BMJ Health & Care Informatics

Association of persistent acute kidney injury and renal recovery with mortality in hospitalised patients

Tezcan Ozrazgat-Baslanti,[1,2] Tyler J Loftus,[2,3] Yuanfang Ren,[1,2] Esra Adiyeke,[1,2] Shunshun Miao,[1,2] Haleh Hashemighouchani,[1,2] Rubab Islam,[1] Rajesh Mohandas,[1] Saraswathi Gopal,[1] Elizabeth A Shenkman,[4] Panos Pardalos,[5] Babette Brumback,[6] Mark S Segal,[1] Azra Bihorac [1,2]

To cite: Ozrazgat-Baslanti T, Loftus TJ, Ren Y, *et al*. Association of persistent acute kidney injury and renal recovery with mortality in hospitalised patients. *BMJ Health Care Inform* 2021;**28**:e100458. doi:10.1136/bmjhci-2021-100458

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bmjhci-2021-100458).

Received 05 August 2021
Accepted 08 November 2021

For numbered affiliations see end of article.

Correspondence to
Dr Azra Bihorac;
abihorac@ufl.edu

ABSTRACT

Objectives Acute kidney injury (AKI) affects up to one-quarter of hospitalised patients and 60% of patients in the intensive care unit (ICU). We aim to understand the baseline characteristics of patients who will develop distinct AKI trajectories, determine the impact of persistent AKI and renal non-recovery on clinical outcomes, resource use, and assess the relative importance of AKI severity, duration and recovery on survival.

Methods In this retrospective, longitudinal cohort study, 156 699 patients admitted to a quaternary care hospital between January 2012 and August 2019 were staged and classified (no AKI, rapidly reversed AKI, persistent AKI with and without renal recovery). Clinical outcomes, resource use and short-term and long-term survival adjusting for AKI severity were compared among AKI trajectories in all cohort and subcohorts with and without ICU admission.

Results Fifty-eight per cent (31 500/54 212) had AKI that rapidly reversed within 48 hours; among patients with persistent AKI, two-thirds (14 122/22 712) did not have renal recovery by discharge. One-year mortality was significantly higher among patients with persistent AKI (35%, 7856/22 712) than patients with rapidly reversed AKI (15%, 4714/31 500) and no AKI (7%, 22 117/301 466). Persistent AKI without renal recovery was associated with approximately fivefold increased hazard rates compared with no AKI in all cohort and ICU and non-ICU subcohorts, independent of AKI severity.

Discussion Among hospitalised, ICU and non-ICU patients, persistent AKI and the absence of renal recovery are associated with reduced long-term survival, independent of AKI severity.

Conclusions It is essential to identify patients at risk of developing persistent AKI and no renal recovery to guide treatment-related decisions.

Summary

What is already known?

- In surgical sepsis, acute kidney injury (AKI) trajectory subgroups have unique physiologic signatures, suggesting utility for targeted, therapeutic interventions; it is unknown whether similar subgroups exist among all hospitalised patients.
- Early recovery after AKI is associated with favourable long-term outcomes; it is unclear whether this association is affected by critical illness and AKI severity.

What does this paper add?

- To our knowledge, this study is the first large scale, granular description of associations among patient baseline characteristics, illness severity, AKI trajectory and severity and other clinical outcomes.
- Among large and diverse cohort of hospitalised patients and in subset of critically ill patients, persistent AKI and the absence of renal recovery were associated with fourfold to fivefold increased risk to die within a period of 3 years compared with patients who did not develop AKI, independent of AKI severity.
- Our study is strengthened by the use of validated computable phenotype for kidney health encompassing both chronic kidney disease and AKI while maintaining consistency with Kidney Disease: Improving Global Outcomes and Acute Disease Quality Initiative guidelines and addressing the potential racial biases introduced by race adjustments in glomerular filtration rate and creatinine using comprehensive reference creatinine calculations.
- The identification of AKI trajectory subgroups facilitates prognostication and identifies patients who may benefit from nephrology consultation and preventive measures.

INTRODUCTION

Acute kidney injury (AKI) affects nearly one-quarter of hospitalised patients worldwide and up to 60% of patients in the intensive care unit (ICU).[1–3] The delayed or incomplete recovery of renal function confers increased risk for chronic critical illness with poor long-term survival and quality of life.[4] Prevention, early diagnosis, and appropriate treatment with euvolaemia, avoidance of nephrotoxic substances, and relief of obstructive uropathy have variable efficacy in improving patient outcomes. To optimise these management strategies and their early

delivery, it is necessary to understand the trajectories of AKI and recovery among hospitalised patients.

AKI trajectories can be classified as rapidly reversed, persistent with renal recovery or persistent without renal recovery. These trajectory subgroups are important for risk-stratification in surgical sepsis patients, for whom AKI trajectory subgroups have unique physiological signatures of immunological and endothelial dysfunction, suggesting potential utility for targeted, therapeutic interventions.[5–7] Yet, it remains unknown whether these clinical trajectories apply to broader, heterogeneous cohorts of hospitalised patients and associated long-term outcomes remain unclear.[8–11]

We performed a retrospective, longitudinal study of 355 678 adult hospitalisations, 78 769 of which included ICU admission. Our objectives were to understand the baseline characteristics of patients who will develop distinct AKI trajectories, determine the impact of persistent AKI and renal non-recovery on clinical outcomes, resource use and assess the relative importance of AKI severity, duration and recovery on survival.

METHODS

Study design

Using the University of Florida Health (UFH) Integrated Data Repository as Honest Broker, we created a single-centre, longitudinal dataset extracted directly from the electronic health records of 156 699 patients ≥18 years admitted to UFH between 1 January 2012 and 22 August 2019. After exclusion of encounters with no serum creatinine measurement to determine AKI status during hospitalisation and within 48 hours of hospital admission, our final cohort included 355 678 hospital encounters from 138 140 patients (online supplemental figure 1, supplemental methods).

Assessment of kidney function

We developed and validated computable phenotype algorithms for comprehensive kidney health assessments during hospital admission to determine AKI status and classification.[12] Kidney Disease: Improving Global Outcomes (KDIGO) serum creatinine criteria[13] and consensus report of the Acute Disease Quality Initiative (ADQI) 16 Workgroup on renal recovery were used as conceptual frameworks for our computable phenotype algorithms.[5 7 14 15] Stage 1 AKI was termed 'mild AKI'; stages 2 and 3 were termed 'severe AKI'. Duration and evidence of renal recovery[5] were used to define rapidly reversed and persistent AKI with and without renal recovery at discharge. We defined an episode of AKI as beginning with AKI onset and ending if there are two consecutive days without AKI identified, thus allowing us to identify a new episode of AKI in a patient who has recovered from a previous episode of AKI. Persistent AKI was defined as an AKI episode lasting beyond 48 hours. Rapid reversal of AKI was defined as complete reversal of AKI by KDIGO criteria within 48 hours of AKI onset, and remaining as such. Frequency of creatinine testing within the first 2 days of AKI onset is reported in online supplemental table 1. Renal recovery was adjudicated for each episode of AKI based on normalisation criteria at the time of hospital discharge. We grouped each encounter based on the worst trajectory group during hospitalisation as persistent AKI without renal recovery, persistent AKI with renal recovery, rapidly reversed AKI or no AKI. Reference creatinine was determined using preadmission measurements (n=302 349, 85%)[7 16] or the estimated creatinine using the Modification of Diet in Renal Disease (MDRD) Study equation assuming that baseline estimated glomerular filtration rate (eGFR) is 75 mL/min/per 1.73 m^2 (n=52 544, 15%) (online supplemental methods).[13 17 18] Reference creatinine was used to estimate preadmission reference GFR using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[19] The race multiplier was removed to avoid the undesirable effects of racial corrections in MDRD and CKD-EPI formulae.[20–22] Online supplemental table 2 shows results of sensitivity analyses that shows reclassification in AKI trajectory group when race correction was included. For each patient, we calculated daily kinetic GFR using the estimate of creatinine production rate and per cent change in creatinine.[23]

Outcomes

Primary clinical outcomes were hospital, 1-year and 3-year mortality. Primary renal outcomes were new renal replacement therapy (RRT) and new CKD within 90 days or 1 year of hospital discharge as well as CKD progression within 1 year of hospital discharge. Other exploratory outcomes included hospital and 30-day outcomes (online supplemental methods).

Statistical analysis

Overall survival of each trajectory group was evaluated in 138 140 patients using log-rank and Kaplan-Meier methods. Propensity score-based inverse weighting was used to plot adjusted Kaplan-Meier curves in which the probability of being in a trajectory group was calculated using multinomial logistic model that included patient demographics (age, gender, African-American race) and Charlson Comorbidity Index score. Cox proportional-hazards regression used to assess associations between groups of interest (AKI, AKI severity, AKI trajectories and combination of AKI trajectory and severity) and time to death while controlling for demographics, Charlson Comorbidity Index score and provision of mechanical ventilation and ICU admission for ≥2 days, with the exception of exclusion of variable for prolonged ICU admission and mechanical ventilation for subgroup analysis of non-ICU cohort. Multivariate logistic regression was used to model hospital mortality with similar baseline characteristics variables. Models were also run with and without AKI severity to examine change in association after further adjustment of AKI severity included as indicators of severe AKI or stage 3 AKI. Survival models

were started at hospital discharge and followed up to 3 years. Model discrimination was assessed using Harrell's concordance index. Kinetic GFR values were visualised using line plots illustrating average values with 95% CIs over time. All p values were adjusted for multiple comparisons using Bonferroni methods.[24] Statistical analyses were performed with R V.3.5.3 and Python V.3.8 software (online supplemental methods).

RESULTS

Clinical characteristics of patients

Average age was 54 years with female and male sex approximately equally distributed (table 1, online supplemental table 3). The most common comorbidity was hypertension (63%) and the most common admission diagnosis was disease of the circulatory system (18%). Eighty-three per cent of all patients had urgent admission and 15% were transferred from another hospital. While 20% of all admissions included inpatient surgery, about 22% (78 769/355 678) of hospitalisations required ICU admission. Average age was higher for the ICU cohort (59 vs 54 years) with a higher proportion of male sex (54% vs 42%) and lower proportion of African-American race (18% vs 26%) (online supplemental tables 4 and 5).

Clinical trajectories of patients with AKI during hospitalisation

Overall, 54 212 patients (15%) developed AKI; 37 973 (11%) had AKI within 48 hours of admission (table 1, figure 1A). While 58% (31 500/54 212) had AKI that rapidly reversed within 48 hours, the remaining 42% (22 712/54 212) had persistent AKI. By the time of discharge or death, 62% (14 122/22 712) of all subjects with persistent AKI did not recover renal function.

We examined clinical trajectories of AKI in encounters stratified by requirement of ICU admission. Prevalence of AKI was higher in ICU cohort (35%, 27 711/78 769) than the non-ICU cohort (10%, 26 501/276 909) (figure 2A,D). In the non-ICU cohort, 69% (18 222/26 501) had rapidly reversed AKI; the remaining 31% (8279/26 501) had persistent AKI with 67% (5549/8279) of them not recovering renal function at discharge or death. Meanwhile, among ICU cohort, 48% (13 278/27 711) had rapidly reversed AKI; the remaining 52% (14 433/27 711) had persistent AKI with 59% (8573/14 433) of them not recovering renal function at discharge or death.

Regardless of trajectory and ICU admission, AKI patients had a greater burden of comorbid disease and had lower reference eGFR, especially for patients with persistent AKI (table 1, online supplemental tables 3–5). Forty per cent of all AKI patients had CKD with moderate/severe stage (55%). A greater proportion of AKI patients were transferred from another hospital (25% vs 13%). Sepsis, acute renal failure, congestive heart failure and respiratory disease were the most common admission diagnosis for persistent AKI patients (online supplemental figure 2). Patients without AKI had greater incidence of abdominal and chest pain as the admission diagnosis. Within 48 hours of admission, patients with persistent AKI had significantly higher blood urea nitrogen (mean range 35–36 mg/dL, SD range 25–26 mg/dL), serum creatinine (median range 1.5–1.6 mg/dL, IQR range 0.9–2.4 mg/dL), serum creatinine-reference creatinine ratio (mean range 1.9–2.1, SD range 1.4–1.8) and cystatin C (median 1.4 mg/L, IQR range 0.9–2.1 mg/L) compared with others (table 1, online supplemental table 6). Similar trends have been observed in ICU and non-ICU cohorts (online supplemental tables 7 and 8). We have observed that nephrotoxic exposure within first 2 and 3 days of hospital admission and between hospital admission and first AKI onset was significantly higher in persistent AKI patients compared with patients rapidly reversed AKI (table 1, online supplemental tables 6–8).

Compared with patients with rapidly reversed AKI, patients with persistent AKI were more likely to present with more severe stage (stage 3) (18%, 4143/22 712 vs 4%, 1221/31 500) and had greater incidence of RRT within 48 hours of admission (3%, 731/22 712 vs 0.03%, 10/31 500), with similar trends for the entire hospitalisation (table 2). Persistent AKI patients received significantly more blood products than others (14%, n=3259) and exhibited significantly greater fluid retention with an average fluid overload of approximately 1.2% of admission volume within 48 hours of admission. Volumes of intravenous saline infusions were higher in patients that developed AKI.

Early and sustained decline in kinetic GFR below 60 mL/min/1.73 m^2 was demonstrated among persistent AKI patients (online supplemental figure 3). Among patients with persistent AKI, those who failed to recover renal function at discharge had sustained kinetic GFR approximately 60 mL/min/1.73 m^2; those with renal recovery exhibited gradually increasing kinetic GFR.

Correlation of trajectories with biomarker profile

There were significant differences in biomarker distributions across trajectory groups within 24 hours of admission (online supplemental tables 6–8). Regardless of AKI trajectories and ICU admission requirement, AKI patients had lower systolic, diastolic and mean blood pressure, higher average glucose, lower average platelet counts and average albumin compared with patients without AKI. These differences were greatest within the ICU cohort.

Persistent AKI patients sustained longer duration of mean arterial blood pressure below 60 mm Hg (median range 111–120 min, IQR range 40–300 min) and received more vasopressors compared with patients without persistent AKI. Almost half of all patients with persistent AKI were admitted to the ICU and had greater incidence of mechanical ventilation (19%,

Table 1 Baseline and early admission characteristics by trajectory groups in all cohort

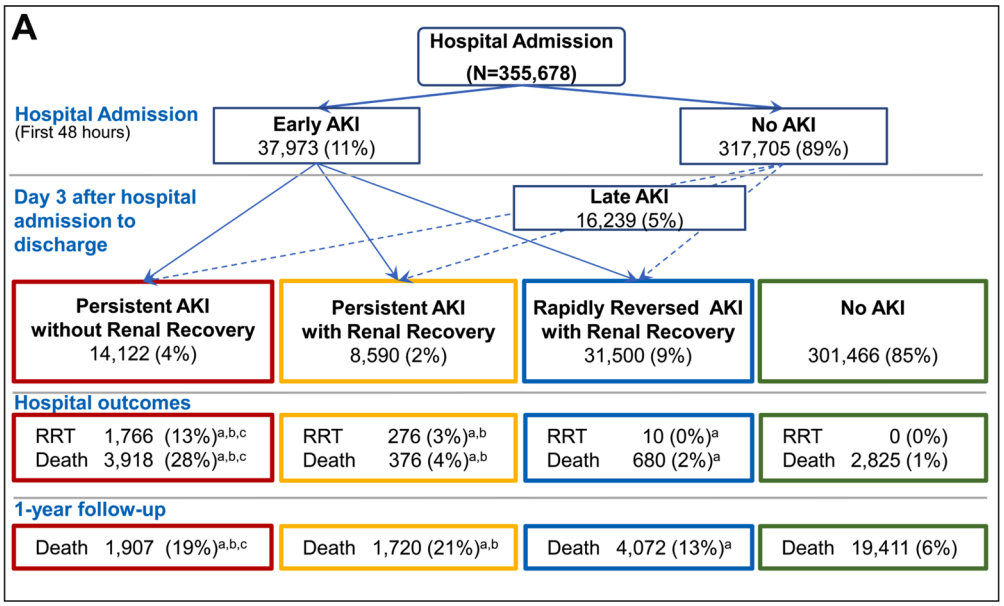
Variables	All subjects (N=355 678)	AKI (N=54 212, 15%)	Persistent AKI without renal recovery (N=14 122, 4%)	Persistent AKI with renal recovery (N=8590, 2%)	Rapidly reversed AKI (N=31 500, 9%)	No AKI (N=301 466, 85%)
Preadmission clinical characteristics						
Age, years, mean (SD)	54 (19)	60 (17)*	61 (17)*†	60 (17)*†	59 (17)*	53 (19)
Female sex, n (%)	196 023 (55)	27 146 (50)*	7137 (51)*‡	4116 (48)*†	15 893 (50)*	168 877 (56)
African American ethnicity, n (%)	85 825 (24)	12 411 (23)*	3057 (22)*†	1928 (22)*	7426 (24)*	73 414 (24)
Distance from hospital (mile), median (IQR)	14 (3–30)	21 (3–37)*	23 (9–41)*†‡	24 (10–42)†	18 (3–36)*	14 (3–27)
Comorbidities, n (%)						
Hypertension	225 192 (63)	36 556 (67)*	9100 (64)*†‡	5929 (69)*	21 527 (68)*	188 636 (63)
Chronic pulmonary disease	149 551 (42)	23 044 (43)*	5517 (39)*†‡	3771 (44)*	13 756 (44)*	126 507 (42)
Cardiovascular disease	129 930 (37)	23 451 (43)*	5619 (40)*†‡	3960 (46)*†	13 872 (44)*	106 479 (35)
Diabetes mellitus	104 546 (29)	18 331 (34)*	4359 (31)*†‡	2928 (34)*	11 044 (35)*	86 215 (29)
Chronic kidney disease	85 942 (24)	21 421 (40)*	5442 (39)*‡	3864 (45)*†	12 115 (38)*	64 521 (21)
Moderate/severe (≥G-stage 3)	34 956 (41)	11 739 (55)*	3025 (56)*	2211 (57)*†	6503 (54)*	26 236 (41)
Preadmission estimated glomerular filtration rate (mL/min per 1.73 m^2), median (IQR)	63.6 (46.4–85.1)	55.9 (37.9–78.7)*	53.9 (32.6–81.1)*†	54.1 (36.6–76.2)*†	57.2 (40.1–78.6)*	65.6 (49.5–86.6)
Admission characteristics, n (%)						
Emergent admission	295 286 (83)	45 927 (85)*	12 091 (86)*†	7355 (86)*†	26 481 (84)*	249 359 (83)
Transfer from another hospital	53 265 (15)	13 706 (25)*	4626 (33)*†	2721 (32)*†	6359 (20)*	39 559 (13)
Surgery on admission day	51 310 (14)	8327 (15)*	2179 (15)*‡	1455 (17)*†	4693 (15)*	42 983 (14)
Surgery at any time	72 541 (20)	15 216 (28)*	4068 (29)*†‡	3272 (38)*†	7876 (25)*	57 325 (19)
Kidney function within 48 hours of the admission						
AKI, n (%)	37 973 (11)	37 973 (70)*	9706 (69)*†	5908 (69)*†	22 359 (71)*	0 (0)
Stage 1	25 963 (68)	25 963 (68)*	4538 (47)*†‡	3132 (53)*†	18 293 (82)*	0 (0)
Stage 2	6646 (18)	6646 (18)*	2328 (24)*†	1473 (25)*†	2845 (13)*	0 (0)
Stage 3	5364 (14)	5364 (14)*	2840 (29 *†‡	1303 (22)*†	1221 (5)*	0 (0)
Stage three without RRT	4623 (12)	4623 (12)*	2217 (23)*†‡	1195 (20)*†	1211 (5)*	0 (0)
Stage three with RRT	741 (2)	741 (2)*	623 (6)*†‡	108 (2)*†	10 (0)*	0 (0)
Highest blood urea nitrogen (mg/dL), mean (SD)	18 (13)	30 (22)*	35 (26)*†‡	36 (25)*†	27 (17)*	15 (9)

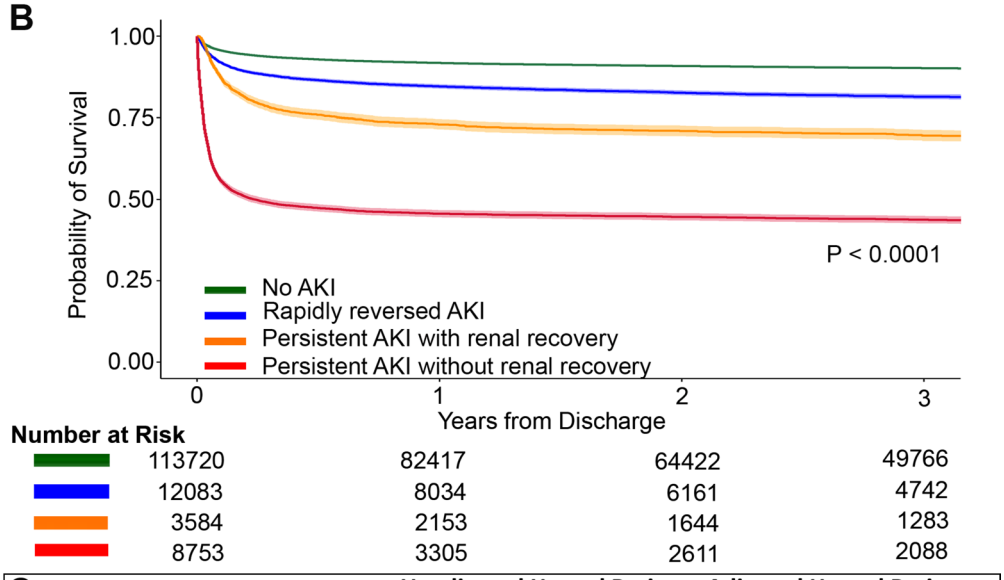
Continued

Table 1 Continued

Variables	All subjects (N=355 678)	AKI (N=54 212, 15%)	Persistent AKI without renal recovery (N=14 122, 4%)	Persistent AKI with renal recovery (N=8590, 2%)	Rapidly reversed AKI (N=31 500, 9%)	No AKI (N=301 466, 85%)
Highest serum creatinine (mg/dL), median (IQR)	0.9 (0.7–1.1)	1.4 (1.0–1.9)*	1.5 (0.9–2.4)*†‡	1.6 (1.0–2.4)*†	1.3 (1.0–1.7)*	0.8 (0.7–1.0)
Reference creatinine (mg/dL), median (IQR)	0.8 (0.7–1.0)	0.8 (0.7–1.1)*	0.8 (0.7–1.1)*†‡	0.9 (0.7–1.2)*†	0.8 (0.7–1.1)*	0.8 (0.7–0.9)
Highest/reference creatinine, mean (SD)	1.2 (0.6)	1.8 (1.2*	2.1 (1.8)*†	1.9 (1.4)*†	1.6 (0.7)*	1.1 (0.2)
Count of nephrotoxic drug, mean (SD)						
Within 2 days after hospital admission	0.86 (0.97)	1.26 (1.03)*	1.41 (1.03)*†	1.39 (1.03)*†	1.17 (1.02)*	0.79 (0.94)
Within 3 days after hospital admission	0.92 (1.00)	1.39 (1.07)*	1.54 (1.07)*†	1.55 (1.07)*†	1.27 (1.06)*	0.83 (0.97)
Between hospital admission and first AKI onset	1.33 (1.18)	1.33 (1.18)	1.49 (1.20)†	1.47 (1.20)†	1.23 (1.15)	NA

*P<0.05 compared with no AKI.
†P<0.05 compared with rapidly reversed AKI.
‡P<0.05 compared with persistent AKI with renal recovery.
§Cardiovascular disease was considered if there was a history of congestive heart failure, coronary artery disease of peripheral vascular disease.
AKI, acute kidney injury; NA, not applicable; RRT, renal replacement therapy.



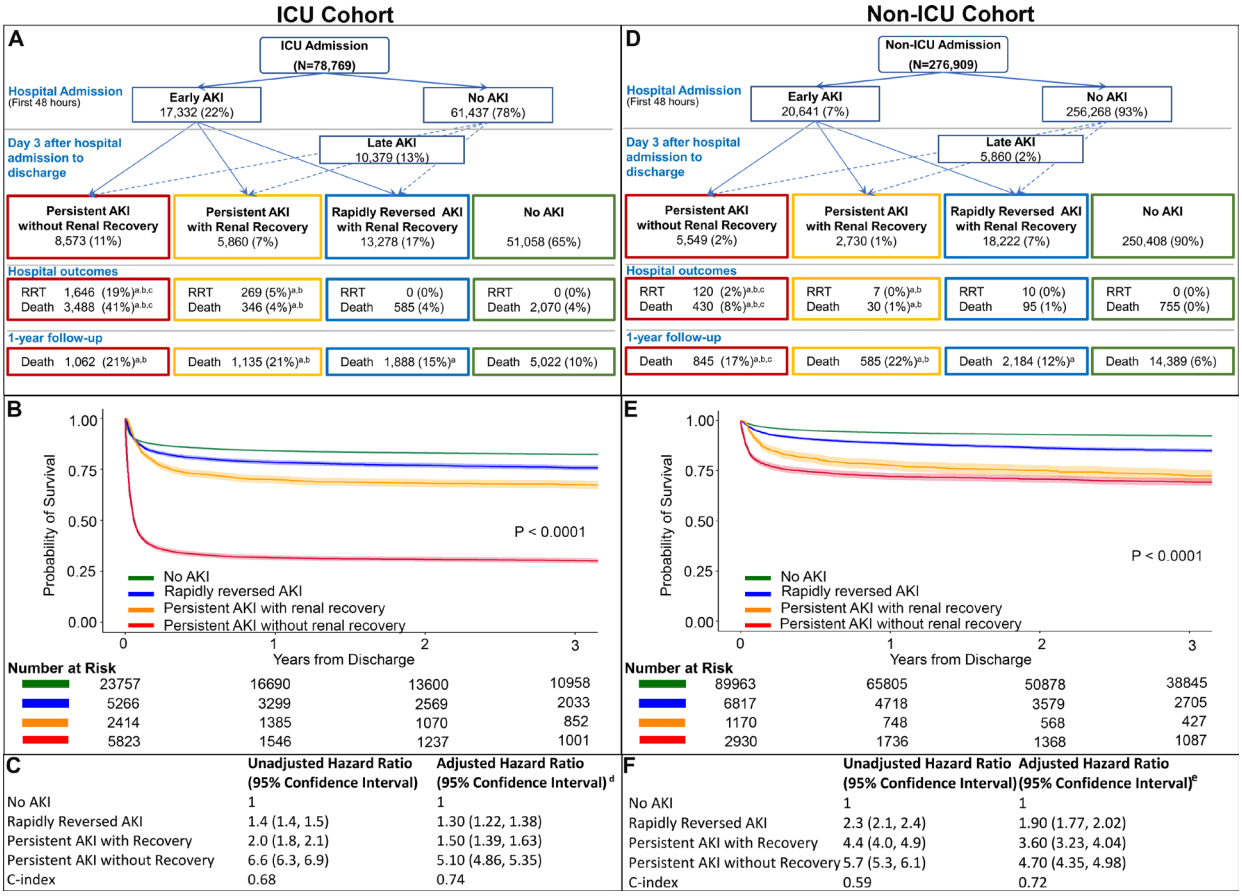


C

	Unadjusted Hazard Ratio (95% Confidence Interval)	Adjusted Hazard Ratio (95% Confidence Interval)[d]
No AKI	1	1
Rapidly Reversed AKI	2.2 (2.1, 2.3)	1.60 (1.50, 1.67)
Persistent AKI with Recovery	3.8 (3.5, 4.0)	1.90 (1.80, 2.03)
Persistent AKI without Recovery	9.7 (9.4, 10.0)	5.63 (5.40, 5.86)
C-index	0.67	0.77

Figure 1 Hospital and long-term outcomes by trajectories of acute kidney injury (AKI) in hospitalised adult patients. (A) Trajectories of AKI in hospitalised adult patients. 1-year follow-up outcome was reported among hospital survivors. (B) Adjusted Kaplan-Meier survival curves and number at risk by AKI trajectories. Propensity score based inverse weighting was used to plot adjusted Kaplan-Meier curves where propensity of being in a trajectory group was calculated using multinomial logistic model that included patient demographics (age, gender, ethnicity), and Charlson Comorbidity Index score. (C) Hazard ratios for all-cause mortality by AKI trajectories. [a]Significantly different from no AKI group (Bonferroni-adjusted p<0.05). [b]Significantly different from rapidly reversed AKI group (Bonferroni-adjusted p<0.05). [c]Significantly different from persistent AKI with renal recovery (Bonferroni-adjusted p<0.05). [d]Adjusted for age, gender, ethnicity, Charlson Comorbidity Index score, and need for mechanical ventilation for more than 2 days and need for intensive care unit admission for more than 2 days. RRT, renal replacement therapy.

4363/22 712) within 24 hours of hospital admission. Other biomarkers that were significantly different in patients with persistent AKI included lower average arterial oxygen tension/fractional inspired oxygen ratio (mean range 295–314, SD range 199–205), higher average lactate (mean range 2.9–3.6 mmol/L,



C

	Unadjusted Hazard Ratio (95% Confidence Interval)	Adjusted Hazard Ratio (95% Confidence Interval)[d]
No AKI	1	1
Rapidly Reversed AKI	1.4 (1.4, 1.5)	1.30 (1.22, 1.38)
Persistent AKI with Recovery	2.0 (1.8, 2.1)	1.50 (1.39, 1.63)
Persistent AKI without Recovery	6.6 (6.3, 6.9)	5.10 (4.86, 5.35)
C-index	0.68	0.74

F

	Unadjusted Hazard Ratio (95% Confidence Interval)	Adjusted Hazard Ratio (95% Confidence Interval)[e]
No AKI	1	1
Rapidly Reversed AKI	2.3 (2.1, 2.4)	1.90 (1.77, 2.02)
Persistent AKI with Recovery	4.4 (4.0, 4.9)	3.60 (3.23, 4.04)
Persistent AKI without Recovery	5.7 (5.3, 6.1)	4.70 (4.35, 4.98)
C-index	0.59	0.72

Figure 2 Hospital and long-term outcomes by trajectories of acute kidney injury (AKI) in hospitalised adult patients stratified by ICU admission. (A) Trajectories of AKI in hospitalised adult patients who have been admitted to ICU during hospitalisation. 1-year follow-up outcome was reported among hospital survivors. (B) Adjusted Kaplan-Meier survival curves and number at risk by AKI trajectories injury in hospitalised adult patients who have been admitted to ICU during hospitalisation. Propensity score based inverse weighting was used to plot adjusted Kaplan-Meier curves where propensity of being in a trajectory group was calculated using multinomial logistic model that included patient demographics (age, gender, ethnicity) and Charlson Comorbidity Index score. (C) HRs for all-cause mortality by AKI trajectories in hospitalised adult patients who have been admitted to ICU during hospitalisation. (D) Trajectories of AKI in hospitalised adult patients who have not been admitted to ICU during hospitalisation. 1-year follow-up outcome was reported among hospital survivors. (E) Adjusted Kaplan-Meier survival curves and number at risk by AKI trajectories in hospitalised adult patients who have not been admitted to ICU at any time during hospitalisation. Propensity score based inverse weighting was used to plot adjusted Kaplan-Meier curves where propensity of being in a trajectory group was calculated using multinomial logistic model that included patient demographics (age, gender, ethnicity) and Charlson Comorbidity Index score. (F) Hazard ratios for all-cause mortality by AKI trajectories in hospitalised adult patients who have not been admitted to ICU at any time during hospitalisation. [a]Significantly different from no AKI group (Bonferroni-adjusted p<0.05). [b]Significantly different from rapidly reversed AKI group (Bonferroni-adjusted p<0.05). [c]Significantly different from persistent AKI with renal recovery (Bonferroni-adjusted p<0.05). [d]Adjusted for age, gender, ethnicity, Charlson Comorbidity Index score, and need for mechanical ventilation for more than 2 days and need for ICU admission for more than 2 days. [e]Adjusted for age, gender, ethnicity, and Charlson Comorbidity Index score. ICU, intensive care unit; RRT, renal replacement therapy.

SD range 2.7–4.0 mmol/L) and lower average haematocrit (31%, SD 7%).

Persistence of kidney dysfunction and absence of recovery affect short-term and long-term outcomes

Median duration of AKI was 5 (IQR 3–8) days among patients with persistent AKI (table 2, online supplemental table 9). Persistent AKI patients required significantly more hospital resources, with longer mechanical ventilation (5 days), ICU admission (7 days) and hospital admission (10 days) compared with patients without AKI. Patients who required ICU admission had worse AKI stage, more AKI days and higher percentage of recurrent AKI (online supplemental tables 9–11), especially in the subset of persistent AKI patients.

Patients with persistent AKI without recovery of renal function had significantly higher in-hospital mortality (28%), followed by the next highest mortality rate in patients with persistent AKI with renal recovery (4%). Even after for adjustment for AKI severity and baseline

Table 2 Renal characteristics, resource utilisation and hospital outcomes during entire hospitalisation by trajectories of AKI in all cohort

Variables	All subjects (N=355 678)	AKI (N=54 212, 15%)	Persistent AKI without renal recovery (N=14 122, 4%)	Persistent AKI with renal recovery (N=8590, 2%)	Rapidly reversed AKI (N=31 500, 9%)	No AKI (N=301 466, 85%)
Renal characteristics during entire hospitalisation						
Worst AKI staging, n (%)						
Stage 1	36 258 (10)	36 258 (67)*	5210 (37)*†‡	4176 (49)*†	26 872 (85)*	0 (0)
Stage 2	9551 (3)	9551 (18)*	3762 (27)*†‡	2492 (29)*†	3297 (10)*	0 (0)
Stage 3	8403 (2)	8403 (16)*	5150 (36)*†‡	1922 (22)*†	1331 (4)*	0 (0)
Stage three without RRT	6351 (2)	6351 (12)*	3384 (24)*†‡	1646 (19)*†	1321 (4)*	0 (0)
Stage three with RRT	2052 (1)	2052 (4)*	1766 (13)*†‡	276 (3)†	10 (0)*	0 (0)
AKI duration, days, median (IQR)	2 (1–4)	2 (1–4)	5 (3–9) b‡	4 (3–7)	1 (1–2)	NA
Recurrent AKI, n (%)	6466 (2)	6466 (12)*	2173 (15)*†‡	1957 (23)*†	2336 (7)*	0 (0)
No renal recovery at discharge/death, n (%)	22 240 (6)	22 240 (41)*	14 122 (100)*†‡	0 (0)†	8118 (26)*	0 (0)
Resource utilisation during entire hospitalisation						
Hospital days, median (IQR)	3 (1–6)	7 (4–14)*	8 (4–15)*†‡	14 (8–24)*†	6 (3–10)*	2 (1–5)
Admission to ICU, n (%)	78 769 (22)	27 711 (51)*	8573 (61)*†‡	5860 (68)*†	13 278 (42)*	51 058 (17)
Days in ICU, median (IQR)	4 (2–7)	6 (3–12)*	6 (3–13)*†‡	9 (5–18)*†	5 (3–9)*	3 (–5)
Mechanical ventilation, n (%)	23 286 (7)	11 876 (22)*	4779 (34)*†	2876 (33)*†	4221 (13)*	11 410 (4)
Mechanical ventilation calendar days, median (IQR)	3 (2–6)	4 (2–9)*	4 (2–9)*†‡	5 (2–12)*†	3 (2–7)*	2 (1–4)
Vasopressor or inotropes used, n (%)	55 415 (16)	17 261 (32)*	6016 (43)*†	3781 (44)*†	7464 (24)*	38 154 (13)
Hospital disposition, n (%)						
Hospital mortality	7799 (2)	4974 (9)*	3918 (28)*†‡	376 (4)*†	680 (2)*	2825 (1)
Another hospital, LTAC, SNF, Hospice	34 092 (10)	10 028 (18)*	3011 (21)*†‡	2494 (29)*†	4523 (14)*	24 064 (8)
Home/rehab	313 787 (88)	39 210 (72)*	7193 (51)*†‡	5720 (67)*†	26 297 (83)*	274 577 (91)
30-day outcomes (among survivors), n (%)	347 879	49 238 (14)	10 204 (3)	8214 (2)	30 820 (9)	298 641 (86)
Death in 30 days of discharge	4934 (1)	1776 (4)*	570 (6)*†	418 (5)*†	788 (3)*	3158 (1)
Trajectory group for encounter with readmission within 30 days of discharge	83 592 (24)	12 748 (26)*	2528 (25)‡	2381 (29)*†	7839 (25)*	70 844 (24)
Persistent AKI with no renal recovery	2764 (3)	1297 (10)*	536 (21)*†‡	223 (9)*†	538 (7)*	1467 (2)

Continued

Table 2 Continued

Variables	All subjects (N=355 678)	AKI (N=54 212, 15%)	Persistent AKI without renal recovery (N=14 122, 4%)	Persistent AKI with renal recovery (N=8590, 2%)	Rapidly reversed AKI (N=31 500, 9%)	No AKI (N=301 466, 85%)
Persistent AKI with renal recovery	2118 (3)	933 (7)*	231 (9)*†	239 (10)*†	463 (6)*	1185 (2)
Rapidly reversed AKI	7505 (9)	2504 (20)*	502 (20)*	448 (19)*	1554 (20)*	5001 (7)
No AKI	59 164 (71)	7096 (56)*	1100 (44)*†‡	1337 (56)*†	4659 (59)*	52 068 (73)
Unknown	12 041 (14)	918 (7)	159 (6)*†	134 (6)*†	625 (8)*	11 123 (16)
Other complications during entire hospitalisation						
Venous thromboembolism, n (%)	15 755 (4)	5180 (10)*	1589 (11)*†‡	1290 (15)*†	2301 (7)*	10 575 (4)
Sepsis, n (%)	29 836 (8)	13 995 (26)*	5102 (36)*†‡	3275 (38)*†	5618 (18)*	15 841 (5)
Cardiovascular complication, n (%)	31 780 (9)	15 229 (28)*	5553 (39)*†	3469 (40)*†	6207 (20)*	16 551 (5)
Thirty-day mortality, n (%)	11 082 (3)	5655 (10)*	3962 (28)*†‡	506 (6)*†	1187 (4)*	5427 (2)
One-year mortality, n (%)	34 687 (10)	12 570 (23)*	5802 (41)*†‡	2054 (24)*†	4714 (15)*	22 117 (7)
Three-year mortality, n (%)	49 144 (14)	15 703 (29)*	6414 (45)*†‡	2669 (31)*†	6620 (21)*	33 441 (11)

*P<0.05 compared with rapidly no AKI.
†P<0.05 compared with rapidly reversed AKI.
‡P<0.05 compared with persistent AKI with renal recovery.
AKI, acute kidney injury; ICU, intensive care unit; LTAC, long-term acute care hospital; NA, not applicable; RRT, renal replacement therapy; SNF, skilled nursing facility.

characteristics (age, gender, Charlson Comorbidity Index score), odds of hospital mortality was significantly higher in all, ICU and non-ICU cohorts with OR range of 1.1–4.8 for persistent AKI without renal recovery and range of 12.0–40.6 for persistent AKI with renal recovery compared with no AKI group (online supplemental table 12). One-year mortality for patients with persistent AKI (35%, n=7856) was significantly higher compared with patients with rapidly reversed AKI (15%, n=4714) and those without AKI (7%, n=22 117).

One-year survival following persistent AKI without renal recovery was 46%, significantly lower than patients with persistent AKI with renal recovery (73%), rapidly reversed AKI (85%) and no AKI (92%) (figure 1B). Persistent AKI without renal recovery was associated with increased all-cause mortality with unadjusted and adjusted hazard ratios (HR) of 9.7 (95% CI 9.4 to 10.0) and 5.63 (95% CI 5.40 to 5.86), compared with no AKI group (figure 1C). One-year survival was substantially lower for persistent AKI without renal recovery group who required ICU admission. Adjusted hazard rate of all-cause mortality was approximately five times greater for persistent AKI without renal recovery group both in non-ICU and ICU cohorts (figure 2B, E, C and F). When further adjusted for AKI severity, HRs remained similar (online supplemental table 13).

A combination of AKI stage, duration and renal recovery at discharge classifications were used to perform analysis for seven subphenotypes. One-year survival after AKI was significantly lower relative to no AKI (figure 3A) while severe AKI was associated with lower survival compared with no AKI and mild AKI (figure 3B). One-year survival following severe-persistent AKI without renal recovery was 39%, significantly lower than for mild-persistent AKI without renal recovery (60%), severe-persistent AKI with renal recovery (73%), mild-persistent AKI with renal recovery (73%), severe-rapidly reversed AKI (84%), mild-rapidly reversed AKI (85%) and no AKI (92%) (figure 3D). While survival rates did not differ significantly between mild and severe AKI for rapidly reversed AKI and persistent AKI with renal recovery trajectories, they were significantly lower for the persistent AKI without renal recovery trajectory and mild-persistent AKI was associated with markedly worse outcomes than severe-rapidly reversed AKI (figure 3C,D). Similar trends were observed for ICU and non-ICU cohort (online supplemental figures 4 and 5). Sensitivity analysis excluding encounters whose reference creatinine was calculated using MDRD creatinine yielded similar HRs (online supplemental figure 6).

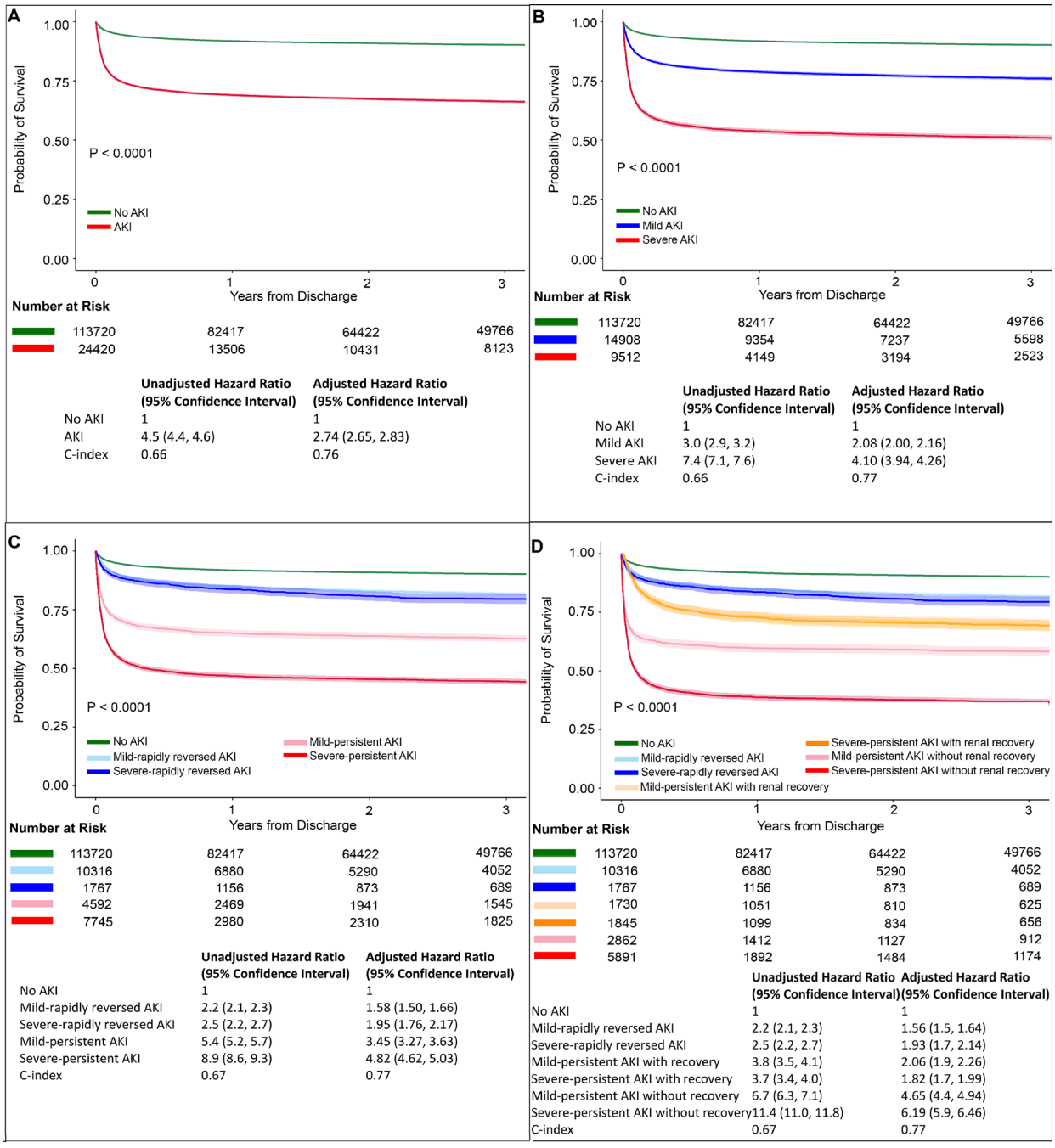


Figure 3 Adjusted Kaplan-Meier survival curves and number at risk by AKI subphenotypes obtained stratifying by (A) no AKI vs any AKI (B) AKI stratified by severity (C) AKI stratified by severity and duration (D) AKI stratified by severity and trajectories of AKI using duration and recovery of AKI. Propensity score based inverse weighting was used to plot adjusted Kaplan-Meier curves where propensity of being in a trajectory group was calculated using multinomial logistic model that included age, gender, ethnicity and Charlson Comorbidity Index score. Adjusted hazard ratios were obtained adjusting for the same variables as well as need for mechanical ventilation for more than 2 days and need for intensive care unit admission for more than 2 days. AKI, acute kidney injury.

Regardless trajectories, among 347 811 patients who survived 1 year after hospital discharge, AKI patients with CKD on admission had greater incidence of CKD progression (18%) within 1 year of admission compared with those without AKI (11%) (online supplemental tables 14–16). Incidence of new CKD and new RRT within 1-year follow-up were significantly higher among patients with AKI (16% and 3%, respectively) compared with patients without AKI (4% and 0.5%, respectively).

DISCUSSION

In a retrospective, longitudinal large cohort of hospitalised patients and in subset of patients who required and did not require ICU admission, we characterised distinct

AKI clinical trajectories and associated survival and resource use. A high proportion (15%) of all hospitalised patients developed AKI, and almost half (42%) developed persistent AKI. Compared with patients who did not develop critical illness during hospitalisation, the ICU cohort had higher proportions of AKI (35% vs 10%) and persistent AKI (52% vs 31%), consistent with evidence of burden of sepsis and organ dysfunction among ICU patients. Among patients with persistent AKI, most (62%) did not recover renal function prior to hospital discharge.

Hypotension, hyperglycaemic, thrombocytopaenia and hypoalbuminaemia were more frequent among patients with AKI; greater severity of these conditions was associated with worse AKI trajectory. There were significant, stepwise increases in 1-year mortality for patients with no AKI (7%), rapidly reversed AKI (15%), persistent AKI with renal recovery (24%) and persistent AKI without renal recovery (41%). Worse AKI trajectory was also associated with greater resource use, manifest as greater incidence of ICU admission, mechanical ventilation and vasopressor administration. Finally, the severity of AKI was combined with recovery trajectory to generate a more granular subphenotyping scheme that augmented discrimination for outcomes after persistent AKI with vs without renal recovery.

Our rationale for performing this work was that clinical trajectories of hospitalised patients with AKI had not been sufficiently described, although similar work has been performed using different patient populations. In a similar prospective, observational study performed at our centre, critically ill patients with surgical sepsis and AKI had a greater overall incidence of AKI compared with this study of hospitalised adults. Yet, associations between AKI trajectories and outcomes were similar between that study and this study, for which only 22% of all admissions involved surgery.[7] A previous retrospective analysis of critically ill patients classified AKI recovery phenotypes by AKI reversal within 7 days of onset and renal recovery at discharge, reporting that sepsis patients had greater incidence of AKI relapse without recovery and increased 1-year mortality, consistent with this study.[25] Similarly, a retrospective study of 5443 patients with septic shock found that subjects with rapid reversal of AKI within 24 hours of onset had lower in-hospital mortality.[26] A recent retrospective study of 350 patients admitted in ICU presented the value of accounting for time-dependent competing risk of discharge or death when assessing recovery pattern in determining AKI recovery trajectories.[27 28] A prospective study of ICU patients from two ICU populations (n=1914; 1867) identified higher mortality rates among non-resolving AKI.[6] Another prospective cohort study of 1538 hospitalised patients demonstrated graded associations among incident or progressive CKD, long-term dialysis, and all-cause death with worse outcomes after non-resolving AKI, intermediate outcomes after resolving AKI, and best outcomes among participants without AKI.[27] Collectively, previous studies have used similar methods to evaluate different patient populations, producing results that are consistent with ours. To our knowledge, this study is the first large-scale, granular description of associations among patient baseline characteristics, illness severity, AKI trajectory and severity, and other clinical outcomes. Using a large, diverse cohort of hospitalised patients as well as in ICU and non-ICU subcohorts, we have shown that significant decreases in long-term survival with persistent AKI and the absence of renal recovery, independent of AKI severity, suggesting importance of identification of AKI trajectories.

The clinical trajectories of AKI and recovery among hospitalised patients described herein could be applied to optimise prevention, early diagnosis and appropriate treatment of AKI. One strength of our study is the use of validated computable phenotype for kidney health encompassing both CKD and AKI while maintaining consistency with KDIGO and ADQI guidelines and addressing the potential racial biases introduced by race adjustments in GFR and creatinine using comprehensive reference creatinine calculations.[12] By defining a relevant classification system with strong associations among clinical trajectories, outcomes and resource use, we can develop standardised methods for predictive modelling and clinical decision support. Our findings suggest that patients from different AKI subgroups have distinct pathophysiological mechanisms related to hypotension, hyperglycaemic, thrombocytopaenia and hypoalbuminaemia. It remains plausible that these elements represent therapeutic targets for specific AKI subtypes. Systematic investigation of preventative and therapeutic strategies tailored to AKI trajectories may yield more consistent and generalisable results than diffuse, non-standardised investigations using variable classification systems.

Our single-institution design limits generalisability to other practice settings. As a retrospective study, our results may be influenced by selection bias. We sought to minimise selection bias by including all consecutive hospital admissions meeting relatively broad inclusion criteria. Due to lack of data on contrast agents and home medications, these were not reported and due to limitations on accurate data on urine output, only serum creatinine definition was used for defining AKI. Finally, biomarkers evaluated herein were limited to those collected for routine clinical use. Future investigations should seek development and validation of models that predict AKI trajectories at the time of hospital admission with subsequent dynamic predictions, and assess the efficacy of targeted preventative and therapeutic measures for patients at high risk for persistent AKI.

CONCLUSIONS

Among hospitalised patients and ICU cohorts, persistent AKI and the absence of renal recovery were associated with poor short-term and long-term survival, independent of AKI severity. Accurate and early identification of patients at increased risk for persistent AKI may facilitate the

provision of targeted treatments that prevent persistent AKI or promote renal recovery to improve survival and optimise resource use.

Author affiliations
[1]Department of Medicine, University of Florida, Gainesville, Florida, USA
[2]Precision and Intelligent Systems in Medicine (PrismaP), University of Florida, Gainesville, Florida, USA
[3]Department of Surgery, University of Florida, Gainesville, Florida, USA
[4]Department of Health Outcomes and Biomedical Informatics, University of Florida, Gainesville, Florida, USA
[5]Department of Industrial and Systems Engineering, University of Florida, Gainesville, Florida, USA
[6]Department of Biostatistics, University of Florida, Gainesville, Florida, USA

Contributors AB is the guarantor of this manuscript. TOB and AB had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: TOB and AB. Acquisition, analysis or interpretation of data: TOB, YR, EA, SM, TJL and AB. Drafting of the manuscript: TOB, TJL, YR, EA, SM, HH, RI and AB. Critical revision of the manuscript for important intellectual content: AB, TOB, TJL, YR, EA, SM, HH, RI, RM, SG, EAS, PP, BB and MSS. Obtained funding: TOB and AB. Supervision: AB, EAS, PP, BB and MSS.

Funding TOB was supported by K01 DK120784, R01 DK123078, and R01 DK121730 from the National Institute of Diabetes and Digestive and Kidney Diseases (NIH/NIDDK), R01 GM110240 from the National Institute of General Medical Sciences (NIH/NIGMS), R01 EB029699 from the National Institute of Biomedical Imaging and Bioengineering (NIH/NIBIB), and R01 NS120924 from the National Institute of Neurological Disorders and Stroke (NIH/NINDS). AB was supported R01 GM110240 from the National Institute of General Medical Sciences (NIH/NIGMS), R01 EB029699 and R21 EB027344 from the National Institute of Biomedical Imaging and Bioengineering (NIH/NIBIB), R01 NS120924 from the National Institute of Neurological Disorders and Stroke (NIH/NINDS), and by R01 DK121730 from the National Institute of Diabetes and Digestive and Kidney Diseases (NIH/NIDDK). TJL was supported by the National Institute of General Medical Sciences of the National Institutes of Health under Award Number K23 GM140268. BB and MSS were supported by Sepsis and Critical Illness Research Center Award P50 GM-111152 from the National Institute of General Medical Sciences. Additionally, the Research reported in this publication was supported by the National Center for Advancing Translational Sciences of the National Institutes of Health under University of Florida Clinical and Translational Science Awards UL1TR000064 and UL1TR001427. National Institute of Diabetes and Digestive and Kidney Diseases (NIH/NIDDK), National Institute of General Medical Sciences (NIH/NIGMS), National Institute of Biomedical Imaging and Bioengineering (NIH/NIBIB), National Institute of Neurological Disorders and Stroke (NIH/NINDS) and National Center for Advancing Translational Sciences (NIH/NCATS).

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval The study was designed and approved by the Institutional Review Board of the University of Florida and the University of Florida Privacy Office (IRB 201901123).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

ORCID iD
Azra Bihorac http://orcid.org/0000-0002-5745-2863

REFERENCES

1 Darmon M, Ostermann M, Cerda J, *et al*. Diagnostic work-up and specific causes of acute kidney injury. *Intensive Care Med* 2017;43:829–40.
2 James MT, Bhatt M, Pannu N, *et al*. Long-Term outcomes of acute kidney injury and strategies for improved care. *Nat Rev Nephrol* 2020;16:193–205.
3 Sawhney S, Fraser SD. Epidemiology of AKI: utilizing large databases to determine the burden of AKI. *Adv Chronic Kidney Dis* 2017;24:194–204.
4 Gardner AK, Ghita GL, Wang Z, *et al*. The development of chronic critical illness determines physical function, quality of life, and long-term survival among early survivors of sepsis in surgical ICUs. *Crit Care Med* 2019;47:566–73.
5 Chawla LS, Bellomo R, Bihorac A, *et al*. Acute kidney disease and renal recovery: consensus report of the acute disease quality initiative (ADQI) 16 Workgroup. *Nat Rev Nephrol* 2017;13:241–57.
6 Bhatraju PK, Mukherjee P, Robinson-Cohen C, *et al*. Acute kidney injury subphenotypes based on creatinine trajectory identifies patients at increased risk of death. *Crit Care* 2016;20:372.
7 Ozrazgat-Baslanti T, Loftus TJ, Mohandas R, *et al*. Clinical trajectories of acute kidney injury in surgical sepsis: a prospective observational study. *Ann Surg* 2020. doi:10.1097/SLA.0000000000004360. [Epub ahead of print: 13 Nov 2020].
8 Bellomo R, Kellum JA, Ronco C, *et al*. Acute kidney injury in sepsis. *Intensive Care Med* 2017;43:816–28.
9 Morrell ED, Kellum JA, Pastor-Soler NM, *et al*. Septic acute kidney injury: molecular mechanisms and the importance of stratification and targeting therapy. *Crit Care* 2014;18:501.
10 Poston JT, Koyner JL. Sepsis associated acute kidney injury. *BMJ* 2019;364:k4891.
11 Seymour CW, Kennedy JN, Wang S, *et al*. Derivation, validation, and potential treatment implications of novel clinical phenotypes for sepsis. *JAMA* 2019;321:2003–17.
12 Ozrazgat-Baslanti T, Hobson C, Motaei A. Development and validation of computable phenotype to identify and characterize kidney health in adult hospitalized patients. *arXiv preprint* 2019;2604673.
13 Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. Clinical practice guideline for acute kidney injury. *Kidney inter, Suppl* 2012;2:1–138.
14 Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. *Nephron Clin Pract* 2012;120:c179–84.
15 Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney inter, Suppl* 2013;3:1–150.
16 Selby NM, Hill R, Fluck RJ, *et al*. Standardizing the early identification of acute kidney injury: the NHS England national patient safety alert. *Nephron* 2015;131:113–7.
17 Bellomo R, Ronco C, Kellum JA, *et al*. Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care* 2004;8:R204–12.
18 Závada J, Hoste E, Cartin-Ceba R, *et al*. A comparison of three methods to estimate baseline creatinine for RIFLE classification. *Nephrol Dial Transplant* 2010;25:3911–8.
19 Levey AS, Stevens LA, Schmid CH, *et al*. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;150:604–12.
20 Ahmed S, Nutt CT, Eneanya ND, *et al*. Examining the potential impact of race multiplier utilization in estimated glomerular filtration rate calculation on African-American care outcomes. *J Gen Intern Med* 2021;36:464–71.
21 Diao JA, Wu GJ, Taylor HA, *et al*. Clinical implications of removing race from estimates of kidney function. *JAMA* 2021;325:184–6.
22 Norris KC, Eneanya ND, Boulware LE. Removal of race from estimates of kidney function: first, do no harm. *JAMA* 2021;325:135–7.
23 Chen S. Retooling the creatinine clearance equation to estimate kinetic GFR when the plasma creatinine is changing acutely. *J Am Soc Nephrol* 2013;24:877–88.
24 Dolgun A, Demirhan H. Performance of nonparametric multiple comparison tests under heteroscedasticity, dependency, and skewed error distribution. *Commun Stat Simul Comput* 2017;46:5166–83.10.1080/03610918.2016.1146761

25 Kellum JA, Sileanu FE, Bihorac A, *et al*. Recovery after acute kidney injury. *Am J Respir Crit Care Med* 2017;195:784–91.
26 Sood MM, Shafer LA, Ho J, *et al*. Early reversible acute kidney injury is associated with improved survival in septic shock. *J Crit Care* 2014;29:711–7.
27 Bhatraju PK, Zelnick LR, Chinchilli VM, *et al*. Association between early recovery of kidney function after acute kidney injury and long-term clinical outcomes. *JAMA Netw Open* 2020;3:e202682.
28 Abdel-Nabey M, Ghrenassia E, Mariotte E, *et al*. Acute kidney injury recovery patterns in critically ill patients: results of a retrospective cohort study. *Crit Care Med* 2021;49:e683–92.