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Longer time to recovery from acute kidney injury is associated with major adverse kidney events in patients with cirrhosis

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Summary

Background: In patients with cirrhosis and acute kidney injury (AKI), longer time to AKI-recovery may increase the risk of subsequent major-adverse-kidney-events (MAKE).

Aims: To examine the association between timing of AKI-recovery and risk of MAKE in patients with cirrhosis.

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CONFLICT OF INTEREST STATEMENT

ASA has received consulting fees from Mallinckrodt Pharmaceuticals, Ocelot Bio, and Cymabay therapeutics. None of the aforementioned disclosures are related to the study. Remaining authors have no disclosures to report.

SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

Methods: Hospitalised patients with cirrhosis and AKI (n = 5937) in a nationwide database were assessed for time to AKI-recovery and followed for 180-days. Timing of AKI-recovery (return of serum creatinine <0.3 mg/dL of baseline) from AKI-onset was grouped by Acute-Disease-Quality-Initiative Renal Recovery consensus: 0–2, 3–7, and >7-days. Primary outcome was MAKE at 90-180-days. MAKE is an accepted clinical endpoint in AKI and defined as the composite outcome of ≥25% decline in estimated-glomerular-filtration-rate (eGFR) compared with baseline with the development of de-novo chronic-kidney-disease (CKD) stage ≥3 or CKD progression (≥50% reduction in eGFR compared with baseline) or new haemodialysis or death. Landmark competing-risk multivariable analysis was performed to determine the independent association between timing of AKI-recovery and risk of MAKE.

Results: 4655 (75%) achieved AKI-recovery: 0–2 (60%), 3–7 (31%), and >7-days (9%). Cumulative-incidence of MAKE was 15%, 20%, and 29% for 0–2, 3–7, >7-days recovery groups, respectively. On adjusted multivariable competing-risk analysis, compared to 0-2-days, recovery at 3–7 and >7-days was independently associated with an increased risk for MAKE: sHR 1.45 (95% CI 1.01–2.09, p = 0.042), sHR 2.33 (95% CI 1.40–3.90, p = 0.001), respectively.

Conclusion: Longer time to recovery is associated with an increased risk of MAKE in patients with cirrhosis and AKI. Further research should examine interventions to shorten AKI-recovery time and its impact on subsequent outcomes.

1 | INTRODUCTION

Acute kidney injury (AKI) is the sudden loss of kidney function that occurs frequently in hospitalised patients with cirrhosis. It develops in up to 53%[1-5] and is independently associated with high short-term mortality.[1-7] AKI in cirrhosis is also associated with major adverse kidney events (MAKE) which includes the development of de-novo chronic kidney disease (CKD) and progressive loss of kidney function in patients with pre-existing CKD.[4,8-10] MAKE can lead to recurrent AKI (i.e., AKI on top of CKD) and other organ failures[11] and therefore contributes to significant morbidity and mortality.[8,11,12]

To prevent MAKE and their associated downstream outcomes in patients with cirrhosis, identifying patients at high risk is essential. Most studies attempting to identify risk factors for MAKE following AKI have focused on patient characteristics, baseline kidney function, and AKI severity.[4,8-10,13] However, in those who recover from AKI, it is unknown whether a longer time to AKI recovery affects the risk of MAKE. An improved understanding of this association is important as it would help identify which patients with recovery are at the highest risk for MAKE to allow for targeted personalised care, and it would provide critical insight on clinical trial design for interventions aimed to prevent MAKE. Thus, we aimed to examine the association between timing of recovery and risk of MAKE in patients with AKI recovery in a nationwide US cohort of hospitalised patients with cirrhosis and AKI.

2 | MATERIALS AND METHODS

2.1 | Data source and study population

Consecutive patients with cirrhosis over the age of 18 with AKI (see Definitions: AKI, AKI Recovery, and CKD) who were hospitalised between January 1, 2009, and September

1, 2017, were identified in the Cerner Health Facts Database (Cerner Corporation, Kansas City, Missouri). Details of the database and study cohort (N = 6250) have been previously described.[10] We excluded patients who were started on haemodialysis (HD) during the index hospitalisation (N = 313) for our outcome analysis (see Outcomes). Cirrhosis and its aetiology, liver-related complications, comorbidities, infections, history of liver or kidney transplantation, and HD status were extracted through previously validated international classification of diseases (ICD) 9 and 10 codes,[5,14,15] which are summarised on Table S1. This study was approved by the Indiana University Institutional Review Board.

2.2 | Outcomes

Patients were followed for 180 days from the time of initial AKI event to assess for outcomes. The primary outcome was MAKE 90–180 days from AKI onset. MAKE was defined as a composite outcome: in those without pre-existing CKD, a ≥25% decline in eGFR compared to baseline with the development of de-novo CKD stage ≥3 (see Definitions: AKI, AKI Recovery, and CKD); in those with pre-existing CKD, a ≥50% reduction in eGFR compared to baseline; or new haemodialysis or death in any patient. This definition is consistent with previous work and is an accepted clinical endpoint in AKI.[16-21]

2.3 | Definitions: AKI, AKI recovery, and CKD

2.3.1 | AKI—AKI was defined by the International Club of Ascites (ICA),[22] which is in line with the Kidney Disease Improving Global Outcomes (KDIGO) definition,[23] as either: (1) a rise in serum creatinine (sCr) of ≥0.3 mg/dL from baseline within 48 h or (2) increase in sCr to 1.5x baseline, which is known or presumed to have occurred within the prior 7 days. AKI stage was defined by the ICA[22] which is also in line with KDIGO.[23] Baseline sCr was defined per the ICA,[22] which was based on the availability of sCr within the previous 3 months of AKI onset. In patients who did not have a baseline sCr within the previous 3 months, the last sCr value between month 4 and 1 year before AKI onset was used as the baseline. If a sCr was not available within 1 year of hospitalisation, the first sCr value at the time of hospitalisation was considered as baseline as recommended by the ICA.[22] The median time between baseline sCr and admission sCr was 33 days. Recurrent AKI was defined as AKI occurring at least 48 hours after AKI recovery.[24]

2.3.2 | AKI recovery—AKI recovery was defined by Acute Disease Quality Initiative (ADQI) Acute Kidney Disease (AKD) and Renal Recovery consensus definition: return of sCr within 0.3 mg/dL of baseline sCr.[24] Timing of AKI recovery from AKI onset were grouped per ADQI AKD and Renal Recovery consensus: 0–2 days (rapid recovery), 3–7 days (persistent AKI with recovery), and >7 days (AKD with recovery).[24] AKI non-recovery was defined as a lack of recovery throughout 89 days.

2.3.3 | CKD—CKD was defined per KDIGO guidelines, as the persistence of eGFR <60 mL/min per 1.73 m^2 for least 3 months.[25] The Chronic Kidney Disease Epidemiology Collaboration equation was used to calculate eGFR.[26]

2.4 | Hospitalisation details

Demographic details (age, gender, race), hospital type (rural, urban teaching, urban non-teaching), co-morbid conditions [via Charlson Comorbidity Index[27,28] excluding liver disease component], baseline sCr, mean arterial blood pressure (MAP), laboratory data at the time of AKI, and all sCr measurements during the follow up period were also extracted. Cirrhosis aetiology [alcohol, hepatitis C, non-alcoholic steatohepatitis (NASH), and other] and data on cirrhosis-related complications [oesophageal variceal haemorrhage, ascites, hepatic encephalopathy, spontaneous bacterial peritonitis (SBP)] and non-SBP infections were obtained via inpatient ICD-9 and 10 codes (see Table S1). In addition, intensive care unit (ICU) transfer and its associated interventions (vasopressor and mechanical ventilation use) were extracted. Model for end-stage liver disease sodium score (MELD-Na)[29] was captured at the time of AKI.

2.5 | Statistical analysis

Patient clinical and laboratory characteristics were compared between AKI recovery groups. Categorical variables were presented as percentages and continuous variables were presented as median with interquartile range (IQR). Differences across groups with respect to categorical variables were analysed using chi-square tests and continuous variables were analysed using analysis of variance.

2.5.1 | Primary outcome analysis—To account for immortal time bias related to different recovery groups, a landmark analysis was performed,[30] where recovery times were defined at day 90 from AKI onset (landmark time) and all patients with outcomes (mortality or liver transplant) prior to that time were excluded. MAKE between recovery groups was compared using Fine and Grey competing risks regression, with creation of a cumulative incidence function. Liver transplantation during the follow up period was considered as competing risks, and patients lost to follow up were censored. Differences between cumulative incidence functions were determined using Grey's test. Univariable competing risk regression analyses were performed to identify factors associated with the primary outcome (i.e., MAKE). Variables with a p value of <0.1 for the primary outcome were then entered into a multivariable competing risk analysis to determine the independent association between AKI recovery groups and the primary outcome. Sensitivity analysis excluding patients with recurrent AKI was performed. In addition, to examine the impact of AKI non-recovery for the primary outcome, a sensitivity analysis was performed where all AKI recovery groups were compared to AKI non-recovery. Unadjusted sub-group analyses stratified by pre-existing CKD was performed. Since MAKE is a composite endpoint that combines the development of de-novo CKD and progression of underlying CKD, MAKE outcome was modified for those without pre-existing CKD (MAKE: ≥25% decline in eGFR compared to baseline with the development of de-novo CKD stage ≥3, new haemodialysis, and death) and with pre-existing CKD (MAKE: ≥50% reduction in eGFR compared to baseline; or new haemodialysis or death). Sub-hazard ratios (sHR) and their corresponding 95% confidence intervals (CI) were reported.

A two-sided nominal p-value <0.05 was considered statistically significant. All analytic assumptions were verified, and all analyses were performed using SAS v9.4 (SAS Institute).

3 | RESULTS

5937 patients met eligibility criteria. The median age (IQR) was 61 (52, 70) years and the majority were white (70.5%) and male (60.9%). The most common etiologies of cirrhosis were NASH (37.8%) followed by alcohol (26.1%) and hepatitis C (17.8%). The median baseline sCr and eGFR were 1.0 (0.70, 1.50) mg/dL and 71.8 (43.4103.0) ml/min per 1.73 m^2, respectively; 33.0% had CKD, 51.9% had diabetes, and 62.8% had ascites. The median MELD-Na score at the time of AKI was 23 (17, 28) and most patients were at urban teaching hospitals (63.0%). The median (IQR) hospital length of stay was 9 (5, 15) and 13.6% had in-hospital death.

3.1 | Comparisons of patient and clinical characteristics between AKI recovery groups

4655 (75%) achieved AKI recovery of which ninety six percent ($n = 4493$) achieved recovery during hospitalisation. Most patients achieved recovery within 0–2 days ($n = 2791$, 60.0%) followed by 3–7 days ($n = 1455$, 31.2%), and >7 days [409, 8.8%; median (IQR) days to recovery 13 (9, 28) days]. Comparisons of demographic and clinical characteristics between AKI recovery groups can be found on Table 1. Patients with longer recovery were more likely to have baseline CKD [3–7 days 34.2% ($n = 498$) and >7 days 45.5% ($n = 186$) vs. 0–2 days 23.5% ($n = 656$)] and ascites [3–7 days 65.6% ($n = 955$) and >7 days 70.4% ($n = 288$) vs. 0–2 days 56.2% ($n = 1569$)]. At the time of AKI, patients with longer recovery had higher sCr ($p < 0.001$), MELD-Na scores ($p < 0.001$) and severity of AKI ($p < 0.001$) (Table 1). In addition, patients in who recovered within 0–2 days had a higher proportion of hospital acquired AKI (59.4%) compared to patients who recovered at 3–7 days (48.0%) and >7 days (52.1%).

There were significant differences between the recovery groups for peak AKI stage (Figure 1). Patients with who recovered >7 days had higher rates of peak AKI stage 3 compared to the rest of the recovery groups 55.5% ($n = 227$) vs. 3–7 days 25.6% ($n = 372$) vs. 0–2 days 11.8% ($n = 328$) ($p < 0.001$). Similarly, patients who recovered >7 days had significantly higher rates of infection, intensive care unit admission, vasopressor use, and mechanical ventilation use compared to patients who recovered within 0–2 and 3–7 days ($p < 0.001$ for all) (Figure 2).

3.2 | Outcomes: Major adverse kidney events

Kinetics of eGFR stratified by AKI recovery groups during follow up can be found on Figure 3. The median (IQR) follow up time was 123 (99, 151) days. After 90 days (landmark time), 3860 patients were analysed for MAKE. Comparisons of cumulative incidence of MAKE between AKI recovery groups can be found on Figure 4. Compared to patients who recovered within 0–2 days, the cumulative incidence of MAKE at 180 days was significantly higher in patients who recovered within 3–7 and >7 days: 0–2 days 14.9% (95% CI 13.0, 17.0) vs. 3–7 days 20.3% (95% CI 17.3, 23.4) vs. >7 days 28.8% (95% CI 22.5, 35.3) (Grey's test $p < 0.001$). Comparisons of individual components of MAKE can be found on Table S2. Patients with longer recovery times had significantly higher rates of de-novo CKD ($p = 0.036$) and progression of CKD ($p < 0.001$). On unadjusted competing risk analysis (Table 2), compared to recovery group 0–2 days, recovery at 3–7, and >7

days was associated with an increased risk for MAKE: sHR 1.41 (95% CI 1.14–1.75, p = 0.001) and sHR 2.22 (95% CI 1.65–2.98, p = 0.001), respectively. Additional factors associated with MAKE are shown in Table S3. On adjusted multivariable competing risk analysis (Table 2), compared to 0–2 days, recovery at 3–7, and >7 days were independently associated with an increased risk for MAKE: sHR 1.45 (95% CI 1.03–2.04, p = 0.035), sHR 2.28 (95% CI 1.39–3.73, p = 0.001), respectively.

3.2.1 | Subgroup analysis—

2802 and 1058 patients had no pre-existing and pre-existing CKD, respectively. In patients without pre-existing CKD, compared to patients who recovered within 0–2 days, recovery at 3–7 and >7 days was associated with an increased risk for MAKE: unadjusted sHR 1.48 (95% CI 1.17, 1.88, p = 0.001) and unadjusted sHR 2.40 (95% CI 1.68, 3.42, p < 0.001), respectively. However, in patients with pre-existing CKD, only recovery at >7 days was associated with an increased risk for MAKE: 3–7 days [unadjusted sHR 1.23 (95% CI 0.78–1.93), p = 0.371] and >7 days [unadjusted sHR 2.13 (95% CI 1.27–3.57), p = 0.004].

3.2.2 | Sensitivity analysis

Recurrent AKI: After excluding patients who had recurrent AKI (n = 1367) during the follow up period, 2493 patients were analysed for MAKE. On multivariable competing risk analysis, compared to days 0–2, recovery at 3–7 and >7-days was independently associated with an increased risk for MAKE: sHR 2.08 (95% CI 1.21–2.59, p = 0.009), sHR 2.50 (95% CI 1.11–5.61, p = 0.027), respectively.

AKI non-recovery vs. recovery: 4751 patients (n = 891 with non-recovery and 3860 with recovery) were analysed for MAKE. The cumulative incidence of MAKE at 180 days in patients with AKI non-recovery was 32.0% (95% CI 28.0, 36.2). Compared to patients who recovered within 0–2 days and 3–7 days, AKI non-recovery was independently associated with an increased risk for MAKE, sHR 2.63 [(95% CI 1.87–3.73), p < 0.001] and sHR 1.79 [(95% CI 1.28–2.50), p < 0.001], respectively. However, the risk for MAKE was not significantly different in those with non-recovery compared to those with recovery >7 days (sHR 1.26, 95% CI 0.80–1.98) (Table 3).

4 | DISCUSSION

In this nationwide study of hospitalised patients with cirrhosis and AKI, we found most patients achieve AKI recovery within 7 days of AKI onset and a minority of patients have protracted recovery >7 days. Patients with longer recovery times were more likely to have diabetes, CKD, and ascites. Importantly, we found that the risk of MAKE increases with longer times to recovery, even when controlling for AKI and liver disease severity.

Most studies attempting to risk stratify patients for MAKE have focused on factors that include baseline kidney function, co-morbid conditions, and severity of AKI.[4,8-10,13] The recovery interval following AKI, however, has become increasingly recognised as carrying significant prognostic information,[24] and only few studies have examined how AKI recovery might affect prognosis in patients with cirrhosis.[10,31] Mindikoglu et al identified 5 different AKI recovery patterns in hospitalised patients with cirrhosis and found patients with severe

AKI with minimal improvement were at higher risk for death compared to patients with mild AKI with full improvement.[31] However, characterisation of recovery patterns in this study were restricted to hospitalisation, timing of AKI recovery was not considered, and long-term kidney outcomes were not examined. In another study performed by our group, where long term kidney outcomes were examined, we found patients who transitioned to AKD (i.e., AKI persistence >7 days), were at a higher risk for developing de-novo CKD.[10] This study extends upon these findings by including patients with underlying CKD, analysing various AKI/AKD recovery periods that extended to 89 days, and using the important consensus endpoint of MAKE. More importantly, our results demonstrate that not all recovery is the same and that protracted recovery carries important prognostic information.

A critical finding in our study was that the risk for MAKE was not significantly different between patients without recovery and those who recovered after 7 days (Table 3). These findings confirm the prognostic significance of AKD[10,24] and highlight a high-risk target population worthy of further investigation. These findings also highlight the importance of achieving AKI recovery before 7 days, which could be regarded as an important clinical endpoint for interventions targeting AKI. Possible early interventions that require further study include point of care ultrasound guided resuscitation to rapidly improve hypovolemia[32] and vasoconstrictors to maintain a mean arterial pressure >65–75 mmHg.[33,34]

Our findings have important clinical and research implications. KDIGO and the American Society of Nephrology have highlighted the transition of care for AKI survivors as an opportunity to reduce the long term sequalae associated with AKI which includes MAKE and death.[23,35] In a large US veterans' study of hospitalised patients with cirrhosis and AKI, outpatient follow-up with specialist providers within 15 days of discharge was associated with improved patient survival but only ~2.5% were seen within this time frame.[31] These data suggest close follow up after discharge for an AKI related hospitalisation could improve outcomes. Our findings suggest that the time to AKI recovery could help identify those at highest risk who may benefit from targeted interventions, such as early nephrology consultation, and inform on therapeutic clinical trial design. Our findings are also supported by recent findings by Balzer et al showing maladaptive/profibrotic proximal tubule pathways (pyroptsosis and ferroptosis) to be heightened after long ischemia and offer a potential target for therapeutics to hasten AKI recovery and prevent the transition from AKI to CKD.[36]

Our study had several limitations. First, although we used validated ICD-9/10 codes to capture hospitalised patients with cirrhosis, which carries >90% positive predictive value, the possibility of cirrhosis misclassification may exist. Second, we were unable to account for sarcopenia, which could lead to overestimation of eGFR[37] and therefore underestimate the incidence of MAKE. Third, because of the nature of the dataset, we lacked specific information to adjudicate AKI phenotypes. While it could be assumed that patients with recovery are more likely to have hypovolemic or pre-renal AKI, a study utilising point of care ultrasound after a volume challenge found a quarter of patients to remain hypovolemic.[38] These data shed light where specific interventions, like point of care ultrasound, could hasten recovery and therefore decrease the risk for MAKE. Similarly, we were not able to adjudicate the precipitant of AKI (i.e., over diuresis, etc.). As a result,

the probability of residual confounding by AKI causation cannot be completely ruled out. Future research is required to determine how the precipitant of AKI and its phenotype alters the relationship between the timing of recovery and long-term effects.

The strengths of this study include examination of a diverse nationwide cohort of hospitalised patients with cirrhosis and use of strict guideline sCr based definitions for AKI and AKI/AKD recovery. Also, the large sample size and longitudinal follow up in our study allowed for meaning comparisons for between recovery groups and its associated outcomes. Importantly, we utilised MAKE as an endpoint, which is a consensus derived clinical endpoint in AKI, that has not been described in a hospitalised cirrhotic population previously. Estimates of MAKE can inform on power calculations for interventional trials focused on hastening recovery and therefore preventing MAKE.

In conclusion, the duration of AKI recovery is heterogenous and longer time to recovery is independently associated with subsequent MAKE. Patients with protracted recovery following AKI, especially those who recovered >7 days, represented the highest risk group. Therefore, duration of recovery should be regarded as useful information to risk stratify survivors of AKI who require close monitoring, early nephrology referral, and if eligible, evaluation for liver transplantation. Future interventional randomised controlled trials that can modify the trajectories of recovery and therefore prevent MAKE in this patient population are warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

FUNDING INFORMATION

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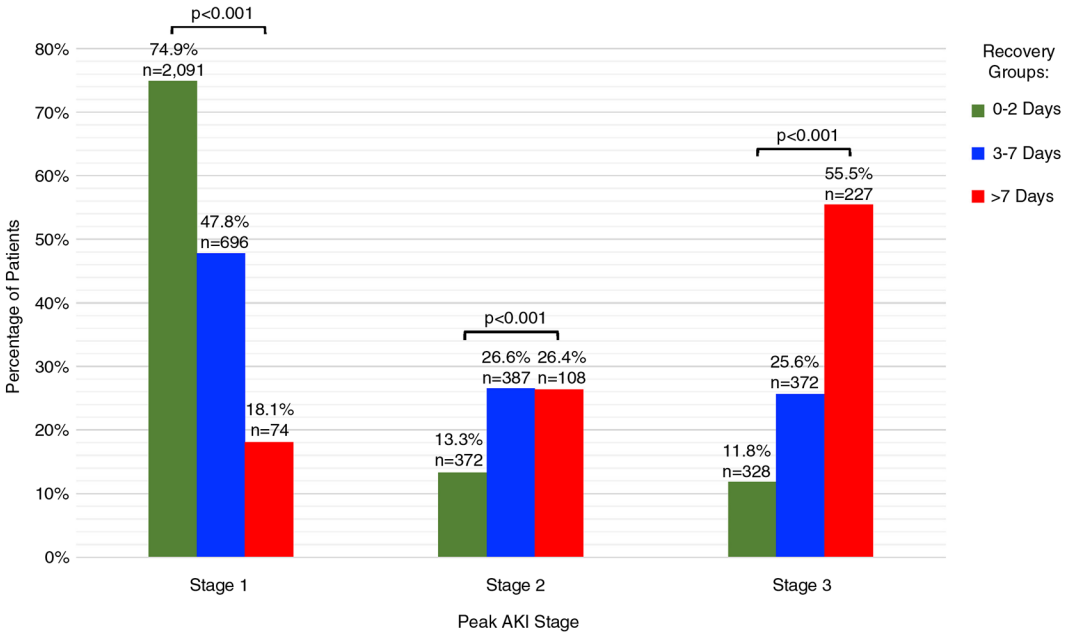

FIGURE 1.
Comparison of peak AKI stages between recovery groups. AKI, acute kidney injury.

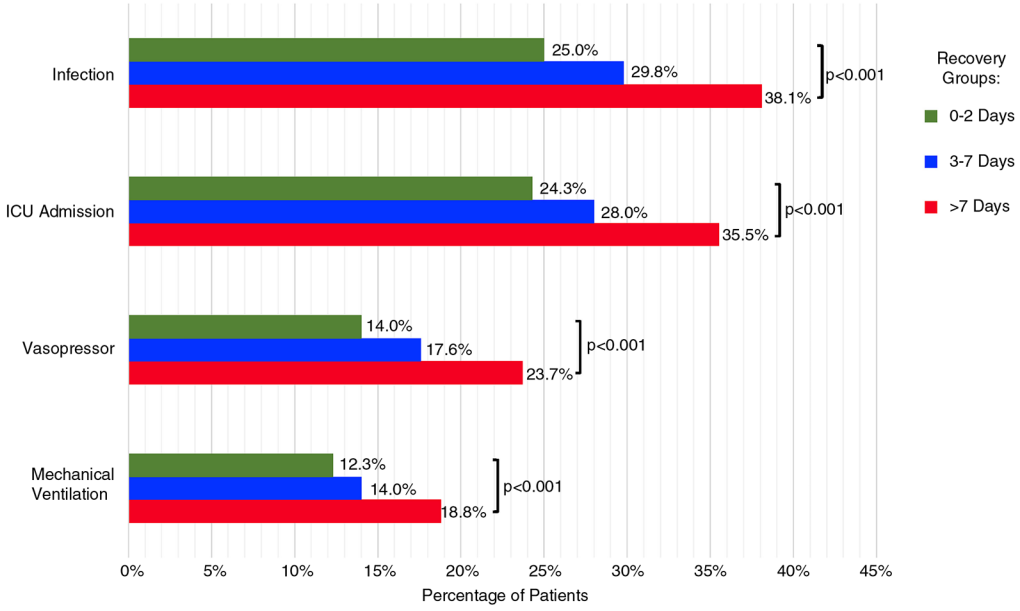

FIGURE 2.

Comparisons of infection, ICU admission, and ICU interventions between AKI recovery groups. AKI, acute kidney injury; ICU, intensive care unit.

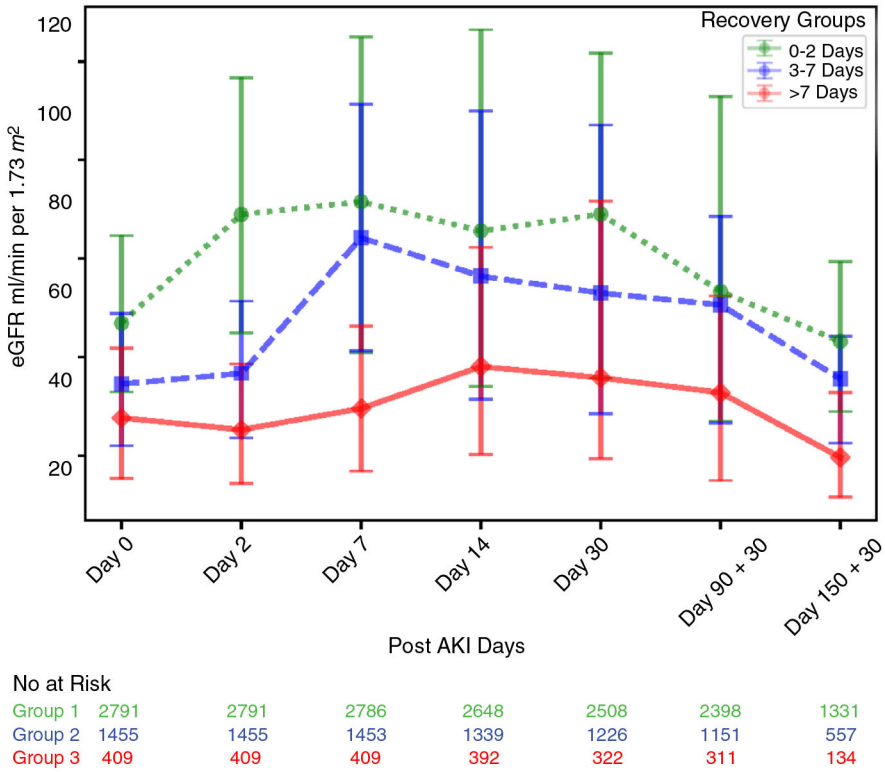

FIGURE 3.

Kinetics of eGFR stratified by AKI recovery group during follow up. Day 0 is time of AKI. AKI, acute kidney injury; eGFR, estimated glomerular filtration rate.

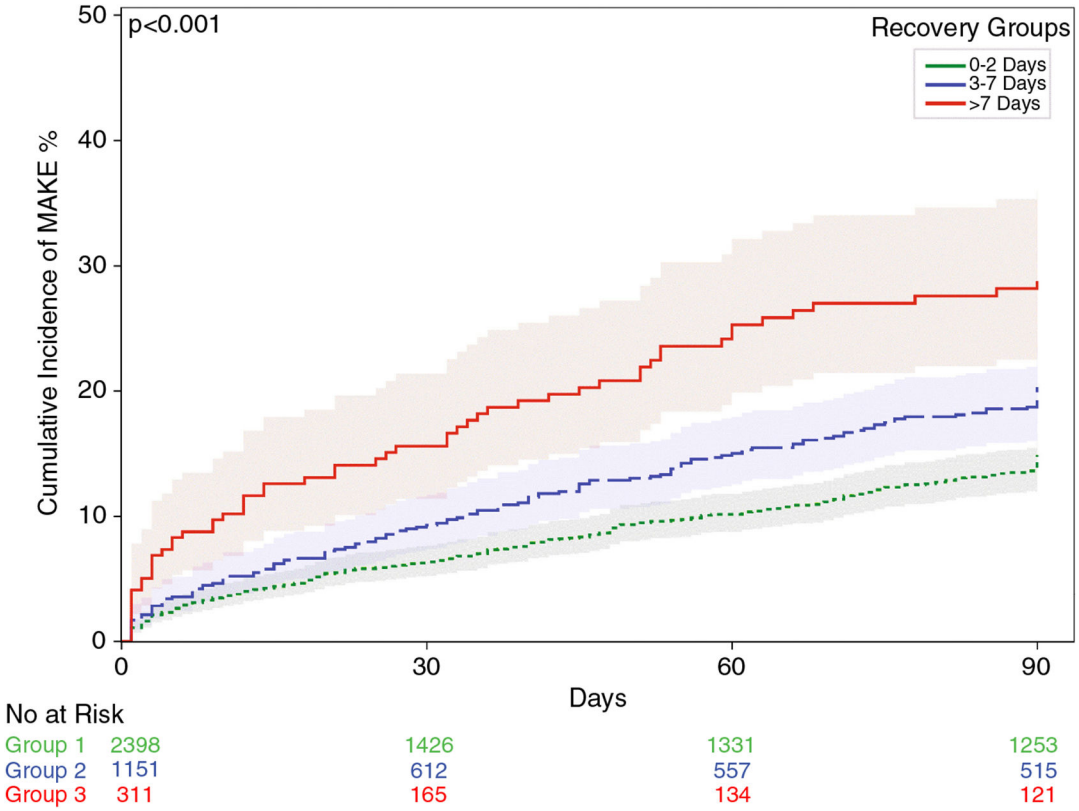

FIGURE 4.

Comparisons of cumulative incidence of MAKE between AKI recovery groups. Time 0 is 90 days from AKI event. AKI, acute kidney injury; MAKE, major adverse kidney events.

TABLE 1

Comparisons of patient and clinical characteristics between AKI recovery groups.

Variable	0–2 days *N* = 2791	3–7 days *N* = 1455	>7 days *N* = 409	*p*-value
Age	60 (52, 69)	62 (53, 71)	61 (53, 70)	< 0.001
Race, *n* (%)				
White	1994 (71.4)	1039 (71.4)	278 (68.0)	
Black	347 (12.5)	210 (14.4)	72 (17.6)	0.020
Other	450 (16.1)	206 (14.2)	59 (14.4)	
Sex, male *n* (%)	1699 (60.9)	861 (59.2)	245 (59.9)	0.925
Hospital type, *n* (%)				
Rural	576 (20.6)	287 (19.7)	91 (22.2)	
Urban non-teaching	440 (15.8)	227 (15.6)	59 (14.5)	0.796
Urban teaching	1775 (63.6)	941 (64.7)	259 (63.3)	
Aetiology of cirrhosis, *n* (%)				
Hepatitis C	475 (17.0)	256 (17.6)	76 (18.6)	
Alcohol	809 (29.0)	355 (24.4)	92 (22.5)	0.034
NASH	1027 (36.8)	578 (39.7)	169 (41.3)	
Other	140 (5.0)	87 (6.0)	25 (6.1)	
Unknown aetiology	340 (12.2)	179 (12.3)	47 (11.5)	
CCI without liver disease	2 (1,4)	2 (1,6)	3 (1, 6)	< 0.001
Diabetes, *n* (%)	1400 (50.2)	797 (54.8)	224 (54.8)	< 0.001
Hypertension, *n* (%)	1591 (57.0)	880 (60.5)	257 (62.8)	0.018
BMI, kg/m^2	27 (23.2, 32.4)	27.7 (23.7, 33.4)	27.6 (23.9, 33.5)	0.010
Baseline CKD, *n* (%)	656 (23.5)	498 (34.2)	186 (45.5)	< 0.001
Baseline creatinine, mg/dL	0.9 (0.7, 1.4)	1.0 (0.7, 1.4)	1.10 (0.80, 1.75)	< 0.001
Baseline eGFR, mL/min/1.73m^2	75.0 (45.4, 98.0)	70.1 (45.4, 98.0)	64.1 (36.1, 95.5)	< 0.001
Ascites, *n* (%)	1569 (56.2)	955 (65.6)	288 (70.4)	< 0.001
Hepatic encephalopathy, *n* (%)	701 (25.1)	398 (27.4)	127 (31.1)	0.022
Variceal haemorrhage, *n* (%)	150 (5.4)	58 (4.0)	12 (2.9)	0.026
MAP at time of AKI, mmHg	81 (72, 93)	78 (68, 89)	79 (70, 91)	< 0.001
Laboratory at time of AKI				

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Variable	0–2 days *N* = 2791	3–7 days *N* = 1455	>7 days *N* = 409	*p*-value
WBC, 10^3	9.0 (6.0, 13.0)	9.5 (6.4, 14.0)	9.7 (6.6, 13.7)	0.062
Sodium, mmol/L	135 (128, 139)	134 (126, 138)	133 (126, 138)	0.851
Creatinine, mg/dL	1.4 (1.1, 1.9)	1.8 (1.4, 2.7)	2.2 (1.6, 3.6)	< 0.001
Albumin, g/dL	2.8 (2.3, 3.4)	2.7 (2.2, 3.3)	2.6 (2.1, 3.1)	< 0.001
Total bilirubin, mg/dL	1.6 (0.8, 3.9)	2.0 (0.9, 4.1)	1.7 (0.8, 4.3)	0.002
INR	1.3 (1.1, 1.7)	1.4 (1.2, 1.8)	1.5 (1.2, 1.9)	< 0.001
MELD-Na	20 (14, 26)	24 (19, 29)	26 (22, 30)	< 0.001
Stage of AKI at diagnosis, *n* (%)				
1	2430 (87.1)	1005 (69.1)	254 (62.1)	
2	275 (9.8)	289 (19.9)	72 (17.6)	< 0.001
3	86 (3.1)	161 (11.0)	83 (20.3)	
Hospital acquired AKI, *n* (%)	1659 (59.4)	699 (48.0)	217 (53.1)	< 0.001

Abbreviations: AKI, acute kidney injury; BMI, body mass index; CCI, charlson comorbidity index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; INR, international normalised ratio; MAP, mean arterial pressure; MELD-Na, Model for Endstage Liver Disease Sodium; NASH, non-alcoholic steatohepatitis; WBC, white blood count.

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TABLE 2

Unadjusted and adjusted models for risk of MAKE by AKI recovery groups.

Recovery groups	sHR (95% CI)	*p*-value
Unadjusted		
0–2 days	Reference	—
3–7 days	1.41 (1.14–1.75)	0.001
> 7 days	2.22 (1.65–2.98)	< 0.001
Adjusted		
0–2 days	Reference	—
3–7 days	1.45 (1.03–2.04)	0.035
>7 day	2.28 (1.39–3.73)	0.001

Note: Covariates in multivariable competing risk model: age, sex, race, ascites, race, ascites, alcohol cirrhosis, baseline eGFR, MAP at time of AKI, MELD-Na at time of AKI, SBP infection, peak AKI stage ≥2, ICU transfer during index hospitalisation, vasopressor use during index hospitalisation, and AKI recurrence.

Abbreviations: AKI, acute kidney injury; CI, confidence interval; eGFR, estimated glomerular filtration rate; MAP, mean arterial pressure; MELD-Na, Model for End-Stage Liver Disease Sodium; SBP, spontaneous bacterial peritonitis; sHR, sub hazard ratio.

TABLE 3

Unadjusted and adjusted multivariable competing risk model for MAKE: AKI non-recovery vs. AKI recovery groups.

Comparator groups	sHR for AKI non-recovery (95% CI)	*p*-value
Unadjusted		
0–2 days	2.44 (1.99–2.99)	< 0.001
3–7 days	1.73 (1.38–2.17)	< 0.001
> 7 days	1.10 (0.81–1.50)	0.530
Adjusted		
0–2 days	2.63 (1.87–3.73)	< 0.001
3–7 days	1.79 (1.28–2.50)	< 0.001
> 7 days	1.26 (0.80–1.98)	0.328

Note: Covariates in multivariable competing risk model: age, sex, race, ascites, race, ascites, alcohol cirrhosis, baseline eGFR, MAP at time of AKI, MELD-Na at time of AKI, SBP infection, peak AKI stage ≥2, ICU transfer during index hospitalisation, and vasopressor use during index hospitalisation. Note: AKI recurrence was not included in the model as patients with non-recovery could not have AKI recurrence as they did not achieve recovery.

Abbreviations: AKI, acute kidney injury; CI, confidence interval; eGFR, estimated glomerular filtration rate; MAP, mean arterial pressure; MELD-Na, Model for End-Stage Liver Disease Sodium; SBP, spontaneous bacterial peritonitis; sHR, sub hazard ratio.