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Authors

Wong, Florence
Reddy, K
OLeary, Jacqueline
et al.

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Impact of Chronic Kidney Disease on Outcomes in Cirrhosis

Florence Wong[1], **K. Rajender Reddy**[2], **Jacqueline G. O'Leary**[3], **Puneeta Tandon**[4], **Scott W. Biggins**[5], **Guadalupe Garcia-Tsao**[6], **Benedict J. Maliakkal**[7], **Jennifer C. Lai**[8], **Michael B. Fallon**[9], **Hugo E. Vargas**[10], **Ram Subramanian**[11], **Paul J. Thuluvath**[12], **Patrick S. Kamath**[13], **Leroy Thacker**[14], **Jasmohan S. Bajaj**[15]

[1]Toronto General Hospital, University of Toronto, Toronto, Ontario, Canada

[2]University of Pennsylvania, Philadelphia, PA

[3]VA Medical Center, Dallas, TX

[4]University of Alberta, Edmonton, Alberta, Canada

[5]University of Washington, Seattle, WA

[6]Yale University School of Medicine, New Haven, CT

[7]University of Tennessee, Knoxville, TN

[8]University of California, San Francisco, CA

[9]University of Arizona, Tucson, AZ

[10]Mayo Clinic Arizona, Phoenix, AZ

[11]Emory University, Atlanta, GA

[12]Mercy Medical Center, Baltimore, MD

[13]Mayo Clinic, Rochester, MN

[14]Department of Statistics, Commonwealth University of Virginia, Richmond, VA

[15]Commonwealth University of Virginia and McGuire VA Medical Center, Richmond, VA

Abstract

We hypothesize that the prevalence of chronic kidney disease (CKD) among patients with cirrhosis has increased due to the increased prevalence of CKD-associated comorbidities, such as diabetes. We aimed to assess the characteristics of hospitalized patients with cirrhosis with CKD and its impact on renal and patient outcomes. The North American Consortium for the Study of End-Stage Liver Disease (NACSELD) prospectively enrolled nonelectively admitted patients with cirrhosis and collected data on demographics, laboratory results, in-hospital clinical course, and postdischarge 3-month outcomes. CKD positive (CKD+) patients, defined as having an estimated glomerular filtration rate (eGFR; Modification of Diet in Renal Disease–4 variable formula) of ≤60 mL/minute for >3 months, were compared with chronic kidney disease negative (CKD−)

Address reprint requests to Florence Wong, M.B.B.S., M.D., F.R.A.C.P., F.R.C.P.C., Toronto General Hospital, University of Toronto, 9EN/222, 200 Elizabeth Street, Toronto M5G2C4, Ontario, Canada. FAX: 416-340-5019; florence.wong@utoronto.ca.

patients for development of organ failures, hospital course, and survival. There were 1099 CKD+ patients (46.8% of 2346 enrolled patients) who had significantly higher serum creatinine (2.21 ± 1.33 versus 0.83 ± 0.21 mg/dL in the CKD− group) on admission, higher prevalence of nonalcoholic steatohepatitis cirrhosis etiology, diabetes, refractory ascites, and hospital admissions in the previous 6 months compared with the CKD− group (all $P < 0.001$). Propensity matching (n = 922 in each group) by Child-Pugh scores (9.78 ± 2.05 versus 9.74 ± 2.04, $P = 0.70$) showed that CKD+ patients had significantly higher rates of superimposed acute kidney injury (AKI; 68% versus 21%; $P < 0.001$) and eventual need for dialysis (11% versus 2%; $P < 0.001$) than CKD− patients. CKD+ patients also had more cases of acute-on-chronic liver failure as defined by the NACSELD group, which was associated with reduced 30- and 90-day overall survival ($P < 0.001$ for both). A 10 mL/minute drop in eGFR was associated with a 13.1% increase in the risk of 30-day mortality. In conclusion, patients with CKD should be treated as a high-risk group among hospitalized patients with cirrhosis due to their poor survival, and they should be monitored carefully for the development of superimposed AKI.

Renal dysfunction is a common complication of liver cirrhosis and is estimated to occur in nearly half of patients with cirrhosis who are admitted into the hospital.[1] The majority of these are cases of acute kidney injury (AKI) that are mostly related to worsening of the existing hemodynamic abnormalities of advanced cirrhosis. It can be brought on by a precipitating event, which, when treated, can lead to a reversal of the renal dysfunction.[2] Chronic kidney disease (CKD), especially organic CKD, in contrast, was once thought to be extremely uncommon among hospitalized patients with cirrhosis and was estimated to occur in 1% of these patients about a decade ago.[3] However, recent reports suggest that organic CKD may be more common than previously thought, occurring in 3.4%–13% of hospitalized patients with cirrhosis.[4,5] With the recent change in the definition of CKD in cirrhosis from the persistent elevation of serum creatinine (SCr) to >1.5 mg/dL to one that requires the glomerular filtration rate (GFR) to be <60 mL/minute/1.73 m^2 for more than 3 months,[6] CKD now encompasses both organic CKD due to structural renal damage as well as functional CKD that is brought on by the gradual deterioration of hemodynamics as the liver dysfunction worsens, ie, so-called hepatorenal syndrome type 2 (HRS2).[7] This has led to an apparent increase in the prevalence of CKD, ranging between 22% and 32%, especially when one considers both inpatients and outpatients with cirrhosis.[8–11] This may be related to the recent increase in the prevalence of nonalcoholic fatty liver disease (NAFLD) worldwide and the associated type 2 diabetes and cardiovascular disease, which can lead to structural damage to the kidneys, such as diabetic nephropathy.[12] Better recognition of HRS2 may also be a factor leading to more patients with cirrhosis being identified as having CKD. However, exactly how common CKD is in patients with cirrhosis remains unknown. The presence of CKD in populations without cirrhosis has been shown to be associated with increased morbidity and mortality.[13,14] The presence of CKD has also been recognized as a risk factor for AKI in other patient populations.[15] Whether the presence of CKD will lead to other renal complications is unknown. The impact of CKD on the natural history and prognosis of hospitalized patients with cirrhosis, who by the nature of their hospitalization are sicker, is not well documented. Therefore, the aims of this study were to assess the prevalence and characteristics of CKD, associated comorbid conditions, and the impact of CKD on renal and patient outcomes in hospitalized patients with cirrhosis.

Patients and Methods

This is a prospective study conducted by the North American Consortium for the Study of End-Stage Liver Disease (NACSELD), which consists of 14 participating centers in the United States and Canada. Their respective institutional review boards approved of the study. Data were managed using Research Electronic Data Capture (REDCap) tools[16] located at Virginia Commonwealth University, Richmond, VA. REDCap is a secure, Web-based application designed to support data capture for research studies and to provide the following:

1. An intuitive interface for validated data entry.
2. Audit trails for tracking data manipulation and export procedures.
3. Automated export procedures for seamless data downloads to common statistical packages.
4. Procedures for importing data from external sources.

Patients with cirrhosis who were nonelectively admitted into the hospital were approached for inclusion into the study. Patients were enrolled after obtaining informed consent if they had cirrhosis on liver biopsy or cirrhosis diagnosed on a combination of biochemical, radiological, and endoscopic findings if the liver biopsy confirmation was not available. Exclusion criteria were patients with human immunodeficiency virus infection, prior solid organ transplant, disseminated malignancies, patients who had acute-on-chronic kidney disease at admission, and those already on dialysis. To identify cases of CKD, the estimated glomerular filtration rate (eGFR) was calculated for the 3 months prior to enrollment from all available blood work results. Because this cohort of patients had regular medical contacts, regular blood tests were part of their standard of care. The eGFR for this study was estimated using the Modification of Diet in Renal Disease (MDRD)–4 variable equation, which includes SCr, age, sex, and ethnicity (GFR in $\text{mL/minute/1.73 m}^2 = 175 \times \text{SCr}^{-1.154} \times \text{age}^{-0.203} \times 1.212 \left[\text{if patient is black}\right] \times 0.742 \left[\text{if female}\right]$).[17] The MDRD–6 variable formula was not used because blood urea nitrogen was not uniformly collected. Furthermore, we preferred the MDRD4 formula to the Chronic Kidney Disease Epidemiology Collaboration (CKD-Epi) formula because the MDRD4 formula seems to approximate closer to the real GFR than the CKD-Epi formula,[18] especially in patients with low GFR. Data collected included patient demographics, past medical history, medication use, vital signs, baseline full blood count, biochemistry, liver and renal functions, and details of any infection. Patients were then followed for the development of cirrhotic complications, organ failures, and acute-on-chronic liver failure (ACLF) as per the NACSELD criteria[19,20] and for their hospital course and survival.

Because of the concern that patients with CKD, including HRS2, may have more advanced liver cirrhosis, a propensity score matching was done matching patients with CKD (cases) to patients without CKD (controls) to within 0.1 point of Child-Pugh scores using a greedy match algorithm[21] on a 1:1 basis so that the effects of CKD alone could be evaluated without the confounding effects of liver disease severity. The Child-Pugh score was chosen for matching patients because the Model for End-Stage Liver Disease (MELD) score also

includes SCr, which might be confounding. Patients with CKD were further divided into those with stage 3 (eGFR ≥30–59 mL/minute/1.73 m^2) or stage 4 and 5 (eGFR ≤29 mL/minute/1.73 m^2)[22] to determine whether the severity of renal dysfunction had any impact on patient and renal outcomes.

STATISTICAL ANALYSIS

Statistical analysis was done using SAS statistical software, version 9.4 (SAS Institute, Cary, NC). Categorical data are presented as a percentage as well as the actual numbers used to calculate the percentages. Continuous data are presented as means ± standard deviations (SDs). Group comparisons for categorical variables were done using the χ^2 test with the corresponding degrees of freedom, whereas group comparisons for continuous variables were done with either a 2-sample *t* test or a 1-way analysis of variance if 3 or more groups were compared. Group comparisons for discrete and nonnormally distributed continuous data were done using a nonparametric Wilcoxon rank sum test (Mann-Whitney U test) for 2 groups or the Kruskal-Wallis test for more than 2 groups. For all analyses, a *P* value <0.05 was considered to be statistically significant.

The determinants of CKD outcomes in the propensity score–matched sample were calculated using a binary logistic regression model. A backward elimination multivariate binary logistic regression model was fitted to determine the outcome of CKD. The variables considered were age, nonalcoholic steatohepatitis (NASH) etiology, Child-Pugh score, diabetes, refractory ascites, serum Na, and hospitalization in the past 6 months. The same binary logistic regression model was used to calculate the risks for various organ failures per quantum change in renal function and for 30-day mortality.

Results

From December 2011 to February 2017, 2346 patients were enrolled; 1099 had CKD (chronic kidney disease positive [CKD+] group) as defined by the International Club of Ascites (ICA) as an eGFR of <60 mL/minute/1.73 m^2 for >3 months prior to the index admission[6]; and 1247 did not have CKD (chronic kidney disease negative [CKD−] group). These were mostly middle-aged men with alcohol as the most common etiology of their liver cirrhosis. Table 1 shows the demographics, comorbid conditions, and medications used in all the study patients. CKD+ patients were significantly older and more commonly had NASH as an etiology of their cirrhosis. In addition, significantly more CKD+ patients had diabetes and a more complicated preadmission cirrhosis course, as indicated by a significantly higher Child-Pugh score. Of these, a significantly higher percentage had ascites or refractory ascites, which required lactulose and rifaximin as treatment for hepatic encephalopathy, and had a higher probability of hospital admission in the previous 6 months (Table 1). Furthermore, significantly more CKD+ versus CKD− patients had spontaneous bacterial peritonitis (SBP) and urinary tract infections (UTIs). This may have contributed to the significantly higher white blood cell (WBC) count at study enrollment among the CKD+ patients (Table 1).

Propensity matching paired 922 CKD+ patients with 922 CKD− patients (Child-Pugh score of 9.78 ± 2.05 versus 9.74 ± 2.04, respectively; $P = 0.70$). The same differences with

respect to the demographic parameters were also observed in the matched cohorts (Table 2) as when all the enrolled patients were considered. That is, the matched CKD+ patients were significantly older than their CKD− counterparts and significantly more had NASH as an etiology of their liver cirrhosis, diabetes as a comorbid condition, and complications of cirrhosis (Table 2) despite similar Child-Pugh scores. Likewise, similar differences in baseline laboratory findings between the CKD+ versus the CKD− patients were observed whether the entire cohort of patients was assessed (Table 1) or when the matched patients were evaluated (Table 3).

Further separation of the CKD+ group into stage 3 (eGFR = 30–59 mL/minute/1.73 m^2) versus stages 4 (eGFR = 15–29 mL/minute/1.73 m^2) and 5 (eGFR <15 mL/minute/1.73 m^2) subgroups[21] (Tables 2 and 3) did not find significant differences between the 2 subgroups of CKD+ patients, other than more refractory ascites in the patients who had more severe CKD.

RENAL OUTCOMES AND HOSPITAL COURSE

Concentrating on the matched cohorts, the CKD+ patients (627 patients or 68%) had significantly more episodes of AKI during their hospitalization compared with the CKD− patients (194 patients or 21%; $P < 0.001$; Fig. 1), especially among patients with stages 4 and 5 CKD (265 patients or 79%; $P < 0.001$ versus stage 3 CKD [363 patients or 62%]). Our data cannot specifically characterize the AKI episode, and therefore, we are unable to define how many of these AKI episodes were hepatorenal syndrome type 1 (HRS1). As a result of more frequent AKI episodes, significantly more CKD+ patients required initiation of renal replacement therapy (Table 4). In addition, more CKD+ patients developed other organ failures (circulatory, brain, and respiratory failures as per NASCELD ACLF criteria[18]), and hence more CKD+ patients required admission into intensive care units (ICUs), which was associated with significantly more prolonged hospital stays. Despite the demographic similarity between patients with stages 4 and 5 CKD and stage 3 CKD, the renal outcomes and the hospital course of the stage 4 and 5 CKD+ patients were significantly worse compared with the stage 3 CKD+ patients, with the exception of the severity of their renal function (Table 3) and extent of their ascites (Table 2). These patients also had more organ failures[18] (Table 4), which was associated with lower 30- and 90-day overall survival (Fig. 2). For those patients who survived 30 days and did not receive a transplant, the CKD+ group also had significantly more hospital readmissions when compared with the CKD− group (Table 4). However, the hospital readmission rates were no different between those who had stage 3 CKD versus those with stages 4 and 5 CKD (Table 4).

PREDICTORS FOR THE PRESENCE OF CKD IN CIRRHOSIS

We wanted to know whether there were any significant variables that were associated with CKD in patients with cirrhosis so that we could predict CKD development in future cohorts. Our results show that older age, the presence of diabetes, NASH etiology of cirrhosis, and refractory ascites (Table 5) were associated with the presence of CKD, with the most significant risk factor being the presence of refractory ascites, which confers an 84% likelihood of being associated with CKD in decompensated cirrhosis.

THE eGFR AS A PREDICTOR OF ORGAN FAILURE

Using a binary logistic regression model, we were able to identify an association between a quantum reduction in eGFR and a certain risk for organ failure or death. We found that for every 10 mL/minute drop in eGFR, there is a 13.1% increase in risk for 30-day mortality. For various organ failures, the same 10 mL/minute drop in eGFR increases the risk for circulatory failure by 10.5%, brain failure by 7.0%, and respiratory failure by 5.8%. Figure 3 provides the risk for 30-day mortality and various nonrenal organ failures for a wide range of eGFRs.

Discussion

This study demonstrates that CKD, as defined by the ICA criteria,[6] whether it is related to structural renal disease or HRS2, is common in cirrhosis, occurring in 46.8% of patients admitted to the hospital. The most significant association with CKD development is the presence of refractory ascites, although the presence of diabetes and NASH etiology of cirrhosis may also play a role. The presence of CKD confers significantly worse renal and patient outcomes that are associated with shortened short- and medium-term overall patient survival with the prognosis progressively worsening with increasing severity of renal dysfunction.

Almost a decade ago, CKD related to organic renal disease was regarded as uncommon among hospitalized patients with cirrhosis, occurring in approximately 1% of these patients.[3] Over the course of 10 years, there have been several reports of increasing prevalence of CKD among hospitalized patients with cirrhosis,[4,5] but the high prevalence of CKD seen in our cohort has not been reported. There may be several reasons for this observation. First, the definition of CKD was changed from one using a threshold SCr of 1.5 mg/dL to one that uses eGFR <60 mL/minute/1.73 m^2 for >3 months.[6] This may not have increased the prevalence of CKD, especially because the SCr and GFR are interrelated, with the GFR estimated using an SCr-based formula. Second, improved management of patients with decompensated cirrhosis[23,24] means that these patients are now surviving longer, therefore allowing time for CKD to develop.

Third, CKD in cirrhosis has until recently been equated with HRS2, which has been regarded as a complication of refractory ascites that is related to the abnormal hemodynamics of advanced cirrhosis.[6] Indeed, in our cohort of patients with CKD, significantly more patients had ascites and especially refractory ascites. The more severe the CKD, the higher the proportion of patients with refractory ascites, which supports the contention that the increased prevalence of CKD in cirrhosis is indeed related to the presence of refractory ascites. It is still to be determined if it is the presence of CKD that has led to refractory ascites or if it is the presence of abnormal hemodynamics in advanced cirrhosis that has caused both the CKD and the refractory ascites. However, recent data suggest that abnormal hemodynamics alone cannot explain every case of CKD in cirrhosis.[25] With the worldwide epidemic of obesity, especially in North America, NAFLD and NASH have become important causes of significant morbidity. NAFLD and NASH themselves are also associated with an increased prevalence of CKD independent of the presence of diabetes.[26,27] The increased amounts of nonesterified fatty acids,

resulting from the expansion of intra-abdominal visceral adipose tissue, are associated with activation of inflammatory pathways, impaired insulin signaling, and dysregulation of adipokine production, all of which can promote vascular and renal damage.[28,29] Therefore, the increased number of patients with NASH either as a primary or cofactor to their liver disease may well have increased the prevalence of CKD among our admitted patients with cirrhosis.

Fourth, the presence of diabetes linked to NASH has increased, and with it, diabetic nephropathy may also contribute significantly to the development of CKD. Indeed, the presence of diabetes is a significant predictor for the presence of CKD in our study cohort. A shortcoming of our study is the lack of urinalysis, urine microscopic examinations, or renal biopsy data to determine the relative contributions of structural versus functional renal disease in the development of CKD in our patients. Finally, increased recognition of CKD as an important comorbid condition in cirrhosis may also have led to more CKD patients being identified.

Patients with cirrhosis with CKD seem to have a more complicated course, even when they are matched with their non-CKD counterparts by Child-Pugh score, indicating the severity of liver dysfunction. They had more hospital admissions in the prior 6 months, likely related to the occurrence of SBP, because more were on prophylactic antibiotics, and they had a higher prevalence of hepatic encephalopathy, as evidenced by the need for rifaximin and lactulose. In patients without cirrhosis, the presence of CKD in those who did not require dialysis was associated with a linear and graded risk of infection-related hospitalization, [30] which is a result of alterations in immune functions associated with CKD. It is plausible that the same mechanisms may also be involved in the increased susceptibility to infection in patients with CKD and cirrhosis. Predisposition to the development of hepatic encephalopathy may be attributed to accumulation of nitrogenous waste products in CKD. [31] A reduced capability to excrete free water and to reabsorb Na in patients with CKD, thereby leading to electrolyte abnormalities, may also contribute to the development of hepatic encephalopathy in these patients. Although not specifically assessed in this study, patients with cirrhosis with CKD are also at risk for other complications, such as failure to control variceal bleeding, related to uremic platelet dysfunction.[32] Thus, the development of CKD in cirrhosis significantly adds to their morbidity and mortality.[33,34]

Once admitted, the prognosis of the CKD+ patients becomes significantly worse when compared with the CKD− patients. Regardless of the reason for hospitalization, CKD+ patients were significantly more likely to develop superimposed AKI, with less likelihood to recover from the AKI episodes, hence being more likely to require dialysis. The development of AKI superimposed on CKD has also been recently noted in another cohort of patients with decompensated cirrhosis from Europe,[11] and this occurred in 26% of all AKI episodes, confirming that acute-on-chronic kidney disease is a relatively common entity. It appears that the more severe the baseline renal dysfunction, the worse the renal outcomes. We have previously shown that patients with higher baseline SCr were more likely to develop AKI, with significantly higher delta and peak SCr, which was associated with a more progressive course of their AKI.[1] Because CKD is associated with many metabolic dysfunctions and immune compromises,[35] when added to the

immunocompromised and proinflammatory state of cirrhosis,[36] it is not unexpected that there were more cases of organ failures, leading to more episodes of ACLF, resulting in more frequent admissions into ICUs and prolonged hospital stays.

In addition to the poor renal outcomes, CKD+ patients with cirrhosis also had worse outcomes, with progressively lower short- and medium-term overall survivals as the renal dysfunction worsened. It would have been nice to know exactly how much shorter the survival was in the CKD+ cohort compared with the CKD− cohort. However, at the time of the study design, time to death was not included as one of the parameters to collect. We therefore can only provide information on whether or not death occurred at specific time points. We recognize that this is one of the limitations of the study. However, from the data collected, we were able to calculate the relationship between reduction in eGFR and the probability of death. A reduction of 10 mL/minute/1.73 m^2 in eGFR was associated with a 13% increase in 30-day mortality and an increased risk for various organ failures by 6%–10%.

It is important to recognize that the presence of CKD will not only affect survival of patients while wait-listed for liver transplantation (LT), but it can also affect posttransplant renal outcomes[37] and longterm graft and patient survival.[38] To that end, there has been a new streamlined United Network for Organ Sharing policy that went into effect in 2017 for the prioritization of simultaneous liver-kidney transplantation based on the duration and severity of CKD.[39] It is also imperative that every effort should be made to treat or slow the progression of CKD in patients with cirrhosis. Although not specifically addressed in this study, the literature has reported that the regular use of albumin in patients with ascites can significantly reduce the incidence of renal dysfunction (defined as SCr >1.5 mg/dL/1.73 m^2) and HRS1,[24] most likely related to improved hemodynamics in patients with decompensated cirrhosis and ascites. Likewise, the management of NAFLD or NASH with lifestyle changes or medications could potentially prevent the development of or delay the progression of CKD in these patients,[40] although lifestyle changes may be more difficult to achieve than regular use of albumin.

In conclusion, CKD is becoming more common in patients with cirrhosis, which is associated with more difficult-to-control ascites and a more complicated course of liver disease. The presence of CKD predisposes the admitted patients with cirrhosis to worse renal and hospital outcomes, together with reduced overall survival. Therefore, it is imperative that these patients are monitored carefully and that the risk factors for CKD are treated in order to delay the progression of CKD, which if left unchecked, can lead to a spiraling downhill course of their prognosis.

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Correction Statement: In the x-axis of Fig. 3, GFR has now been corrected to "eGFR." We apologize to the authors and our readers for this error.

Abbreviations:

ACLF	acute-on-chronic liver failure
AKI	acute kidney injury
CI	confidence interval
CKD	chronic kidney disease
CKD+	chronic kidney disease positive
CKD−	chronic kidney disease negative
CKD-Epi	Chronic Kidney Disease Epidemiology Collaboration
eGFR	estimated glomerular filtration rate
GFR	glomerular filtration rate
HCV	hepatitis C virus
HRS1	hepatorenal syndrome type 1
HRS2	hepatorenal syndrome type 2
ICA	International Club of Ascites
ICU	intensive care unit
LT	liver transplantation
MDRD	Modification of Diet in Renal Disease
MELD	Model for End-Stage Liver Disease
NACSELD	North American Consortium for the Study of End-Stage Liver Disease
NAFLD	nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
NSBB	nonselective beta-blockers
OR	odds ratio
PPI	proton pump inhibitor
REDCap	Research Electronic Data Capture

SBP	spontaneous bacterial peritonitis
SCr	serum creatinine
SD	standard deviation
SIRS	systemic inflammatory response syndrome
UTI	urinary tract infection
WBC	white blood cell

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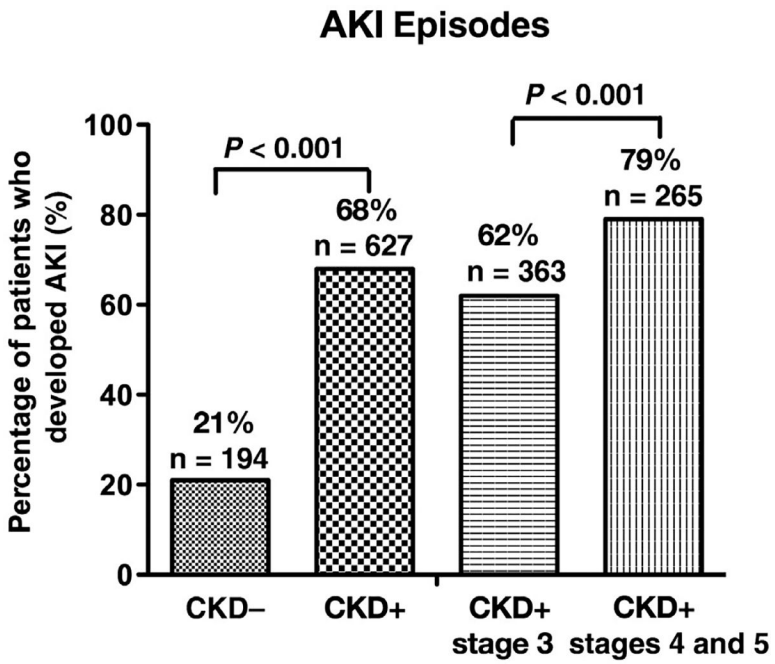

FIG. 1.

Prevalence of AKI episodes among CKD+ and CKD− patients. Stage 3 CKD is defined as eGFR = 30–59 mL/minute/1.73 m^2, and stages 4 and 5 CKD are defined as eGFR <30 mL/minute/1.73 m^2.

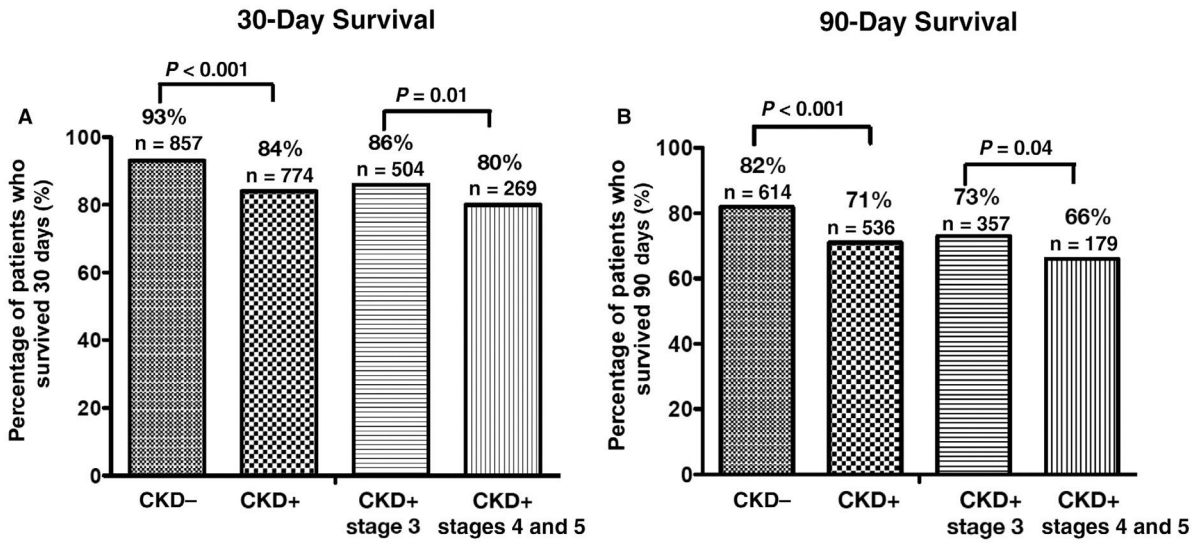

FIG. 2.

(A) The 30-day survival and (B) 90-day survival among CKD+ and CKD− patients. Stage 3 CKD is defined as eGFR = 30–59 mL/minute/1.73 m^2, and stages 4 and 5 CKD are defined as eGFR <30 mL/minute/1.73 m^2.

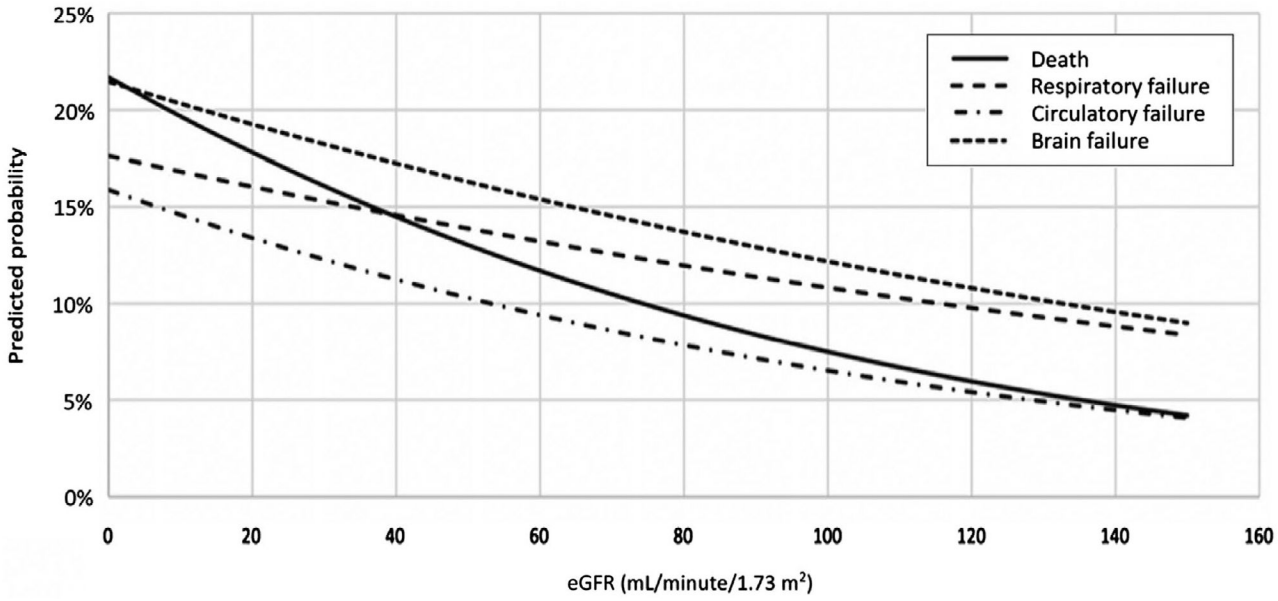

FIG. 3.

Relationship between reduction in eGFR and the probability of occurrence for death, respiratory failure, circulatory failure, and brain failure.

TABLE 1.

Patient Demographics and Laboratory Data at Enrollment of the Entire Study Cohort

	CKD− Patients (n = 1247)	CKD+ Patients (n = 1099)	*P* Value
Age, years	55.15 ± 11.05	59.53 ± 10.23	<0.001
Sex, male	66 (829/1247)	56 (620/1099)	<0.001
Etiology			<0.001
Alcoholic cirrhosis	31 (390/1239)	29 (320/1090)	
HCV	20 (252/1239)	20 (216/1090)	
HCV plus alcoholic cirrhosis	17 (206/1239)	12 (128/1090)	
NASH	17 (209/1239)	26 (288/1090)	
Other	15 (182/1239)	13 (138/1090)	
Diabetes	27 (336/1225)	42 (454/1084)	<0.001
Admitted with infection	26 (323/1240)	28 (308/1091)	0.24
SBP on/during admission	7 (88/1247)	10 (114/1099)	<0.01
UTI on/during admission	10 (120/1247)	13 (142/1099)	0.01
Ascites	64 (790/1242)	76 (839/1098)	<0.001
Refractory ascites	26 (322/1242)	42 (457/1098)	<0.001
Hospitalized in last 6 months	63 (715/1144)	70 (695/1000)	<0.001
Medication used			
PPI	54 (632/1180)	58 (578/998)	0.04
NSBB	38 (470/1221)	42 (448/1070)	0.10
SBP prophylaxis	15 (186/1210)	20 (214/1058)	<0.01
Rifaximin	28 (338/1229)	44 (467/1072)	<0.001
Lactulose	51 (628/1228)	60 (647/1078)	<0.001
Bilirubin, mg/dL	5.49 ± 8.29	6.60 ± 9.09	0.14
Albumin, g/L	2.80 ± 0.64	2.88 ± 0.72	0.01
WBC count, $\times 10^9$/L	4.75 ± 4.88	5.45 ± 5.57	<0.01
INR	1.62 ± 0.56	1.77 ± 0.74	<0.001
Serum Na, mEq/L	134.5 ± 7.9	133.7 ± 6.3	<0.001
SCr, mg/dL	0.83 ± 0.21	2.21 ± 1.33	<0.001
Child-Pugh score	9.41 ± 2.21	9.85 ± 2.14	<0.001
MELD score	16.11 ± 5.91	23.19 ± 7.73	<0.001
SIRS	27 (330/1229)	27 (297/1085)	0.78

NOTE: Data are given as mean ± SD or % (n).

TABLE 2.

Patient Demographics of Propensity Score–Matched Cohorts and According to the Severity of Their Renal Dysfunction in the CKD+ Group

			CKD+ Patients			
	All CKD− Patients (n = 922)	***P* Value (CKD+ Versus CKD−)**	**All Patients (n = 922)**	**Stage 3 (n = 586)***	***P* Value (Stage 3 Versus Stages 4 and 5)**	**Stages 4 and 5 (n = 336)†**
Age, years	54.75 ± 11.17	<0.001	59.75 ± 10.14	59.91 ± 10.00	0.41	59.46 ± 10.39
Sex, male	67 (616/922)	<0.001	56 (520/922)	58 (339/586)	0.24	54 (181/336)
Etiology						
Alcoholic cirrhosis	32 (290/918)	<0.001	29 (265/914)	27 (157/581)	0.15	32 (108/333)
HCV	20 (183/918)		19 (171/914)	21 (121/581)		15 (50/333)
HCV plus alcoholic cirrhosis	17 (153/918)		12 (109/914)	11 (66/581)		13 (43/333)
NASH	17 (153/918)		28 (256/914)	29 (167/581)		27 (89/333)
Other	15 (139/918)		12 (113/914)	12 (70/581)		13 (43/333)
Diabetes	27 (247/907)	<0.001	42 (379/910)	41 (237/580)	0.53	43 (142/330)
Admitted with infection	27 (244/916)	0.54	28 (255/914)	28 (164/581)	0.82	27 (91/333)
SBP on/during admission	7 (67/922)	0.02	10 (95/922)	9 (54/586)	0.18	12 (41/336)
UTI on/during admission	11 (97/922)	0.07	13 (122/922)	12 (68/586)	0.06	16 (54/336)
Ascites	68 (624/920)	<0.001	76 (703/921)	76 (442/585)	0.52	78 (261/336)
Refractory ascites	28 (255/920)	<0.001	41 (381/921)	37 (216/585)	<0.001	49 (165/336)
Hospitalized in last 6 months	64 (539/844)	0.04	69 (583/850)	67 (367/544)	0.36	71 (216/306)
Medication used						
PPI	54 (467/866)	0.26	57 (469/828)	56 (296/529)	0.61	58 (173/299)
NSBB	39 (351/901)	0.34	41 (369/896)	42 (237/571)	0.83	41 (132/325)
SBP prophylaxis	16 (145/890)	0.02	20 (181/884)	20 (113/563)	0.73	21 (68/321)
Rifaximin	29 (262/906)	<0.001	42 (379/897)	42 (243/572)	0.89	42 (136/325)
Lactulose	54 (491/906)	0.06	59 (528/902)	58 (331/573)	0.57	60 (197/329)

NOTE: Data are given as mean ± SD or % (n).

*Stage 3 CKD is defined as GFR ≥30 to <60 mL/minute/1.73 m^2.

†Stages 4 and 5 CKD are defined as GFR <30 mL/minute/1.73 m^2.

TABLE 3.

Baseline Laboratory Data and Hospital Course for the Propensity Score–Matched Cohorts and According to the Severity of Kidney Dysfunction in the CKD+ Group

			CKD+ Patients			
	All CKD− Patients (n = 922)	***P* Value (CKD+ Versus CKD−)**	**All Patients (n = 922)**	**Stage 3 (n = 586)***	***P* Value (Stage 3 Versus Stages 4 and 5)**	**Stages 4 and 5 (n = 336)†**
Bilirubin, mg/dL	6.11 ± 9.09	0.06	6.51 ± 9.20	6.15 ± 8.17	0.55	7.13 ± 10.74
Albumin, g/L	2.75 ± 0.62	<0.001	2.90 ± 0.72	2.83 ± 0.68	<0.001	3.03 ± 0.76
WBC count, $\times 10^9$/L	4.80 ± 4.88	0.03	5.44 ± 5.67	5.50 ± 5.53	0.16	5.35 ± 5.92
INR	1.66 ± 0.57	0.06	1.76 ± 0.74	1.74 ± 0.78	0.03	1.79 ± 0.66
Serum Na, mEq/L	134.1 ± 8.6	0.02	133.7 ± 6.3	134.0 ± 6.2	0.04	133.2 ± 6.3
SCr, mg/dL	0.83 ± 0.21	<0.001	2.19 ± 1.26	1.54 ± 0.35	<0.001	3.32 ± 1.46
Child-Pugh score	9.74 ± 2.04	0.70	9.78 ± 2.05	9.76 ± 2.07	0.68	9.80 ± 2.02
MELD score	16.73 ± 5.88	<0.001	22.94 ± 7.62	20.55 ± 6.91	<0.001	27.09 ± 6.99
SIRS	29 (259/903)	0.87	28 (257/913)	27 (154/579)	0.17	31 (103/334)
Length of hospital stay, days	12.41 ± 42.26	<0.001	14.02 ± 13.56	12.74 ± 13.27	<0.001	16.23 ± 13.79
ICU admission	18 (170/919)	<0.001	30 (276/918)	26 (150/584)	<0.001	38 (126/334)
Started on dialysis	2 (17/917)	<0.001	11 (98/920)	7 (40/584)	<0.001	17 (58/336)
Number of other organ failures		<0.001			<0.01	
0	79 (727/920)		68 (626/922)	72 (424/586)		60 (202/336)
1	15 (142/920)		22 (201/922)	18 (108/586)		28 (93/336)
2	4 (36/920)		8 (70/922)	7 (42/586)		8 (28/336)
3	2 (15/920)		3 (25/922)	2 (12/586)		4 (13/336)
ACLF‡	6 (59/920)	<0.001	14 (132/922)	11 (63/586)	<0.001	21 (69/336)
Received a LT	2 (21/922)	<0.001	7 (62/922)	4 (26/586)	<0.001	11 (36/336)

NOTE: Data are given as mean ± SD or % (n).

*Stage 3 CKD is defined as GFR ≥30 to <60 mL/minute/1.73 m^2.

†Stages 4 and 5 CKD are defined as GFR <30 mL/minute/1.73 m^2.

‡ACLF is defined as ≥2 organ failures as per the NACSELD from Bajaj et al.[19] (2014) and O'Leary et al.[20] (2018).

TABLE 4.

Renal Outcome and Hospital Course of the Propensity Score–Matched Cohorts and According to the Severity of Renal Dysfunction in the CKD+ Group

			CKD+ Patients			
	All CKD− Patients (n = 922)	***P* Value (CKD+ Versus CKD−)**	**All Patients (n = 922)**	**Stage 3 (n = 586)***	***P* Value (Stage 3 Versus Stages 4 and 5)**	**Stages 4 and 5 (n = 336)†**
Length of hospital stay, days	12.4 ± 42.3	<0.001	14.0 ± 13.6	12.7 ± 13.3	<0.001	16.2 ± 13.8
ICU admission	19 (170/919)	<0.001	30 (276/918)	26 (150/584)	<0.01	38 (126/334)
Started on dialysis	2 (17/917)	<0.001	11 (98/920)	7 (40/584)	<0.001	17 (58/336)
Number of other organ failures		<0.001			<0.01	
0	79 (727/920)		68 (626/922)	72 (424/586)		60 (202/336)
1	15 (142/920)		22 (201/922)	18 (108/586)		28 (93/336)
2	4 (36/920)		8 (70/922)	7 (42/586)		8 (28/336)
3	2 (15/920)		3 (25/922)	2 (12/586)		4 (13/336)
Type of organ failure						
HE grade III/IV	12 (112/912)	<0.01	18 (161/906)	16 (93/578)	0.08	21 (68/328)
Mechanical ventilation	10 (93/920)	<0.001	16 (145/922)	13 (75/586)	<0.01	21 (70/336)
Shock	6 (54/895)	<0.001	13 (110/880)	11 (60/559)	0.04	16 (50/321)
ACLF‡	6 (59/920)	<0.001	14 (132/922)	11 (62/586)	<0.001	21 (69/336)
Received a LT	2 (21/922)	<0.001	7 (62/922)	4 (26/586)	<0.001	11 (36/336)
3-month readmission	46 (329/712)	0.01	53 (319/600)	54 (223/411)	0.43	54 (96/189)

*Stage 3 CKD is defined as GFR ≥30 to <60 mL/minutes/1.73 m^2.

†Stages 4 and 5 CKD are defined as GFR <30 mL/minutes/1.73 m^2.

‡ACLF is defined as ≥2 organ failures as per the NACSELD from Bajaj et al.[19] (2014) and O'Leary et al.[20] (2018).

TABLE 5.

Multivariable Model of Variables Associated With CKD in Cirrhosis

Variable	Estimate	Standard Error	Wald χ^2	*P* Value	OR (95% CI)
Age	0.04	0.01	56.85	<0.001	1.04 (1.03–1.05)
NASH etiology	0.32	0.13	6.49	0.01	1.38 (1.08–1.77)
Diabetes	0.42	0.11	15.24	<0.001	1.52 (1.23–1.88)
Refractory ascites	0.61	0.10	34.84	<0.001	1.85 (1.51–2.26)