Sepsis-Associated Acute Kidney Disease Incidence, Trajectory, and Outcomes

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Rationale & Objective: Systematic evaluation of the prognosis from sepsis-associated acute kidney disease (SA-AKD) using real-world data is limited. This study aimed to use data algorithms on the electronic health records to trace the SA-AKD trajectory from acute kidney injury (AKI) to chronic kidney disease (CKD).

Study Design: A retrospective cohort study.

Setting & Participants: Adult inpatients with first sepsis episode surviving 90 days after AKD in a quaternary referral medical center.

Exposure: We defined SA-AKD as having sustained ≥1.5-fold increased serum creatinine levels or initiating kidney replacement therapy after the SA-AKI, and we classified SA-AKD into recovery, relapse, and persistent SA-AKD subgroups.

Outcomes: All-cause mortality, kidney replacement therapy (KRT), *de novo* nondialysis dependent CKD (CKD-ND), and late-recovery AKD during 1-year follow-up.

Analytical Approach: A multivariable Cox proportional hazards models.

Results: Of 24,038 eligible inpatients with sepsis, 42.2% had SA-AKI, and 17.6% progressed to SA-AKD (43.6% recovery, 8.3% relapse, 32.2% persistent, and 15.9% unclassified). Compared with the recovery subgroup, the 1-year mortality risk for the relapse, persistent, and unclassified SA-AKD subgroups were 1.57 (adjusted hazard ratios [aHRs]; 95% CI, 1.22-2.01), 1.36 (1.13-1.63), and 0.65 (0.48-0.89), respectively. Risks of KRT initiation were 3.27 (2.14-4.98), 6.01 (4.41-8.19), and 0.98 (0.55-1.74), respectively, and corresponding aHRs for *de novo* CKD-ND were 3.84 (2.82-5.22), 3.35 (2.61-4.29), and 0.48 (0.30-0.77), respectively. Patients with relapse SA-AKD had a higher likelihood of late recovery (aHR, 3.62; 95% CI, 2.52-5.21) than the persistent SA-AKD.

Limitations: Selection bias and information bias could be present because of limiting population to sepsis survivors and because of no standardized follow-up protocol for kidney function.

Conclusions: SA-AKD without recovery is associated with increased and long-term risks of KRT initiation, mortality, and increased risk of *de novo* CKD-ND for patients initially free of CKD. Further studies are warranted for managing AKI to AKD to CKD in real-world settings.

Complete author and article information provided before references.

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Acute kidney injury (AKI) is associated with accelerated kidney disease progression and death.[1] Acute kidney injury without recovery within 8-90 days can be classified into acute kidney disease (AKD). If the period without recovery is extended beyond 90 days after the index date of AKI, it may be classified into new onset or worsening of existing chronic kidney disease (CKD).[2-4] Although this consensus-based definition for AKD ensures research consistency and provides an understanding of the full course of AKI, its clinical value remains to be verified using real-world evidence.[3,4] One of the urgent priorities for evidence-based assessment is sepsis-associated AKD (SA-AKD).

Sepsis is life-threatening organ dysfunction resulting from a dysregulated host response to infection and is a leading cause of death among patients who are critically ill.[5,6] Almost half of patients with sepsis develop sepsis-associated AKI (SA-AKI).[7,8] Few studies have systematically evaluated the trajectory of SA-AKD in real-world scenarios, specifically from the end of its diagnostic window to a year after the development of SA-AKI. The main challenge to such evaluations is the intricate data algorithms required for defining sepsis status based on, for example, the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) and for categorizing SA-AKD status in patients who might exhibit various recovery trajectories.[5,9] In this study, we applied sophisticated data algorithms to systematically evaluated the clinical characteristics and 1-year prognosis of patients with sepsis who survived for at least 90 days after developing AKI by using a comprehensive data platform that encompasses a source population of 3 million patients from China Medical University Hospital (CMUH) and integrates institutional electronic health records (EHRs) and Taiwan's National Health Insurance Database.

METHODS

Study Population

We obtained data from the iHi Data Platform of CMUH, which contains the carefully verified EHRs data and the National Death Registry data from 3,077,895 patients who sought care at CMUH between 2003 and 2020.[10-13] We further included adult (aged 18-90 years) inpatients with a

PLAIN LANGUAGE SUMMARY

Systematic evaluation of the prognosis for sepsis-associated acute kidney injury (AKI) and sepsis-associated acute kidney disease (AKD) using real-world data remain limited. We applied standard definitions of sepsis and AKI/AKD and comprehensively profiled the AKI-AKD-chronic kidney disease (CKD) trajectory among sepsis survivors in a large, longitudinal hospital-based cohort. Our study showed that sepsis-associated AKD without recovery is associated with elevated and long-term risks of progressing to kidney replacement therapy, mortality, and new onset of CKD. These findings advocate for a paradigm shift toward digital therapies for managing the transition from AKI to AKD to CKD among patients with sepsis.

first sepsis event during their hospital admission between 2003 and 2019. Sepsis was identified using an EHR-based algorithm based on the Sepsis-3 criteria,[5,14] which was defined as a presumed serious infection with concurrent acute organ dysfunction that developed within +/−2 days of the date of blood culture collection for the index sepsis event (Fig S1).

The methods for measuring serum creatinine (Scr) level and converting it to estimated glomerular filtration rate (eGFR) are described in Method S1.A. The baseline Scr ($Scr_{Baseline}$) level was determined as the lowest outpatient stable Scr (SScr; Method S1.B) level measured within the baseline time window, spanning from 365 to 3 days before the sepsis index date. If $Scr_{Baseline}$ data were not available, we imputed a value based on the distribution of SScr levels in the source CMUH population (Method S1.C). Of adult inpatients with a first sepsis event, we excluded individuals who had a history of cancer, kidney replacement therapy (KRT, such as long-term dialysis and kidney transplant), or nephrectomy at any point before the sepsis event; who underwent acute dialysis 90 to 3 days before developing sepsis; who received cardiopulmonary cerebral resuscitation 2 days before to 7 days after developing sepsis; or who had a $Scr_{Baseline}$ measurement of ≥4.0 mg/dL (Fig 1). To accurately categorize the phenotypes of SA-AKI and SA-AKD, we excluded patients who did not have any SScr measurements 2 days before to 7 days after the sepsis index date.[15] In addition, patients who died within the first 90 days after the SA-AKI index date were excluded. This study was approved by CMUH's research ethics committee (approval number: 111-REC3-138; 111-REC2-022; and 111-REC2-155).

Definition of Phenotypes Across the AKI–AKD Continuum

Changes in SScr from $Scr_{Baseline}$ were evaluated within 2 diagnostic time frames: from 2 days before to 7 days after the sepsis index date for SA-AKI and from 8-90 days after the SA-AKI index date for SA-AKD based on KDIGO guideline (Fig 2).[3] SA-AKI was identified using the earliest SScr (SCr_{AKI}) level within 2 days before to 7 days after the sepsis index date that met the KDIGO criteria (Fig 2 [A]; Method S1.D).

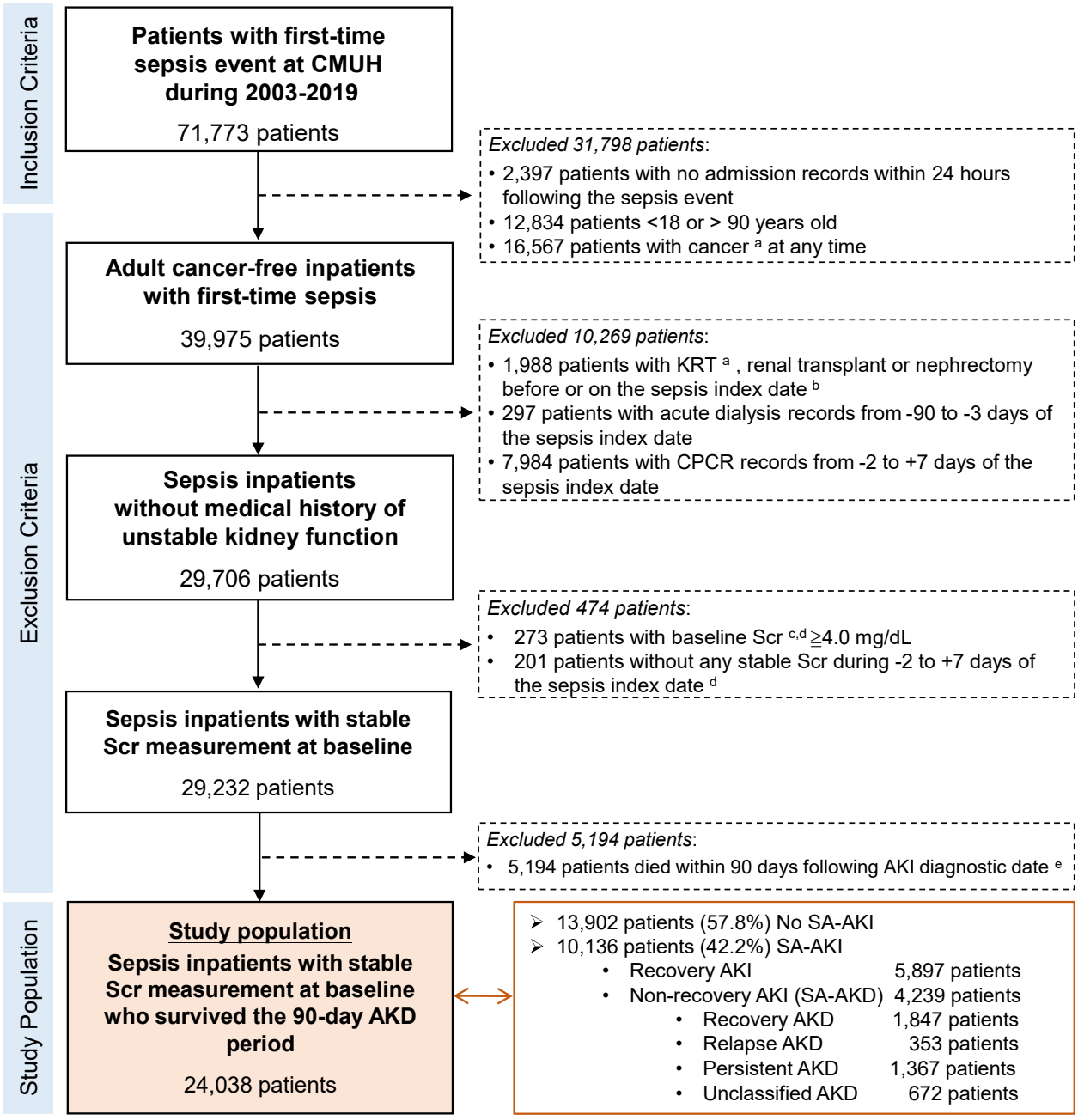
Patients without SA-AKI recovery, whose last SScr in the SA-AKI detection window (0-7 days) continued to be ≥1.5 times than $Scr_{Baseline}$ or who initiated KRT in this time window, were further classified into SA-AKD subgroups of recovery, relapse, persistent, and unclassified using SScr data from 8-90 days after the index AKI date (Fig 2 [B and C]; Method S1.D).

Definitions of the Prognostic Outcomes of SA-AKD

The prognostic outcomes of SA-AKD included all-cause mortality, initiation of KRT, *de novo* nondialysis dependent CKD (CKD-ND), and late-recovery AKD during 1-year follow-up (Fig 2 [D]). Patients' mortality and KRT status were verified by using the National Death Registry and the National Catastrophic Illness Database, respectively (Method S1.E).[16-18] In patients with a baseline $eGFR_{Baseline}$ of ≥60 mL/min/1.73 m^2, *de novo* CKD-ND was defined as having at least 2 $eGFR_{Baseline}$ measurements of < 60 mL/min/1.73 m^2 during follow-up. Late recovery from persistent or relapse AKD was defined as having the lowest outpatient SScr returning to a level less than or equal to the $Scr_{Baseline}$ during follow-up (strict definition) or to a level < 50% above the $Scr_{Baseline}$ during follow-up (general definition). The CKD progression from stage 3 or 4 ($eGFR_{Baseline}$ 15-59 mL/min/1.73 m^2) was defined as having any stage progression or undergoing long-term dialysis during follow-up. Definitions of other covariables are provided in Table S1 and Method S1.F.

Statistical Analyses

Continuous variables are presented as medians and interquartile ranges (IQRs) and were compared using the Kruskal-Wallis test. Categorical variables are expressed as frequencies and percentages and were compared using the χ^2 test. The profile of the trajectory of AKI–AKD–CKD was determined by generating a Sankey plot using the NetworkD3 package in R (R Foundation for Statistical Computing). We used multivariable Cox proportional hazards models to evaluate the risks of various 1-year prognostic outcomes in the SA-AKD subgroups. The entry date was the index date of SA-AKI, and the exit date was set as the dates of death, catastrophic illness certification for KRT, *de novo* CKD, late-recovery attainment, or loss to follow up or the end of the 1-year follow-up. Method S2.A lists the censoring rules for the Cox models. We modeled the effect of SA-AKD subgroups on cause-specific hazard of outcomes other than death, with consideration for the competing risk of overall death.[19] Given that the proportion of missing was high for certain covariables (Table S2), we applied an iterative Markov chain Monte Carlo procedure, involving 20



[a] Cancer and KRT were defined as patients having records of Catastrophic Illness Certificates from the Taiwan's Ministry of Health and Welfare.
[b] Sepsis index date was defined as the blood culture sampling date of index sepsis event.
[c] Baseline Scr was lowest outpatient stable Scr measurement between -365 to -3 days of sepsis index date. If baseline Scr was unavailable, we imputed the value based on the population distribution of the source population from CMUH.
[d] Stable Scr (SScr) included the Scr that was not obtained: (1) within 72 hours after dialysis or CPCR; (2) within 24 hours after the massive blood transfusion (≥ 8 units of packed red blood cell), or (3) from patients who already received nephrectomy procedure or renal transplant.
[e] AKI diagnostic date (during -2 to +7 days of sepsis index date) was defined as the earliest date between the first measurement date of Scr that met the KDIGO AKI definitions and the KRT date. KRT date was defined as the date of dialysis or in-hospital renal transplant, whichever occurred first. For patients without AKI, AKI diagnostic date was the sepsis index date.
Abbreviations: AKI, acute kidney injury; AKD, acute kidney disease; CMUH, China Medical University Hospital; CPCR, Cardio-Pulmonary-Cerebral Resuscitation; KRT, kidney replacement therapy; SA, sepsis-associated; Scr, serum creatinine; SScr, stable serum creatinine.

Figure 1. Selection process of study population who had sepsis during admission and survived for at least 90 days after an AKI event. Abbreviation: AKI, acute kidney injury.

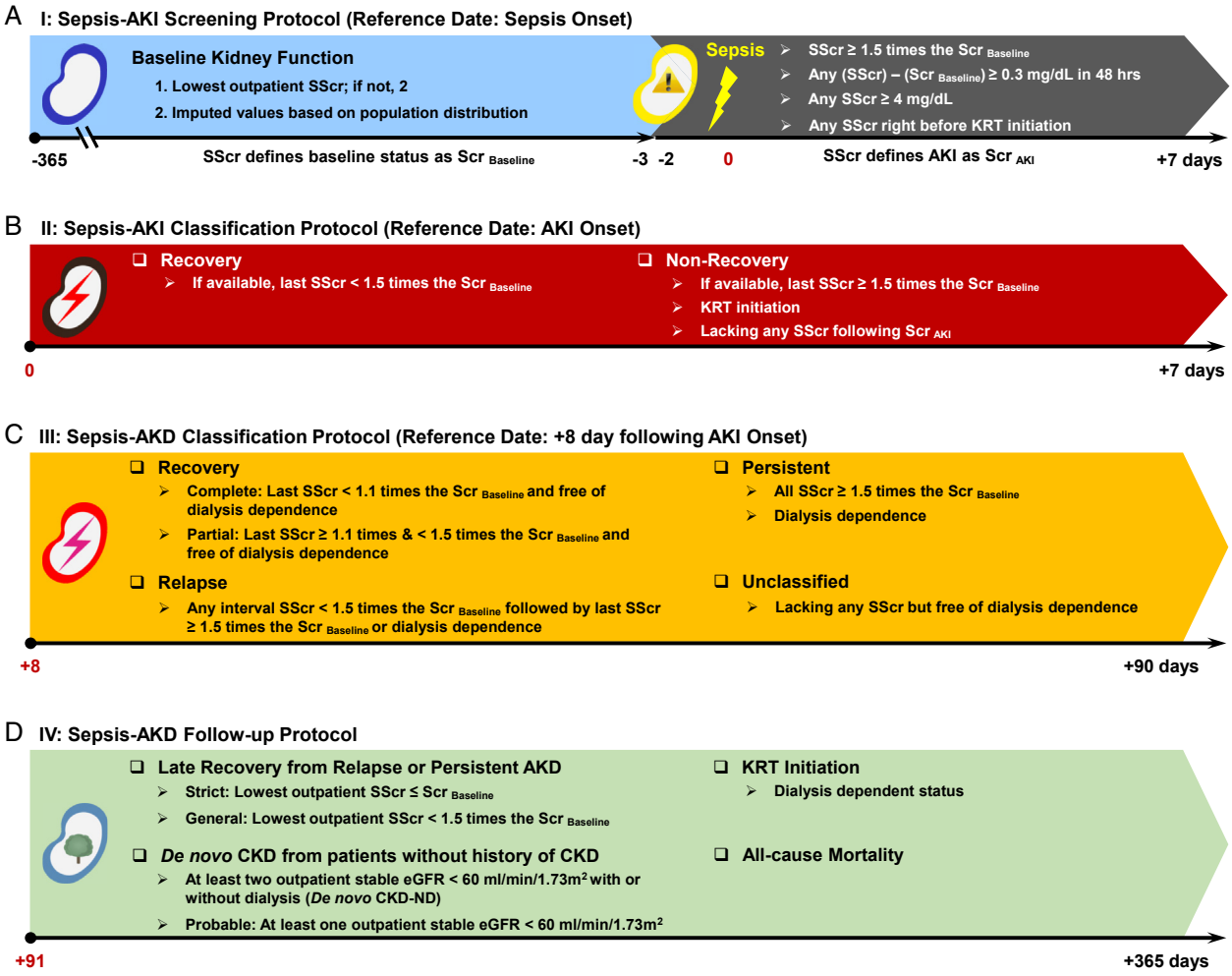


Figure 2. Operational protocols for delineating the entire spectrum of SA-AKI from screening (A) and classification (B) through SA-AKD transition (C) to 1-year follow-up after SA-AKD (D). Abbreviations: CKD-ND, nondialysis dependent chronic kidney disease; eGFR, estimated glomerular filtration rate; KRT, kidney replacement therapy; SA-AKI, sepsis-associated acute kidney injury; SA-AKD, sepsis-associated acute kidney disease; SScr, stable serum creatinine.

imputations and 100 iterations per imputation.[20] We performed multiple sensitivity analyses to test the robustness of our main results (Method S2.B). All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc) and R version 4.2.2. The 2-sided statistical significance level (α) was set at 0.05.

RESULTS

Clinical Characteristics and Outcomes of Sepsis Survivors with Various SA-AKD Subgroups

Of 29,232 patients with sepsis, 24,038 (82.2%) survived for > 90 days after the initial sepsis diagnosis and subsequent SA-AKI, and the cumulative SA-AKI incidence was 42.2% (Fig 1). Among 10,136 patients with SA-AKI, 38.6%, 27.4%, and 34.0% were classified as having KDIGO AKI stages 1, 2, and 3, respectively (Table S3), and 41.8% developed SA-AKD. Patients with SA-AKD were grouped into recovery (43.6%), relapse (8.3%), persistent (32.2%), and unclassified (15.9%) SA-AKD subgroups (Table 1). Sankey plots demonstrated the overall 1-year course from AKI to AKD to CKD progression for patients with SA-AKI (Fig 3) and for SA-AKI patients without CKD at baseline (Fig 4).

Patients experiencing relapse SA-AKD exhibited the highest burden of comorbid conditions, such as diabetes, hypertension, cardiovascular disease, chronic pulmonary disease, and liver cirrhosis. The use of nephrotoxic or AKI-predisposing agents was more prevalent in the recovery and relapse SA-AKD subgroups than in the other subgroups. Patients with either persistent or relapse SA-AKD exhibited significantly elevated proteinuria levels (Table 1). The recovery and unclassified SA-AKD subgroups had comparable $eGFR_{Baseline}$ of 81.4 (IQR, 61.7-98.0 mL/min/1.73 m^2) and 83.6 (IQR, 66.4-98.6 mL/min/1.73 m^2) mL/min/1.73 m^2, respectively, which were higher than those in the relapse and persistent SA-AKD subgroups (75.6 [IQR, 59.2-92.5] and

Table 1. Baseline Demographics and Clinical Characteristics of Sepsis Survivors With SA-AKD Divided Into Recovery, Relapse, Persistent, and Unclassified SA-AKD Subgroups

			SA-AKD Subgroup[a]			
		SA-AKD	Recovery	Relapse	Persistent	Unclassified
Characteristics	Available N	n = 4,239	n = 1,847	n = 353	n = 1,367	n = 672
Baseline demographics and comorbid conditions within −365 to −3 d of sepsis						
Age at sepsis diagnosis, y	4,239	65.7 (52.2-77.1)	64.2 (48.6-76.8)	66.7 (55.5-78.5)	67.8 (56.2-77.5)	63.9 (51.8-76.1)
Female	4,239	2,030 (47.8)	794 (42.9)	167 (47.3)	695 (50.8)	374 (55.6)
Body mass index, kg/m^2	2,298	24.1 (21.5-27.5)	24.2 (21.7-27.8)	24.1 (21.2-27.2)	24.0 (21.5-27.3)	24.1 (21.4-27.5)
Smoking	2,224	825 (19.5)	382 (40.3)	68 (35.2)	282 (37.8)	93 (27.7)
Comorbid conditions						
Diabetes mellitus	4,239	719 (16.9)	329 (17.8)	95 (26.9)	231 (16.9)	64 (9.5)
Hypertension	4,239	937 (22.1)	444 (24.0)	113 (32.0)	293 (21.4)	87 (12.9)
Cardiovascular disease	4,239	845 (19.9)	400 (21.6)	96 (27.2)	262 (19.1)	87 (12.9)
Chronic pulmonary disease	4,239	237 (5.5)	114 (6.1)	20 (5.6)	68 (4.9)	35 (5.2)
Liver cirrhosis	4,239	154 (3.6)	77 (4.1)	30 (8.5)	38 (2.7)	9 (1.3)
Baseline kidney function within −365 to −3day of sepsis						
Stable Scr, mg/dL	4,239	0.94 (0.76-1.08)	0.94 (0.78-1.06)	0.96 (0.78-1.11)	0.95 (0.80-1.11)	0.89 (0.70-1.00)
Stable eGFR, mL/min/1.73m^2	4,239	78.6 (61.3-95.1)	81.4 (61.7-98.0)	75.6 (59.2-92.5)	72.2 (59.1-89.8)	83.6 (66.4-98.6)
eGFR < 60 mL/min/1.73m^2	4,239	933 (22.1)	365 (19.8)	96 (27.2)	375 (27.5)	97 (14.5)
Pooled uACR, mg/g	477	652 (99-2,456)	237 (39-929)	587 (109-1,745)	2393 (791-5,044)	185 (55-951)
Proteinuria	1,228	661 (53.8)	267 (45.4)	83 (58.0)	265 (70.6)	46 (37.4)
Use of nephrotoxic or agents predisposing patients to AKI within −90 to −3 d of sepsis						
NSAID	4,239	430 (10.1)	231 (12.5)	40 (11.3)	107 (7.8)	52 (7.7)
Contrast	4,239	259 (6.1)	142 (7.6)	37 (10.4)	57 (4.1)	23 (3.4)
Antimicrobials	4,239	203 (4.7)	96 (5.2)	25 (7.0)	62 (4.5)	20 (2.9)
Chemotherapy/immunotherapy	4,239	6 (0.1)	4 (0.2)	1 (0.2)	1 (<0.1)	0 (0.0)
ACEI/ARB	4,239	599 (14.1)	289 (15.6)	77 (21.8)	180 (13.1)	53 (7.8)
Diuretics	4,239	837 (19.7)	376 (20.3)	106 (30.0)	288 (21.0)	67 (9.9)
KDIGO stage of SA-AKI	4,239					
Stage 1		875 (20.6)	463 (25.0)	61 (17.2)	88 (6.4)	263 (39.1)
Stage 2		941 (22.2)	426 (23.0)	110 (31.1)	231 (16.9)	174 (25.8)
Stage 3		2,423 (57.1)	958 (51.8)	182 (51.5)	1,048 (76.6)	235 (34.9)
Sepsis-related severity indicators within −48 to +48h of sepsis						
Lowest SBP, mm Hg	3,836	99 (84-115)	95 (80-111)	98 (83-114)	103 (90-121)	99 (85-112)
Proximal hemoglobin, g/dL	4,208	11.2 (9.3-13.2)	12.0 (10.0-13.7)	10.6 (9.0-12.6)	10.0 (8.6-11.8)	12.0 (10.2-13.8)
Proximal serum albumin level, g/dL	2,652	3.00 (2.60-3.50)	3.00 (2.55-3.45)	2.90 (2.45-3.40)	3.00 (2.60-3.45)	3.30 (2.90-3.75)
Lactate, mmol/L	2,658	2.37 (1.50-3.94)	2.54 (1.65-4.48)	2.26 (1.52-4.18)	2.05 (1.20-3.21)	2.60 (1.69-3.92)
Lactate ≥ 2 mmol/L	2,658	1,639 (61.6)	804 (66.2)	124 (58.4)	430 (52.1)	281 (68.8)
Septic shock	4,239	707 (16.7)	428 (23.1)	67 (18.9)	151 (11.0)	61 (9.0)
qSOFA score ≥ 2	3,515	1,912 (54.3)	938 (59.7)	178 (61.5)	621 (55.8)	175 (32.0)
Use of mechanical ventilation	4,239	1,867 (44.0)	893 (48.3)	187 (52.9)	639 (46.7)	148 (22.0)
Use of vasopressors	4,239	1,477 (34.8)	740 (40.06)	145 (41.0)	398 (29.1)	194 (28.8)

(Continued)

Table 1 (Cont'd). Baseline Demographics and Clinical Characteristics of Sepsis Survivors With SA-AKD Divided Into Recovery, Relapse, Persistent, and Unclassified SA-AKD Subgroups

Characteristics	Available N	SA-AKD	SA-AKD Subgroup[a]			
			Recovery	Relapse	Persistent	Unclassified
		n = 4,239	n = 1,847	n = 353	n = 1,367	n = 672
Health care utilization during and after admission						
In-hospital kidney consultation	4,239	953 (22.5)	396 (21.4)	87 (24.7)	430 (31.5)	40 (6.0)
Postsepsis LOS, d	4,239	16 (9-33)	20 (11-41)	26 (16-48)	17 (11-32)	7 (6-10)
Postsepsis ICU admission	4,239	2,006 (47.3)	946 (51.22)	199 (56.3)	694 (50.7)	167 (24.8)
Postsepsis ICU LOS, d	2,006	8.2 (4.1-14.8)	10.2 (5.4-17.1)	8.9 (5.0-14.9)	7.2 (4.5-13.2)	2.9 (2.0-5.1)
In-hospital KRT	4,239	973 (22.9)	371 (20.0)	71 (20.1)	490 (35.8)	41 (6.1)
1-year nephrology follow-up	4,239	1,060 (25.0)	351 (19.0)	86 (24.4)	534 (39.1)	89 (13.2)

Abbreviations: ACEIs, angiotensin-converting enzyme inhibitors; AKI; acute kidney injury; ARBs, angiotensin receptor blockers; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ICU, intensive care unit; KRT, kidney replacement therapy; LOS, length of stay; NSAIDs, nonsteroidal anti-inflammatory drugs; qSOFA, quick sequential organ failure assessment; SA-AKD, sepsis-associated acute kidney disease; SBP, systolic blood pressure; Scr, serum creatinine; uACR, urine albumin/creatinine ratio.
[a]Recovery SA-AKD: The last stable Scr from 8-90 days after the AKI index event was <1.5 times relative to baseline Scr. Relapsed SA-AKD: The lowest stable Scr from 8-90 days after the AKI index event was <1.5 times the baseline Scr, followed by the last stable Scr was ≥1.5 times the baseline Scr or dialysis dependence. Persistent SA-AKD: all stable Scr taken from 8-90 days after the index AKI event was ≥1.5 times the baseline Scr or dialysis dependence. Unclassified SA-AKD: No stable Scr and did not undergo KRT.

72.2 [IQR, 59.1-89.8] mL/min/1.73 m^2, respectively) (Table S4).

A significantly higher proportion (76.6%) of patients had initial stage 3 AKI in the persistent SA-AKD subgroup than in the other SA-AKD subgroups. In total, 16.7% of patients with SA-AKD experienced septic shock, which was prominent in the recovery (23.1%) and relapse (18.9%) subgroups. Moreover, 47.3% of patients with SA-AKD received intensive care unit (ICU) care; such care was more frequent in the relapse SA-AKD subgroup, which had higher utilization rates of mechanical ventilation and vasopressors and a longer hospital stay than the other SA-AKD subgroups. Patients with persistent SA-AKD were more likely to require KRT during their hospital stay (35.8%; Table 1) than other subgroups. Unclassified SA-AKD was common in patients with primary genitourinary or digestive infection, and they had a significantly shorter median hospital stay (8 days, IQR, 6-10 days) than the other subgroups (Table S4). The relapse and persistent SA-AKD subgroups had significantly lower hemoglobin and serum lactate levels and higher serum urea nitrogen levels in the 48 hours before and after sepsis development, compared with the unclassified and recovery SA-AKD subgroups (Table 1; Table S4).

One-year mortality rates were the highest in the relapse SA-AKD subgroup (25.7%), followed by those in the persistent (22.0%), recovery (14.3%), and unclassified SA-AKD (8.0%) subgroups (Table 2). The KRT initiation was more frequent in the persistent (23.5%) and relapse (12.7%) SA-AKD subgroups than in the recovery (2.8%) and unclassified (2.3%) SA-AKD subgroups. Within the 1-year follow-up post the AKD window, only 6% and 22.4% of patients with persistent and relapse SA-AKD, respectively, achieved at least partial recovery. In these subgroups, 23.3% and 29.9% of patients without CKD at baseline developed CKD within the 1-year follow-up.

Association of SA-AKD Subgroups With Mortality and Various Kidney Outcomes

A total of 712 (16.8%) sepsis survivors died over a median (IQR) follow-up period of 176 (125-263 days) days during 1-year follow-up of SA-AKD. When we compared the 1-year risk of mortality in patients with relapse, persistent, and unclassified SA-AKD with those who recovered, the fully adjusted hazard ratios (aHRs) were 1.57 (95% CI, 1.22-2.01), 1.36 (1.13-1.63), and 0.65 (0.48-0.89), respectively. These risk estimates remained stable throughout the follow-up period of up to 3 years (Table 3 and Tables S5-S6). Regarding KRT initiation, the corresponding risk estimates were 3.27 (95% CI, 2.14-4.98), 6.01 (4.41-8.19), and 0.98 (0.55-1.74), respectively, and slightly increased with the follow-up duration (up to 3 years). The aHR of achieving at least partial recovery after the AKD window for patients with relapse SA-AKD was 3.62 (95% CI, 2.52-5.21) compared with those with persistent SA-AKD. Among patients with

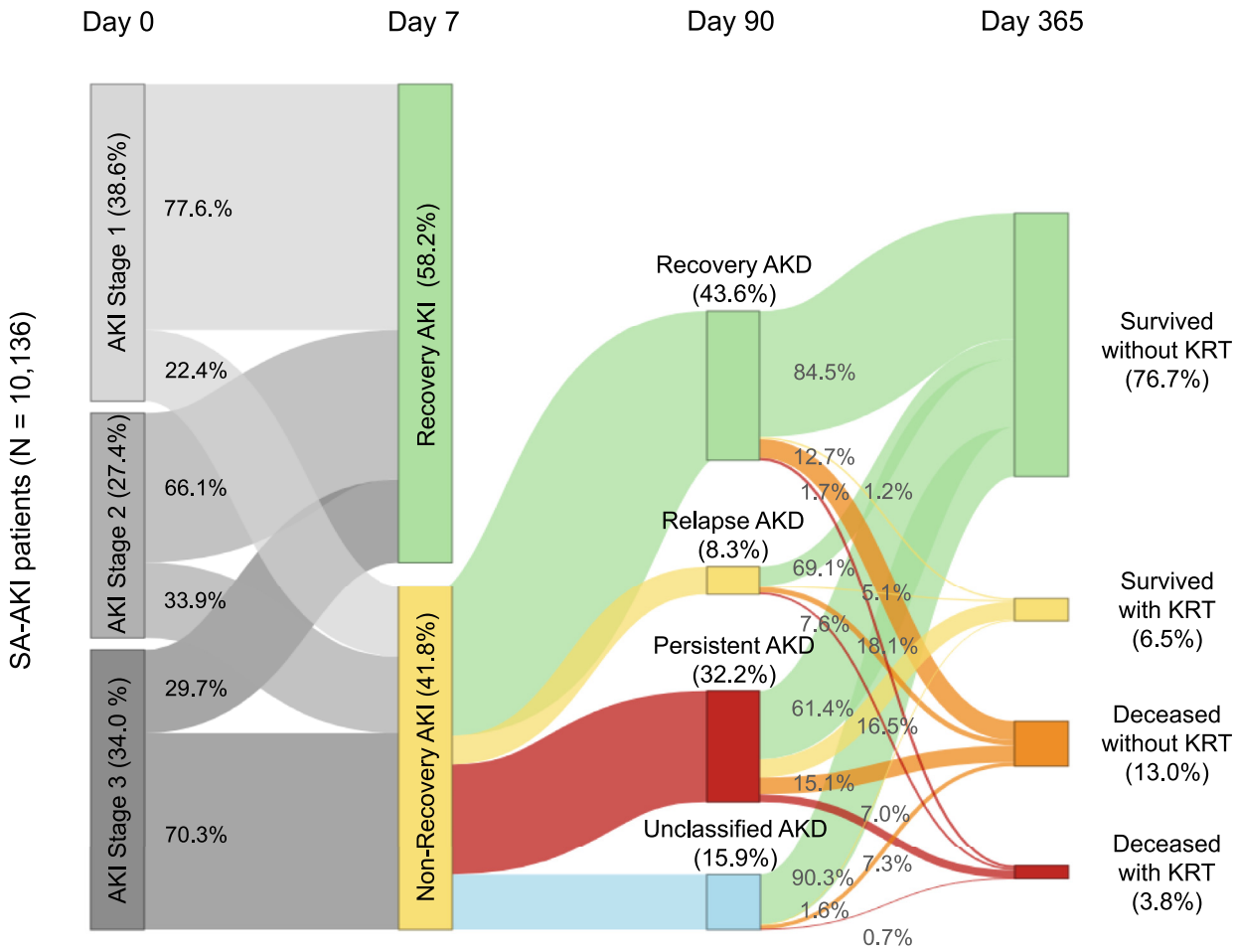


Figure 3. Sankey plot for KRT initiation and mortality within 1 year after SA-AKI among patients with SA-AKI. Abbreviations: AKI, acute kidney injury; AKD, acute kidney disease; KRT, kidney replacement therapy; SA-AKI, sepsis-associated acute kidney injury.

$Scr_{Baseline}$ ≥ 60 mL/min/1.73 m^2, the aHRs of developing *de novo* CKD-ND for patients with relapse SA-AKD, persistent SA-AKD, and unclassified SA-AKD were 3.84 (95% CI, 2.82-5.22), 3.35 (2.61-4.29), and 0.48 (0.30-0.77), respectively. The estimates for late recovery from SA-AKD and *de novo* CKD-ND remained robust even after we applied strict recovery criteria and a relaxed CKD definition (ie, a one-time eGFR of <60 mL/min/1.73 m^2; Table S7). The risk estimates for 1-year KRT were consistently the highest in the persistent SA-AKD subgroup followed by the relapse SA-AKD subgroup (Fig 5). No significant interaction was observed across strata, except for the KRT outcome stratified by the AKI stage; the SA-AKD subgroups with the highest risk for KRT and mortality were not consistent across AKI stages 1, 2, and 3. The subgroup analysis for outcomes during the 2-year and 3-year follow-up periods demonstrated a similar pattern (Figs S2 and S3).

Patterns of Nephrology Follow-Up Among Different SA-AKD Subgroups

A high rate of retention was observed after the SA-AKI event; 98.9%, 99.1%, and 99.1% of patients remained to visit CMUH visit in the first, second, and third years after SA-AKD, respectively. After the SA-AKI event, 21.4%, 24.7%, 31.5%, and 6% of patients in the recovery, relapse, persistent, and unclassified SA-AKD subgroups sought in-hospital nephrology consultations, respectively (Table 1). In the first year after AKI, 19%, 24.4%, 39.1%, and 13.2% of patients from the corresponding SA-AKD subgroups attended at least 1 nephrology clinic follow-up visit.

DISCUSSION

This study systematically investigated the transitional role of SA-AKD in the entire course of SA-AKI; we traced its path from SA-AKI development to subsequent clinical outcomes, including *de novo* CKD-ND, KRT initiation, and all-cause mortality during 1-year, 2-year, and 3-year follow-up among sepsis survivors in a real-world setting. Although approximately half of patients with SA-AKI (58.2%) or SA-AKD (43.6%) had complete recovery within the AKI and AKD time frames, 40.5% of patients with SA-AKD did not recover (Fig 3). Compared with recovery SA-AKD, SA-AKD without recovery is associated

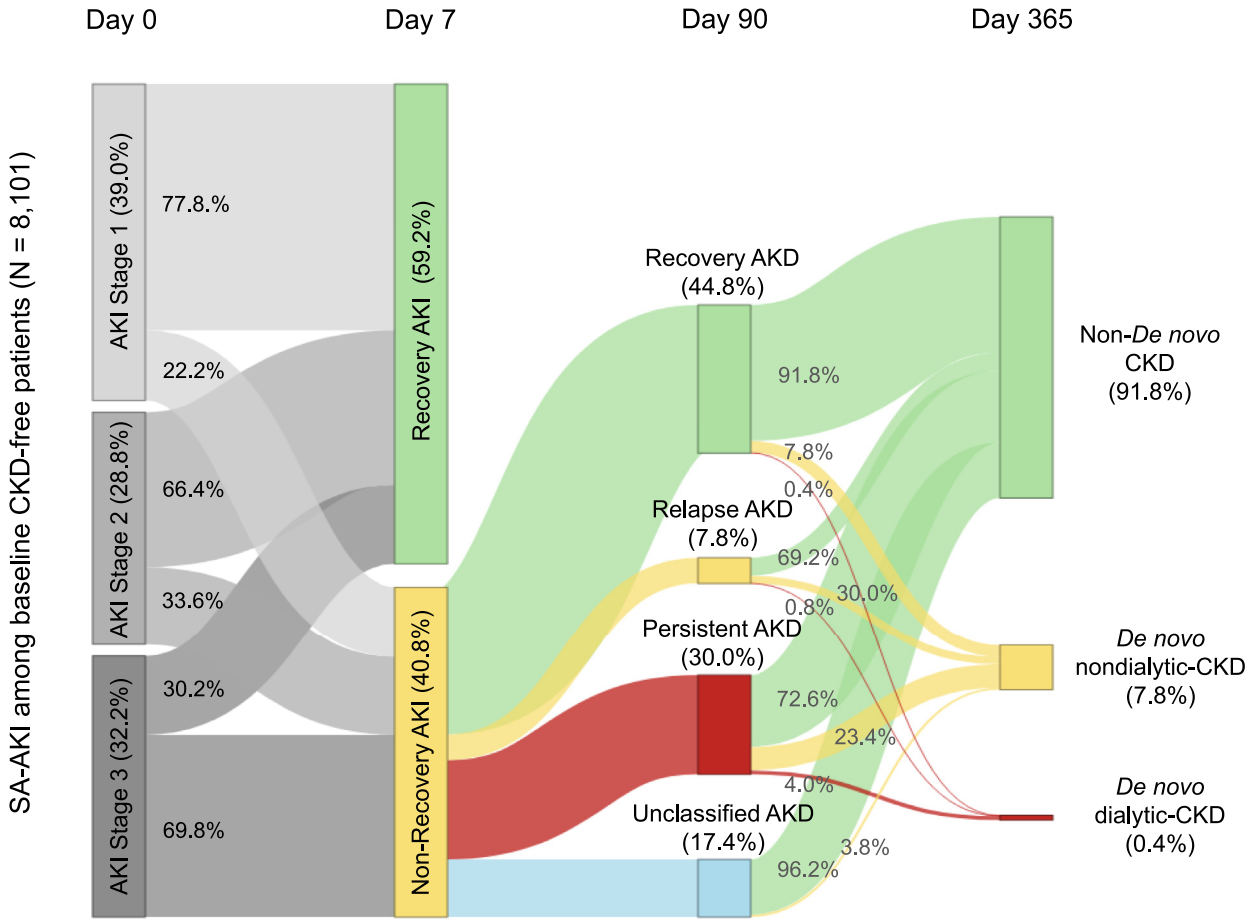


Figure 4. Sankey plot for progression to *de novo* CKD within 1 year after SA-AKI among patients with SA-AKI who were CKD-free at baseline. Abbreviations: SA-AKI, sepsis-associated acute kidney injury; AKD, acute kidney disease; CKD, chronic kidney disease.

with increased and long-term risks of KRT initiation (at least 1.3 times higher) and mortality (at least 3 times higher) for up to 3 years, particularly for the relapse and persistent SA-AKD subgroups. In addition, patients within these subgroups who are initially free from kidney impairment are at 3-fold higher risk of *de novo* CKD-ND

Table 2. One-Year Prognosis of SA-AKD Subgroups

		SA-AKD Subgroup			
	SA-AKD	Recovery	Relapse	Persistent	Unclassified
Characteristics	**n = 4,239**	**n = 1,847**	**n = 353**	**n = 1,367**	**n = 672**
All-cause mortality	712 (16.8)	265 (14.3)	91 (25.7)	302 (22.0)	54 (8.0)
KRT initiation	436 (10.2)	53 (2.8)	45 (12.7)	322 (23.5)	16 (2.3)
***De novo* CKD**		n = 1,482	n = 257	n = 992	n = 575
Available outcome eGFR	1,142 (34.5)	529 (35.7)	129 (50.1)	404 (40.7)	80 (13.9)
Probable *de novo* CKD	739 (22.3)	213 (14.3)	103 (40.0)	376 (37.9)	47 (8.1)
Probable *de novo* CKD-ND	665 (20.1)	207 (14.0)	99 (38.5)	312 (31.5)	47 (8.2)
De novo CKD	495 (14.9)	122 (8.2)	79 (30.7)	272 (27.4)	22 (3.8)
De novo CKD-ND	447 (13.5)	116 (7.8)	77 (29.9)	232 (23.3)	22 (3.8)
Late-recovery AKD			n = 353	n = 1,367	
Strict definition	16 (0.9)		10 (2.8)	6 (0.4)	
General definition	161 (9.4)		79 (22.4)	82 (6.0)	
CKD progression from patients with baseline CKD stage 3 or 4	363 (8.6)	84 (4.5)	47 (13.3)	220 (16.1)	12 (1.8)

Abbreviations: AKD, acute kidney disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; KRT, kidney replacement therapy; SA-AKD, sepsis-associated acute kidney disease.

Table 3. Hazard Ratios (95% Confidence Interval) of the 1-Year Outcomes of SA-AKD Subgroups

SA-AKD Subtypes	Case/Non-Case	Person-Y	Incidence	Crude HRs (95% CI)	Model 1[a] HRs (95% CI)	Model 2[b] HRs (95% CI)	Model 3[c] HRs (95% CI)
All-cause mortality	712/3,527						
Recovery	265/1,582	1,729.1	153.3	Ref	Ref	Ref	Ref
Relapse	91/262	304.4	298.9	1.80 (1.41-2.29)[d]	1.74 (1.36-2.22)[d]	1.67 (1.30-2.13)[d]	1.57 (1.22-2.01)[d]
Persistent	302/1,065	1223.4	246.9	1.53 (1.29-1.81)[d]	1.55 (1.31-1.84)[d]	1.54 (1.29-1.83)[d]	1.36 (1.13-1.63)[d]
Unclassified	54/618	651.7	82.9	0.54 (0.40-0.73)[d]	0.59 (0.44-0.79)[d]	0.64 (0.47-0.86)[d]	0.65 (0.48-0.89)[d]
KRT initiation	436/3,803						
Recovery	53/1,794	1,718.3	30.8	Ref	Ref	Ref	Ref
Relapse	45/308	289.2	155.6	4.82 (3.23-7.21)[d]	3.91 (2.60-5.90)[d]	3.79 (2.50-5.74)[d]	3.27 (2.14-4.98)[d]
Persistent	322/1,045	1,068.5	301.4	9.42 (7.03-12.6)[d]	8.87 (6.60-11.9)[d]	8.44 (6.25-11.3)[d]	6.01 (4.41-8.19)[d]
Unclassified	16/656	648.3	24.7	0.77 (0.43-1.34)	0.95 (0.54-1.67)	0.95 (0.54-1.69)	0.98 (0.55-1.74)
***De novo* CKD-ND**	447/2,859						
Recovery	116/1,366	1,432.4	81	Ref	Ref	Ref	Ref
Relapse	77/180	217.2	354.5	3.97 (2.96-5.32)[d]	3.75 (2.78-5.07)[d]	3.78 (2.79-5.12)[d]	3.84 (2.82-5.22)[d]
Persistent	232/760	873.3	265.7	3.13 (2.49-3.93)[d]	3.38 (2.68-4.26)[d]	3.39 (2.68-4.29)[d]	3.35 (2.61-4.29)[d]
Unclassified	22/553	568.1	38.7	0.45 (0.29-0.72)[d]	0.49 (0.31-0.79)[d]	0.47 (0.29-0.75)[d]	0.48 (0.30-0.77)[d]
Late-Recovery AKD (general definition)	161/1,559						
Persistent	82/1,285	1,193.3	68.7	Ref	Ref	Ref	Ref
Relapse	79/274	270.7	291.8	4.28 (3.08-5.95)[d]	3.80 (2.72-5.32)[d]	3.94 (2.78-5.58)[d]	3.62 (2.52-5.21)[d]

Abbreviations: ACEIs, angiotensin-converting enzyme inhibitors; AKD, acute kidney disease; AKI, acute kidney injury; ARBs, angiotensin receptor blockers; CI, confidence interval; CKD, chronic kidney disease; HRs, hazard ratios; ICU, intensive care unit; KRT, kidney replacement therapy; NSAIDs, nonsteroidal anti-inflammatory drugs; qSOFA, quick sequential organ failure assessment; SA-AKD, sepsis-associated acute kidney disease.
[a]Model 1: Adjusted for age, sex, comorbid conditions (diabetes, hypertension, cardiovascular disease, chronic pulmonary disease, and liver cirrhosis), and serum creatinine level at baseline.
[b]Model 2: Further adjusted for septic shock, qSOFA, post-sepsis ICU admission, and use of nephrotoxic agents or agents predisposing patients to AKI (NSAID, contrast agent, antimicrobials, ACEI/ARBs, and diuretics).
[c]Model 3: Further adjusted for AKI stage, and biochemical profiles within 48 hours before to 48 hours after sepsis (ie, hemoglobin, serum albumin level, and lactate).
[d]$P < 0.05$.

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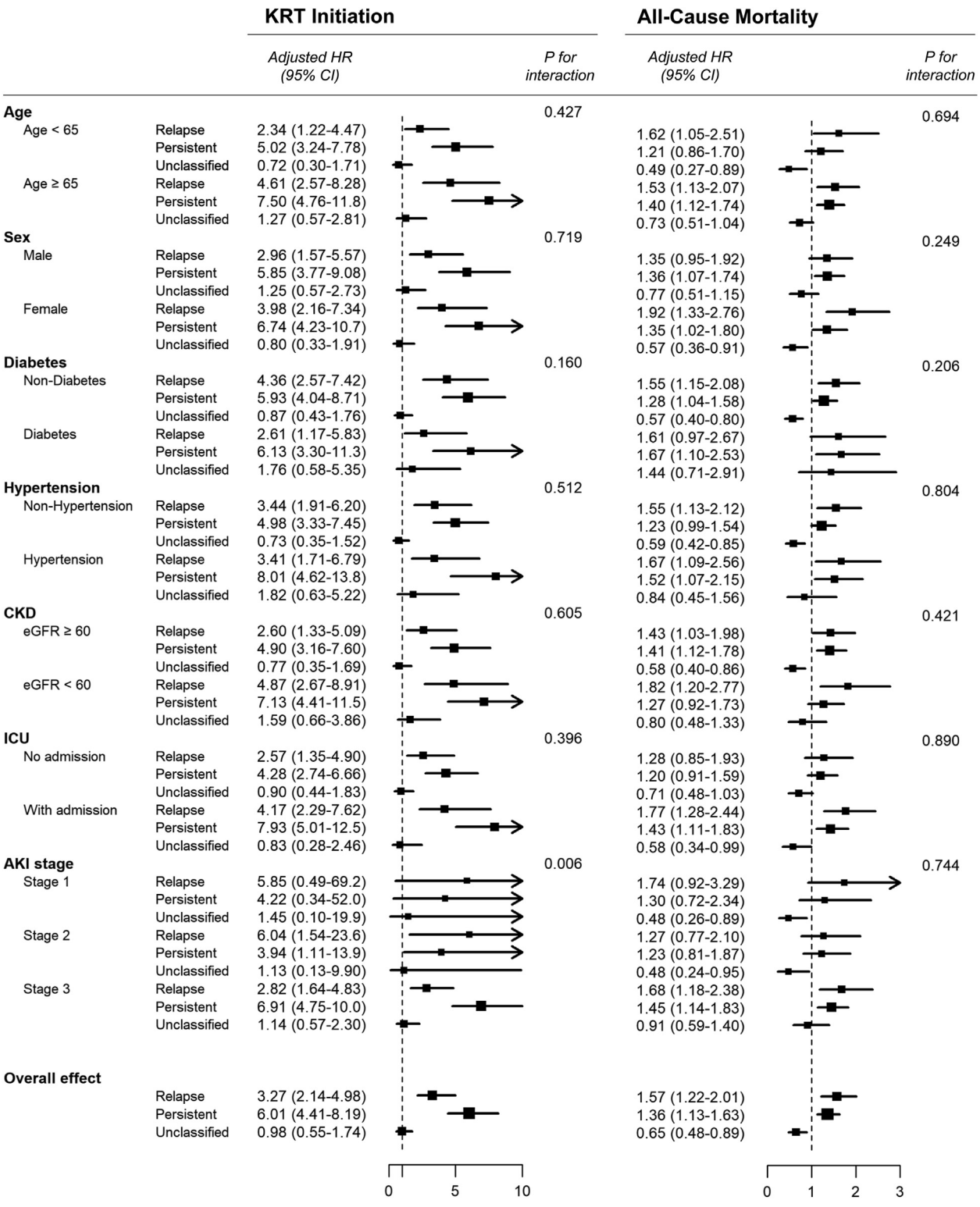

Figure 5. HRs for 1-year KRT and all-cause mortality were compared among the SA-AKD subgroups, with the comparisons stratified by patient characteristics. The reference group for the adjusted HR is the recovery AKD group. Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; ICU, intensive care unit; KRT, kidney replacement therapy; SA-AKD, sepsis-associated acute kidney disease.

compared with those in the recovery and unclassified SA-AKD subgroups. However, ~9% of patients with SA-AKD relapse or persistent SA-AKD achieved late recovery. Further studies are warranted to assess the clinical effectiveness of standardized post-AKD care. In this study, only one-quarter of patients with SA-AKD received either in-hospital

nephrology consultations or postdischarge nephrology follow-up within 1 year.

Although our findings align with those of previous studies that SA-AKD is associated with accelerated progression to end-stage kidney disease and an increased long-term mortality risk,[21-23] the heterogeneity of populations with sepsis and the variability in statistical approaches hinder direct comparisons across these studies. In earlier research, scholars primarily drew conclusions from data on patients who were critically ill either from populations in ICUs[21,22] or from post hoc analysis in the ProCESS trial, which targeted patients with septic shock.[23] This selection approach may have underestimated the effect size of SA-AKD on mortality because sepsis severity could significantly contribute to short-term mortality risk, as demonstrated in the ProCESS population.[23] Wang et al[24] identified a risk pattern between AKD and mortality in a population-based cohort, although their study had a short follow-up period of 1 year. Their findings demonstrated that this association was most pronounced in the short term (≤180 days) and suggested that delayed recovery beyond the first 14 days after AKI is linked with the least favorable outcomes. However, our study found stable relative risk estimates for SA-AKD on mortality over the 1-year to 3-year follow-up period, indicating that disease-specific AKD, such as that related to sepsis, may have unique prognosis trajectories.

The long-term prognostic trajectories of kidney outcomes in patients with SA-AKD have not been well documented. Gameiro et al[21] identified a robust association of SA-AKD with long-term adverse kidney outcomes, which was defined by dialysis dependence or a 25% decrease from discharge eGFR (aHR, 2.87; 95% CI, 2.0-4.1) over almost 4 years. By contrast, our study involved general hospitalized patients and showed an even stronger association between SA-AKD and the risk of KRT initiation, particularly in the persistent SA-AKD subgroup, who had a 6-fold higher risk up to 3 years compared with the recovery SA-AKD subgroup. Our study also provides new information on the transition from AKI to AKD to CKD. Patients without SA-AKD recovery, even those with normal baseline kidney function, had a 4-fold higher risk of CKD-ND, accounting for 30% and 23% of SA-AKD relapse and persistent SA-AKD subgroups, respectively. When combining mortality, KRT initiation, and *de novo* CKD-ND into a single composite outcome, an alarming 33.4% of patients with nonrecovering SA-AKD are projected to experience these outcomes. These findings highlight the urgent requirement for identifying factors that can improve kidney recovery, particularly among the remaining 9.4% of patients who achieved late recovery.

In our study, the low rates of in-hospital and postdischarge nephrology consultations among patients without SA-AKI recovery and patients with SA-AKD are concerning. First, conclusive evaluations of the role of nephrology consultations in SA-AKI/AKD care are lacking, although observational studies suggest their potential benefits.[25,26] In 2021, a sepsis trial protocol, namely the Limiting AKI progression in sepsis trial,[27] was developed to examine the efficacy of kidney-sparing sepsis bundles, which include regular nephrology consultations, although intensivists have expressed contrasting views.[28] Second, consistently low follow-up rates, usually less than 10%, persist as a major impediment to appropriate AKI care,[29-31] despite the known benefits of nephrology follow-up for improving clinical outcomes such as all-cause mortality,[32] rehospitalization,[33] and major cardiovascular events.[34] By contrast, a randomized trial performed in Toronto, Canada, reported a comparable risk of adverse kidney outcomes between patients who received nephrology care and those who received usual care.[31] This finding is also supported by a recent propensity-matched cohort study performed in Ontario, Canada.[35] Given the heterogeneity of AKI etiologies, their interactions with comorbid conditions, and the limited efficacy of renoprotective therapies,[36] a shift toward personalized AKI care is warranted to optimize kidney recovery across the AKI–AKD–CKD continuum. Such a shift can be accomplished by data-driven risk assessments and advanced quantitative kidney health tracking performed through digital technologies. The initiation of universal, systematic, and digital screening for nephrotoxic agents to avoid secondary kidney injury is a pivotal first step and is worthy of further exploration. The integration of technology-driven proactive nephrology follow-up into post–SA-AKD care, which can be extended to other specific AKD etiologies, such as heart failure and oncology, is a promising strategy for disrupting the progression from AKI to CKD.

Our study has several strengths. First, it used a standardized and verified data algorithm to define sepsis based on the latest Sepsis-3 criteria and to define AKI based on KDIGO definition, which are the recommended criteria proposed by the 2023 Acute Disease Quality Initiative workgroup consensus report.[37] Second, the availability of high-quality, high-resolution data enabled the classification of AKD subgroups (recovery, relapse, persistent, and unclassified) in line with the latest consensus.[23,38] We developed a novel imputation method to estimate baseline kidney function. Third, the large sample size and the low rate of loss to follow up over 3 years significantly mitigated information bias. Finally, we performed several sensitivity analyses using different strata, alternative follow-up durations, and entry dates, and we meticulously accounted for loss-to-follow-up status and outcome assumptions, resulting in consistent and robust inferences (Tables S8-S11). Several limitations of this study should be noted. First, our study used the database of a quaternary referral medical center; external validation using data from different health care systems is warranted to confirm the generalizability of the study findings. Second, the retrospective study design and the study population restriction to sepsis survivors may cause the risk of survivor bias.[39] However, multiple sensitivity analyses may have mitigated this limitation. Third, the post-AKD follow-up of

kidney function was not based on a standardized protocol, resulting in many patients not having follow-up eGFR measurements from day 8-90 or from day 91-365 after SA-AKI. This inconsistency in follow-up may lead to information bias, potentially causing an underestimation of the incidence of recovery, relapse, and persistent status of AKD, and *de novo* CKD and a late-recovery AKD status. Nonetheless, the results of our study accurately reflect real-world practice under a universal health care system. Fourth, muscle wasting could have caused the decreased Scr level after sepsis, potentially leading to the underdiagnosis of AKI or AKD and the overdiagnosis of recovery status. This misclassification could result in underestimating the negative outcomes associated with SA-AKD.[40-42] The best way to address this potential bias is by performing a 24-hour creatinine clearance or introducing a 24-hour urine creatinine level to adjust the current eGFR formula that we proposed 2 years ago.[16] We should consider performing 24-hour creatinine clearance for patients who are being discharged from the ICU or during transitions, such as from the general ward to outpatient follow-up, to establish a reliable baseline. Finally, residual confounding factors could not be completely excluded because our database does not contain information on diet, living environments, and physical activity, which could confound clinical outcomes.

CONCLUSION

This study presents a comprehensive, real-world representation of SA-AKD in a quaternary medical center operating under a universal health care system. Consistent with previous findings, our study showed that patients without SA-AKD recovery have the worst prognosis in terms of KRT initiation and all-cause mortality. We demonstrated that late recovery to baseline kidney function was possible, even among patients without SA-AKD recovery. Further research focusing on modifiable factors that can alter the trajectory of AKI–AKD–CKD is warranted; for example, the rate of *de novo* CKD could be reduced among patients with SA-AKD with normal kidney function at baseline. The data algorithm for identifying sepsis and various post–SA-AKI phenotypes provides a foundation for future research incorporating diverse technologies, such as machine learning and artificial intelligence. The study results can serve as the basis for a paradigm shift toward digital therapies for managing the transition from AKI to AKD to CKD.

SUPPLEMENTARY MATERIALS

Supplementary File (PDF)

Figure S1: Sepsis-3 definition using electronic health records data.

Figure S2: HRs for progression to KRT initiation at 2 and 3 years were compared among the SA-AKD subgroups, with the comparisons stratified by patient characteristics. The reference group for the adjusted HR is the recovery AKD group.

Figure S3: HRs for progression to all-cause mortality at 2 and 3 years were compared among the SA-AKD subgroups, with the comparisons stratified by patient characteristics. The reference group for the adjusted HR is the recovery AKD group.

Method S1: Supplementary variable definitions.

Method S2: Supplementary statistical analyses.

Table S1: ICD-9-CM and ICD-10-CM Codes for Comorbid Conditions, Infection Site, and Cardiovascular Mortality.

Table S2: The Number of Missing Observations (missing rate %) of the Variables in the Current Study.

Table S3: Stage Distribution of AKI and AKD Among Eligible Inpatients With Sepsis With and Without Excluded Patients who Deceased Within the AKD Diagnostic Time Frame After the AKI Index Date.

Table S4: Additional Clinical Characteristics of Sepsis Survivors With SA-AKD Divided into Recovery, Relapse, Persistent, and Unclassified SA-AKD Subgroups.

Table S5: HRs (95% CIs) of 1-, 2-, and 3-Year All-Cause Mortality by SA-AKD Subgroup (n = 4,239).

Table S6: HRs (95% CIs) for 1-, 2-, and 3-Year KRT Outcome by SA-AKD Subgroup (n = 4,239).

Table S7: HRs (95% CI) of 1-year De Novo CKD, Probable De Novo CKD, Probable De Novo CKD-ND and Late Recovery From AKD (with strict definition) by SA-AKD Subgroup (n = 4,239).

Table S8: HRs (95% CIs) of 1-, 2-, and 3-Year All-Cause Mortality by SA-AKD Subgroup With Consideration for Patients who Died Within the 90-day AKD Diagnostic Time Frame (n = 5,937).

Table S9: HRs (95% CIs) of 1-, 2-, and 3-Year KRT Outcome by SA-AKD Subgroup With Consideration for Patients who Died Within the 90-day AKD Diagnostic Time Frame (n = 5,937).

Table S10: HRs (95% CIs) of 1-, 2-, and 3-Year All-Cause Mortality by SA-AKD Subgroup for Patients With a True Baseline Scr value (n = 911).

Table S11: HRs (95% CIs) of 1-, 2-, and 3-Year KRT Outcome by SA-AKD Subgroup for Patients With True Baseline Scr values (n = 911).

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