also not significant: (11 [61] *vs.* 47 [71], respectively, p = 0.406).

current findings extend these observations to patients with cirrhosis and indicate that patients with cirrhosis and CKD should be considered a high-risk group for the development of AKI. Of interest, CKD progressed during follow-up in 25% of patients, indicating the dynamic nature of chronic impairment of kidney function in cirrhosis. The current findings are consistent with those of Wong *et al.*[8] showing that baseline serum creatinine is associated with an increased risk of AKI, yet in this particular study the presence of chronic impairment in kidney function was evaluated using several cut-off levels of serum creatinine and not the consensus definition of CKD. Importantly, in addition to an increased risk of AKI, development of CKD was associated with an increased frequency of ascites, refractory ascites, and bacterial infections during follow-up and a trend for an increased frequency of hepatic encephalopathy.

Another relevant clinical finding of the current study was that CKD was associated with an increased risk of 3-month hospital readmission. Many studies have shown that decompensated cirrhosis is characterized by very high readmission rate, which may be as high as 53% within 3 months according to recent studies.[22–26] Of note, the effect of CKD as a possible risk factor for hospital readmission has not been evaluated in most of these studies. To the best of our knowledge, only 1 study included CKD as a study variable[26] and found that CKD increased the risk of 30-day readmission by a factor of 2, a value similar to that found in the current study. This increased risk of hospital readmission is likely related to the impairment that CKD causes on the natural history of cirrhosis, by increasing the risk of several clinically relevant complications as mentioned above.

The requirement of liver transplantation during follow-up was higher in the CKD group compared to the non-CKD group and almost reached statistical significance, a finding that may be related to more marked impairment of kidney function, a component of the model for end-stage liver disease score used for organ allocation, and/or increased frequency of complications of cirrhosis. A final issue that deserves discussion is that transplant-free survival in patients with CKD was not different from that of patients without CKD despite the increased frequency of hospital admissions and higher risk of cirrhotic complications. This finding is intriguing and would require confirmation in larger studies. It is possible that differences in survival were not detected because of the low number of patients with CKD.

The current study has several strengths that are worth mentioning, namely the inclusion of a large number of consecutive patients admitted to hospital for management of complications of cirrhosis during a long time period, evaluation of baseline serum creatinine and eGFR before admission and at several time points throughout follow-up, and assessment of AKI and CKD using consensus definitions. On the other hand, the study has also some limitations that should be acknowledged. First, the investigation was performed in a single tertiary hospital; therefore, it is not known whether results could be extrapolated to other settings. Second, evaluation of clinical outcomes during follow-up was performed retrospectively through the electronic medical record system; nevertheless, since most patients (95%) were followed-up by hepatologists from our own center and were referred to hospital when they developed complications, it is likely that most complications were recorded and analyzed. Finally, the absolute number of patients who transitioned from AKI to CKD was somewhat low and therefore results relative to clinical outcomes should be viewed with caution because of the limited sample size. However, in this regard it is important to underscore that the actual incidence of CKD at 3 months of follow-up was 6% (26 out of 409 patients analyzed). There are 2 main reasons for this relatively low incidence: i) almost 60% of hospitalized patients do not develop AKI and therefore have a very low risk for CKD development; and ii) almost 42% of those who

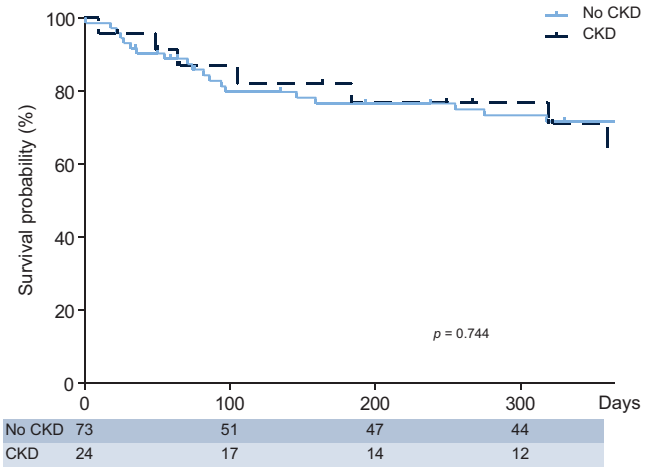

Fig. 3. 12-month probability of survival of the 97 patients with cirrhosis who survived at least 3 months after AKI categorized according to the development of CKD. Patients treated with liver transplantation during follow-up were censored at the time of transplant. Figures under the graphic are patients at risk at each time point. AKI, acute kidney injury; CKD, chronic kidney disease.

develop AKI either do not survive for 3 months or are transplanted, meaning they cannot be diagnosed with CKD, because the diagnosis requires 3 months of follow-up. This high early mortality rate causes an "underestimation" of the potential evolution of AKI to CKD in cirrhosis.

In summary, this study reports that a significant proportion of patients with cirrhosis surviving at least 3 months after an episode of AKI develop CKD, a previously unrecognized complication of AKI in cirrhosis. CKD after AKI in cirrhosis is progressive and associated with impaired clinical outcomes, particularly increased 3-month hospital readmission, higher risk for AKI development, ascites, refractory ascites, and bacterial infections and a trend towards higher frequency of hepatic encephalopathy and liver transplantation. Survival does not seem to be affected but this would require confirmation in future studies. CKD should be included in the list of high-risk conditions in patients with cirrhosis.

Abbreviations

ACLF, acute-on-chronic liver failure; AKI, acute kidney injury; ATN, acute tubular necrosis; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HRS-AKI, hepatorenal syndrome; INR, international normalized ratio; MELD, model for end-stage liver disease.

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Conflicts of interest

PG reports Investigator Research grant and Advisory Board work from Grífols, Investigator Research grant and Advisory Board from Gilead, Investigator Research grant from Mallinckrodt, Advisory Board for Promethera, Advisory Board for Martin-Pharmaceuticals, grants from Ferring Pharmaceuticals, grants and Advisory Board Work from Sequana, outside the submitted work. The other authors have declared no conflict of interests.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

The authors listed above have all contributed to this manuscript and approve the version of this submission. OB, PH, XA, PH, EP, ES, and PG contributed to the conception and design of the study, acquisition of data, the analysis and interpretation of the data and drafting the manuscript; CS, AJ, MC, IG, EP, LN, GdP, MC, JF, JG-G, and NF participated in the generation and collection of data, assembly of data, analyses of the results, interpretation of data, and/or critical revision of the manuscript for important intellectual content.

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Supplementary data

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Author names in bold designate shared co-first authorship

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