Sepsis-associated Acute Kidney Injury Subphenotypes in Critically Ill Patients by Staging Trajectories

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Abstract

Background: Sepsis is the leading cause of acute kidney injury (AKI) in critically ill patients. The current Kidney Disease: Improving Global Outcomes (KDIGO) criteria rely on maximal serum creatinine levels, which do not account for longitudinal changes. This study aimed to examine AKI staging trajectories and hypothesized that subphenotypes based on these trajectories are associated with different outcomes.

Methods: Two independent databases of patients in the intensive care unit (ICU) with AKI in Southeast Asia were analyzed. The SEA-AKI cohort served as the development cohort, while the KCMH cohort was used for validation. Group-based trajectory modelling identified subphenotypes of AKI staging in septic patients during the first seven days after ICU admission. Baseline characteristics, AKI staging, duration, recovery, and the occurrence and staging of acute kidney disease were compared between clusters. Associations between clusters and 28-day mortality, ICU and hospital mortality, and major adverse kidney events at day 28 (MAKE28) were evaluated.

Results: A total of 457 patients were included in the development cohort and 333 in the validation cohort. AKI occurred in 70.7% of the development cohort and 63.4% of the validation cohort. Three distinct clusters of AKI staging trajectories were identified in the development cohort: Cluster 1 (No AKI, 29.3%), Cluster 2 (early mild transient AKI, 50.9%), and Cluster 3 (early severe persistent AKI, 19.7%). Compared with the other clusters, an independent association was found between Cluster 3 and increased 28-day mortality. These findings were confirmed in the validation cohort.

Conclusions: AKI staging trajectories identified distinct subphenotypes associated with different outcomes. Further studies are needed to explore subphenotype-based interventions.

Keywords: acute renal failure; AKD; septicemia; infection; renal failure; survival

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การศึกษาซับฟีโนไทป์ในภาวะไตวายเฉียบพลันที่สัมพันธ์กับภาวะติดเชื้อในผู้ป่วยวิกฤต

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บทคัดย่อ

บทนำ: ภาวะติดเชื้อในกระแสเลือดเป็นสาเหตุที่พบได้บ่อยที่สุดของภาวะไตวายเฉียบพลันในหอผู้ป่วยวิกฤต เกณฑ์การวินิจฉัยภาวะไตวายเฉียบพลันในปัจจุบันใช้การเพิ่มขึ้นของระดับครีแอทินินที่สูงที่สุดเพียงครั้งเดียวโดยไม่ได้ติดตามในระยะยาว การวิจัยครั้งนี้มีวัตถุประสงค์เพื่อค้นคว้าซับฟีโนไทป์โดยจำแนกจากการเปลี่ยนแปลงของระยะภาวะไตวายเฉียบพลัน และนำมาสร้างโมเดลทางคลินิกเพื่อประเมินความสัมพันธ์กับผลลัพธ์

ระเบียบวิธีวิจัย: การศึกษานี้อาศัยการวิเคราะห์ข้อมูลจากฐานข้อมูลของผู้ป่วยภาวะวิกฤตในภูมิภาคเอเชียตะวันออกเฉียงใต้ 2 ฐานข้อมูล คือ 1) SEA-AKI เป็นฐานข้อมูลในการสร้างโมเดล (development cohort) และ 2) ฐานข้อมูล KCMH ในการพิสูจน์โมเดล (validation cohort) และใช้เทคนิค group-based trajectory modelling ในการสร้างซับฟีโนไทป์จากการเปลี่ยนแปลงของระยะภาวะไตวายเฉียบพลันเป็นเวลา 7 วันของผู้ป่วยที่มีภาวะติดเชื้อในกระแสเลือด ผู้วิจัยได้เปรียบเทียบความแตกต่างของลักษณะผู้ป่วย ระยะความรุนแรง ระยะเวลาและการฟื้นตัวของภาวะไตวายเฉียบพลัน การเกิดและระยะความรุนแรงของโรคไตเฉียบพลัน (acute kidney disease) ระหว่างแต่ละกลุ่ม และนำมาสร้างโมเดลทางคลินิกเพื่อศึกษาความสัมพันธ์กับอัตราการเสียชีวิตที่ 28 วัน อัตราการเสียชีวิตในหอผู้ป่วยวิกฤตและในโรงพยาบาล และการเกิดภาวะแทรกซ้อนด้านไตที่ 28 วัน (MAKE28)

ผลการวิจัย: ผู้ป่วยใน development cohort มีจำนวน 457 ราย และใน validation cohort มีจำนวน 333 ราย ความชุกของภาวะไตวายเฉียบพลันอยู่ที่ร้อยละ 70.7 ใน development cohort และร้อยละ 63.4 ใน validation cohort สามารถแบ่งกลุ่มที่จำเพาะของภาวะไตวายเฉียบพลันได้ 3 กลุ่ม (ซับฟีโนไทป์) ประกอบไปด้วย กลุ่มที่ 1: ไม่มีภาวะไตวายเฉียบพลัน (ร้อยละ 29.3) กลุ่มที่ 2: ภาวะไตวายเฉียบพลันที่เกิดเร็ว รุนแรงน้อย และฟื้นตัวเร็ว (ร้อยละ 50.9) กลุ่มที่ 3: ภาวะไตวายเฉียบพลันที่เกิดเร็ว รุนแรงสูง และไม่ฟื้นตัว (ร้อยละ 19.7) จากการวิเคราะห์ทางสถิติพบว่ากลุ่มที่ 3 มีความสัมพันธ์กับอัตราการเสียชีวิตที่ 28 วันสูงกว่ากลุ่มอื่นๆ ข้อมูลจาก development cohort นี้ได้รับการยืนยันจาก validation cohort

สรุป: สามารถใช้การเปลี่ยนแปลงของระยะความรุนแรงของภาวะไตวายเฉียบพลันจำแนกซับฟีโนไทป์ของไตและสร้างโมเดลที่สัมพันธ์กับผลลัพธ์ที่แตกต่างกัน ผลการศึกษานี้อาจนำมาใช้วางแผนการรักษาได้แต่ต้องได้รับการศึกษาเพิ่มเติม

คำสำคัญ: ไตวาย; ไตเสื่อม; ไอซียู; ติดเชื้อ; การอยู่รอด

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Background

Acute kidney injury (AKI) is a common complication in various clinical settings, especially in intensive care units (ICUs).[1] AKI is associated with increased morbidity and mortality, including progression to chronic kidney disease (CKD) and end-stage kidney disease (ESKD).[2] Sepsis is one of the most common causes of AKI in critical illness.[3] Sepsis-associated acute kidney injury (SA-AKI) is a heterogeneous syndrome with complex mechanisms, different temporal courses, and prognoses. The mechanisms include macrocirculatory and microcirculatory alterations, inflammation, neurohormonal activation, mitochondrial dysfunction, metabolic reprogramming, etc. In addition, processes of care or interventions such as fluid therapy or nephrotoxic medications could contribute to AKI occurrence and progression.[4]

While the current Kidney Diseases: Improving Global Outcomes (KDIGO) criteria for AKI diagnosis is well-validated, the utilisation of a single serum creatinine (SCr) might be an oversimplification and only focuses on "peak SCr" or maximal staging.[5] More recent evidence suggests that longer duration of AKI and non-recovery are associated with higher mortality and ESKD.[6,7] Therefore, characterisation of AKI subtypes by clinical trajectory could help predict outcomes, guide tailored treatment and inform post-discharge surveillance.

Previous studies have identified SCr trajectories in sepsis patients but focused on the first few days after ICU admission and excluded patients who received renal replacement therapy (RRT).[8-10] From our previously published literature from Southeast Asia (SEA), approximately 25% of critically ill patients required RRT. Therefore, we aimed to explore the trajectories of AKI staging within the first 7 days after ICU admission by using two independent cohorts and determine if these trajectory patterns were associated with worse clinical outcomes.

Methods

Study design

This study was an observational study of critically ill patients with sepsis. The study was approved by the Institutional Review Board (IRB) of Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand (No. 0731/65). Informed consent was waived due to the retrospective nature. The study was performed in accordance with Good Clinical Practice and the Helsinki Declaration of 1975 and reported according to The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[11]

Data sources

We used data from two independent databases – 1) Southeast Asia – Acute Kidney Injury (SEA-AKI) and 2) King Chulalongkorn Memorial Hospital (KCMH).

SEA-AKI was an international multicentre database prospectively recruiting patients who were admitted to intensive care units (ICUs) from 17 Thai, 5 Lao and 1 Indonesia centres in 2015, for which details were published previously.[12] The SEA-AKI database was used to develop **AKI staging trajectory models** and to assess whether these trajectories impact clinical outcomes in sepsis patients. The KCMH database was a single-centre database of patients who were admitted to ICUs at King Chulalongkorn Memorial Hospital, a tertiary-care centre in Bangkok, Thailand between 2020-2021. The KCMH database was used as an independent external validation cohort.

Study population

We included adult (≥18 years old) patients with sepsis who were admitted to ICUs for at least 7 days. We identified sepsis according to SEPSIS-3 criteria i.e. suspicion of infection and an increase in Sequential Organ Failure Assessment (SOFA) score by two or more within a 24-h period.[13] We assumed a SOFA score of zero before ICU admission. The diagnosis of sepsis was adjudicated by attending clinicians and recorded in the discharge summaries. For patients with multiple ICU admissions, we included data from only the first ICU admission. We included patients who were admitted to ICUs for at least 7 days with available SCr on day 7. We excluded patients under the age of 18 years, those with ESKD or prior kidney transplant, those who received RRT prior to ICU admission or with missing SCr >40% (i.e. 3 time points) in the first week.

Variables

We extracted data on patient demographics, comorbidities, baseline SCr, severity scores including Acute Physiology and Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment (SOFA) scores, mechanical ventilation, vasopressor use during the first 7 days of ICU admission. The receipt of RRT and the date of RRT initiation were recorded. Following published literature, the missing SCr values were imputed using predictive mean matching techniques with five imputations based on Multivariate Imputation via Chained Equations (MICE) function in R.[14] We then used SCr values to diagnose AKI and acute kidney disease (AKD) and to identify their staging. The onset of AKI, the first and the maximal AKI staging were identified. As per KDIGO guidelines, we defined AKI as an increase in serum creatinine (SCr) by 0.3 mg/dL or more within 48 h or an increase by at least 1.5 times the baseline SCr within 7 days. The receipt of RRT was considered AKI stage 3. In accordance with previous literature, we determined baseline SCr as an outpatient SCr within 12 months before ICU admission. In patients without available baseline SCr, the first admission SCr or estimation of SCr by the Modification of Diet in Renal Disease (MDRD) formula equivalent to estimated glomerular filtration rate (eGFR) 75 ml/min/1.73m^2, whichever one was lower, was used.[5, 15] Persistent AKI was defined as the continuance of AKI by SCr criteria beyond 48 hours after AKI onset. AKD was defined as the elevation of SCr as per the KDIGO AKI criteria in survivors at day 7.[16] Recovery was defined by no longer meeting AKI criteria at hospital discharge.[16]

Outcomes

The primary outcome was 28-day all-cause mortality. Secondary outcomes were all-cause ICU mortality, hospital mortality, ICU and hospital length of stay and major adverse kidney events on day 28 (MAKE28). MAKE28 was defined as a composite outcome of death, receipt of RRT or persistent loss of kidney function (≥50% decline in eGFR).

Statistical analysis

To achieve a 20% difference in 28-day mortality between patients without AKI and the most severe cluster based on a previously reported 50% prevalence of AKI in ICU, an approximate 200 patients were needed to offer 80% power with type 1 error < 0.05. We employed group-based trajectory modeling (GBTM), a statistical approach for identifying distinct subgroups of individuals following similar developmental trajectories over time, to determine the optimal number of clusters for AKI staging trajectory. The model was iteratively applied, testing configurations ranging from two to six clusters. To select the best-fit model, we utilized two criteria: first, we identified the model yielding the lowest Bayesian Information Criterion (BIC), a criterion for model selection that balances goodness of fit with model complexity. Second, to avoid overfitting, we mandated that each cluster in the development cohort must comprise at least 5% of the total sample. This dual approach ensured both statistical rigor and practical applicability in our cluster determination process. The model performances were assessed using the average of the posterior probability (AvgPP) assignment, odds of correct classification (OCC) and the relative entropy.[17] For external validation, we applied the classification from the development cohort to cluster AKI staging and SCr trajectories with the validation cohort.

We expressed descriptive results as numbers with percentages, means with standard deviation or median with interquartile range, depending on the distribution. To compare between development and validation cohorts, we compared categorical features using Chi-Square and continuous features using Student t test and Mann-Whitney U tests. To compare clusters, we used Chi-square for categorical variables, one-way analysis of variance (ANOVA) or Kruskal-Wallis test for continuous data. We used logistic regression to determine the association of the trajectory patterns and outcomes. We used Kaplan-Meier survival curve and Cox regression analyses to evaluate the relationship between the trajectories and 28-day mortality. We performed the analyses using R version 4.4.0 and Stata version 18.0.

Results

Baseline characteristics

A total of 6,993 patients from SEA-AKI database and 6,267 patients from the KCMH database were evaluated. After excluding patients with missing SCr, ESKD, had RRT before ICU admission, and did not have sepsis, 457 critically ill patients with sepsis from SEA-AKI database were included as the development set and a total of 333 patients in the KCMH database served as external validation set. **(Figure 1)** More participants in the development cohort were male and had higher baseline SCr. They were more likely to require mechanical ventilation, had higher non-renal SOFA score and higher lactate but were less likely to require vasopressors, have liver dysfunction or coagulopathy compared with the validation cohort. 70.7% and 63.4% of patients in the development and validation cohort developed AKI, respectively. The development cohort had more proportions and more severe AKI with higher ICU and 28-day mortality compared with the validation cohort. **(Table 1)**

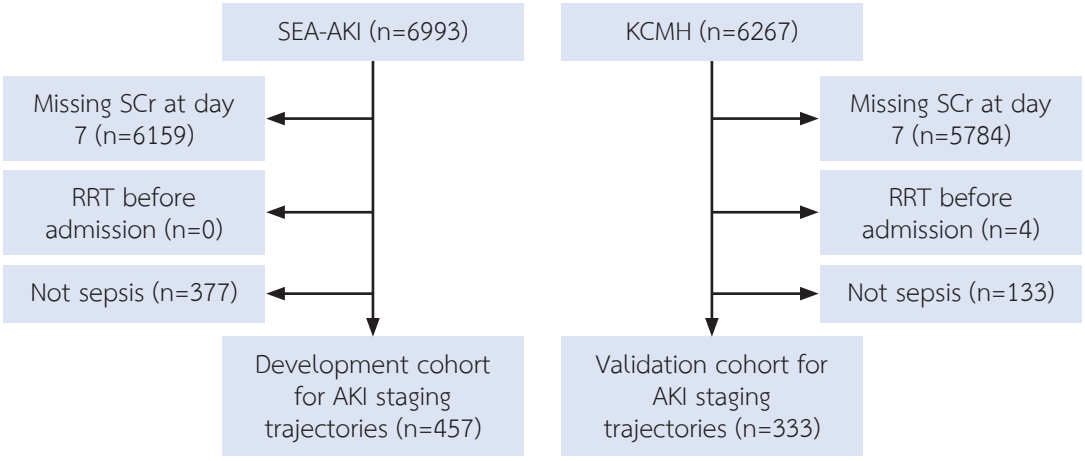

Figure 1 Study flow diagram

Table 1 Characteristics and outcomes between the development (SEA-AKI) and validation (KCMH) cohorts

	SEA-AKI N=457	KCMH N=333	P-value
Age (years)	65 (19)	64 (18)	0.81
Male sex (%)	251 (55%)	141 (42%)	<0.001
Underlying diseases (%)			
Diabetes	129 (28%)	102 (31%)	0.46
Hypertension	172 (37.6%)	160 (48.0%)	0.003
Cerebrovascular disease	40 (8.8%)	19 (5.7%)	0.11
Chronic kidney disease	41 (9.0%)	25 (7.5%)	0.46
Coronary artery diseases	34 (7.4%)	62 (18.6%)	<0.001
Organ support (%)			
Mechanical ventilation	409 (89.5%)	245 (73.6%)	<0.001
Vasopressors	276 (60.4%)	256 (76.9%)	<0.001
SOFA score on ICU admission			
Liver ≥2 (%)	2 (0.4%)	103 (30.3%)	<0.001
Coagulation ≥2 (%)	7 (1.5%)	88 (26.4%)	<0.001

Table 1 Characteristics and outcomes between the development (SEA-AKI) and validation (KCMH) cohorts (continued)

	SEA-AKI N=457	KCMH N=333	P-value
Cardiovascular ≥2 (%)	211 (46.2%)	256 (76.9%)	<0.001
Respiratory ≥2 (%)	306 (67.0%)	31 (9.3%)	<0.001
Non-renal SOFA score	6 (4-8)	2 (1-3)	<0.001
APACHE II	20 (16-25)	19.5 (13-25.5) (n=84)	0.32
Lactate (mmol/L)	2.78 (1.5, 5.8) (n=167)	2 (1.1, 3.5) (n=321)	0.0001
Baseline creatinine (mg/dL)	0.99 (0.77,1.16)	0.86 (0.69, 1.06)	<0.001
AKI in 7 days (%)	323 (70.7%)	211 (63.4%)	0.030
First AKI staging (%)			<0.001
0	134 (29.3%)	122 (36.6%)	
1	113 (24.7%)	117 (35.1%)	
2	46 (10.1%)	20 (6.0%)	
3	164 (35.9%)	74 (22.2%)	
Maximal AKI staging (%)			<0.001
0	134 (29.3%)	122 (36.6%)	
1	74 (16.2%)	84 (25.2%)	
2	56 (12.3%)	35 (10.5%)	
3	193 (42.2%)	92 (27.6%)	
AKI onset (days)	1 (0-1)	1 (0-1)	0.50
Persistent AKI (%)	(n=323) 254 (78.6%)	(n= 211) 158 (74.9%)	0.31
Recovery (%)	(n=323) 128 (39.6%)	(n= 211) 118 (55.9%)	<0.001
RRT (%)	122 (26.7%)	84 (25.2%)	0.64
RRT date from ICU admission (days)	2 (1-4) (n=122)	2 (1-7.5) (n=84)	0.85
ICU mortality (%)	152 (33.3%)	48 (14.4%)	<0.001
Hospital mortality (%)	216 (47.3%)	161 (48.3%)	0.76
ICU length of stay (days)	13 (9-19)	11 (8-16)	<0.001
Hospital length of stay (days)	22 (14-35)	32 (19-53)	<0.001
28-day mortality (%)	166 (36.3%)	94 (28.2%)	0.017
AKD (%)	230 (50.3%)	141 (42.3%)	0.026
AKD staging (%)			0.012
0	227 (49.7%)	192 (57.7%)	
1	49 (10.7%)	45 (13.5%)	
2	44 (9.6%)	18 (5.4%)	
3	137 (30.0%)	78 (23.4%)	

AKD, acute kidney disease; AKI, acute kidney injury; APACHE II, Acute Physiologic and Chronic Health Evaluation II; ICU, intensive care units; RRT, renal replacement therapy; SOFA, Sequential Organ Failure Assessment

AKI staging trajectories

Classification of AKI staging trajectories

With the lowest BIC **(Table S1)**, we identified 3 distinct clusters of AKI staging trajectories in the development cohort. These clusters showed differences in AKI prevalence, staging, duration and AKD prevalence and staging. **(Table 2 and Figure 2A)**

Cluster 1: stable SCr throughout 7 days (No AKI)

Cluster 2: early mild and transient AKI with recovery at day 7 (early mild transient AKI)

Cluster 3: early severe AKI with persistence and non-recovery at day 7 (early severe persistent AKI)

The most prevalent was "early mild transient AKI" (Cluster 2) (50.9%), followed by "no AKI" (Cluster 1) (29.3%) and "early severe persistent AKI" (Cluster 3) (19.7%). There were significant differences among clusters in age (p=0.03), diabetes (p=0.003), hypertension (p<0.001), mechanical ventilation (p<0.001), vasopressor use (p<0.001), APACHE II score (p<0.001) and baseline SCr (p=0.007).

In cluster 2, 48.5% had an initial AKI stage 1, but the maximal AKI stage was predominantly stage 3 (44.2%), followed by stage 1 (31.8%) and stage 2 (24%). In contrast, all patients in cluster 3 had AKI stage 3, which persisted throughout day 7. Both clusters 2 and 3 had the median onset of AKI on day 1, but those in cluster 3 were more likely to receive RRT earlier than cluster 2 (2, interquartile range (IQR) 1,4 days) vs 3 (IQR 2,6) days (p<0.001). Compared with cluster 2, patients in cluster 3 were more likely to have persistent AKI (96.7% vs 71.7%). On day 7, 60.1% of Cluster 2 were diagnosed with AKD, in contrast to all of Cluster 3.

Table 2 Baseline characteristics and outcomes by AKI staging clusters in the development (SEA-AKI) cohort

Parameters	Cluster (N=457)			
	1 N=134 (29.3%)	2 N=233 (51.0%)	3 N=90 (19.7%)	P-value
Age (years)	61.51 (20.34)	66.75 (17.69)	63.38 (18.92)	0.030
Male sex (%)	80 (59.7%)	120 (57.5%)	51 (56.7%)	0.294
Diabetes (%)	24 (17.9%)	71 (30.5%)	34 (37.8%)	0.003
Hypertension (%)	32 (23.9%)	96 (41.2%)	44 (48.9%)	<0.001
Cerebrovascular disease (%)	15 (11.2%)	20 (8.6%)	5 (5.7%)	0.341
Chronic kidney disease (%)	9 (6.7%)	21 (9.0%)	11 (12.2%)	0.368
Coronary artery disease (%)	6 (4.5%)	23 (9.9%)	5 (5.6%)	0.125
Mechanical ventilation (%)	127 (94.8%)	194 (83.3%)	88 (97.8%)	<0.001
Vasopressors (%)	64 (47.8%)	139 (59.7%)	73 (81.1%)	<0.001
Liver SOFA ≥ 2 (%)	0	2 (0.9%)	0	0.700
Coagulation SOFA ≥ 2 (%)	0	7 (3%)	0	0.034
Cardiovascular SOFA ≥ 2 (%)	45 (22.6%)	108 (46.4%)	58 (64.4%)	<0.001
Respiratory SOFA ≥ 2 (%)	86 (64.2%)	161 (69.1%)	59 (65.6%)	0.597
Non-renal SOFA score	5 (4,8)	6 (4,8)	7 (5,9)	<0.001
APACHE II	18 (14,21)	21 (17,25)	23 (19,28)	<0.001
Baseline creatinine (mg/dL)	1.05 (0.70)	1.38 (1.92)	1.75 (1.82)	0.007

Table 2 Baseline characteristics and outcomes by AKI staging clusters in the development (SEA-AKI) cohort (continued)

Parameters	Cluster (N=457)			
	1 N=134 (29.3%)	2 N=233 (51.0%)	3 N=90 (19.7%)	P-value
AKI within 7 days (%)	0	233 (100%)	90 (100%)	<0.001
First AKI stage (%)				
1		113 (48.5%)	0	
2		46 (19.7%)	0	
3	0	74 (31.8%)	90 (100%)	<0.001
Maximal AKI stage (%)				
1		74 (31.8%)	0	
2		56 (24.0%)	0	
3	0	103 (44.2%)	90 (100%)	<0.001
AKI onset (days)	0 (0,0)	1 (1,1)	1 (1,1)	<0.001
Persistent AKI (%)	0	167 (71.7%)	87 (96.7%)	<0.001
RRT (%)	2 (1.5%)	46 (19.7%)	74 (82.2%)	<0.001
RRT date from ICU admission (days)	11 (1,21)	3 (2,6)	2 (1,4)	<0.001
ICU mortality (%)	37 (27.8%)	74 (31.8%)	41 (45.6%)	0.017
Hospital mortality (%)	57 (42.5%)	107 (45.9%)	52 (57.8%)	0.069
ICU length of stay (days)	13 (9,21)	13 (9,19)	13 (10,20)	0.927
Hospital length of stay (days)	23 (14,34)	21 (14,36)	23 (14,33)	0.070
28-day mortality (%)	43 (32.1%)	79 (33.9%)	44 (48.9%)	0.020
AKD (%)	0	140 (60.1%)	90 (100%)	<0.001
AKD staging (%)				
0		93 (39.9%)		
1		49 (21.0%)	0	
2		44 (18.9%)	0	
3	0	47 (20.2%)	90 (100%)	<0.001

AKD, acute kidney disease; AKI, acute kidney injury; APACHE II, Acute Physiologic and Chronic Health Evaluation II; ICU, intensive care units; RRT, renal replacement therapy; SOFA, Sequential Organ Failure Assessment

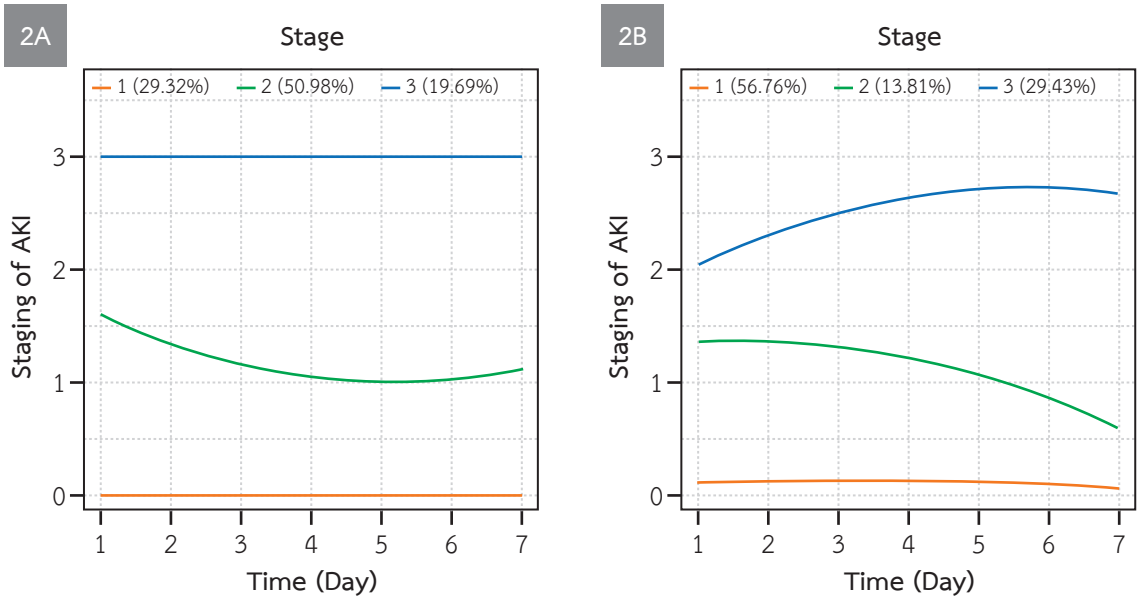

Figure 2 Three AKI staging trajectories from the development (2A) and validation (2B) cohort, including cluster 1: no AKI (yellow line), cluster 2: early mild transient AKI (green line) and cluster 3: early persistent severe AKI (blue line)
AKI, acute kidney injury

Association between AKI staging trajectories and outcomes in the development cohort

Significant differences existed among clusters for 28-day mortality (p=0.020) and ICU (p=0.017). In comparison with cluster 1, cluster 3 was significantly associated with an increased risk of 28-day mortality (Odds ratio (OR) 2.02; 95% confidence interval (CI) 1.17-3.51; p = 0.012), ICU mortality (OR 2.17; 95% CI 1.24-3.81; p = 0.007) and hospital mortality (OR 1.85; 95% 1.08-3.17; p = 0.026). The association persisted after adjustment with non-renal SOFA score. **(Table S2 and S3)** In both unadjusted and adjusted survival analyses, cluster 3 was associated with 28-day mortality with cluster 1 as the reference group (adjusted hazard ratio (aHR) 2.45; 95% CI 1.57-3.84; p < 0.001). **(Table 3 and Figure 3A)**

Table 3 Cox regression analysis by AKI staging trajectory clusters for 28-day mortality

	Unadjusted			Adjusted*		
	HR	95% CI	P value	HR	95% CI	P value
SEA-AKI						
Cluster 1	1					
Cluster 2	1.02	0.62-1.67	0.94	1.41	0.73-2.70	0.302
Cluster 3	3.26	1.99-5.34	<0.001	2.45	1.57-3.84	<0.001
KCMH						
Cluster 1	1					
Cluster 2	1.47	0.69-3.13	0.321	1.34	0.70-2.58	0.376
Cluster 3	2.42	1.42-4.10	0.001	2.26	1.44-3.55	<0.001

*By non-renal SOFA score

CI, confidence interval; HR, hazard ratio

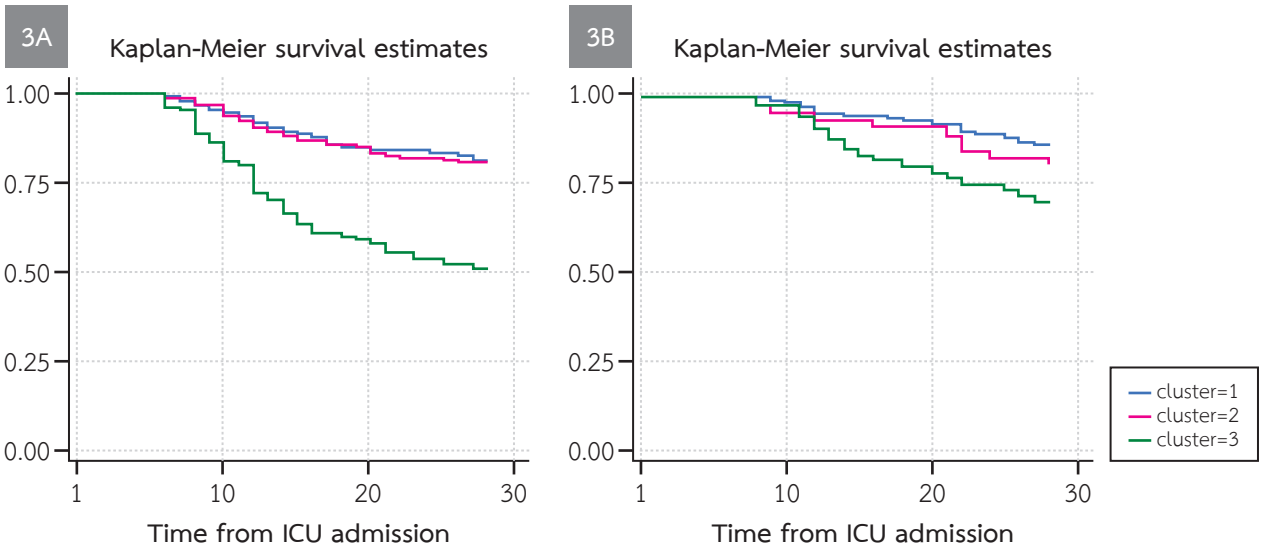

Figure 3 Kaplan-Meier survival estimates among 3 clusters in the development cohort (3A) and the validation cohort (3B). Cluster 1: No AKI, cluster 2: early mild transient AKI (green line) and cluster 3: early persistent severe AKI. ICU; intensive care unit

External validation of AKI staging trajectories

We externally validated the AKI staging trajectories model with the KCMH database. **(Figure 2B)** There were significant differences among clusters in AKI diagnosis (p<0.001), proportions of initial (p<0.001) and maximal AKI staging (p<0.001), persistence (p<0.001) and the development of AKD (p<0.001). **(Table S4)** Cluster 3 was associated with an increased risk of 28-day mortality (OR 2.49; 95% CI 1.46-4.23; p = 0.001), ICU mortality (OR 2.90; 95% CI 1.50-5.62; p = 0.002), and hospital mortality (OR 2.40; 95% CI 1.45-3.96; p = 0.001). (Table S3) Cox regression analysis revealed an increase in 28-day mortality in cluster 3, both in unadjusted (HR 2.42; 95% CI 1.42-4.10; p = 0.001) and adjusted analyses (aHR 2.26; 95% CI 1.44-3.55; p<0.001). **(Table 3 and Figure 3B)**

Table 3 Cox regression analysis by AKI staging trajectory clusters for 28-day mortality

	Unadjusted			Adjusted*		
	HR	95% CI	P value	HR	95% CI	P value
SEA-AKI						
Cluster 1	1					
Cluster 2	1.02	0.62-1.67	0.94	1.41	0.73-2.70	0.302
Cluster 3	3.26	1.99-5.34	<0.001	2.45	1.57-3.84	<0.001
KCMH						
Cluster 1	1					
Cluster 2	1.47	0.69-3.13	0.321	1.34	0.70-2.58	0.376
Cluster 3	2.42	1.42-4.10	0.001	2.26	1.44-3.55	<0.001

*By non-renal SOFA score

CI, confidence interval; HR, hazard ratio

Discussion

In this study, using data from two independent ICU databases from Southeast Asia, we derived and validated 3 AKI staging trajectories from ICU admission to 7 days in critically ill patients with sepsis. There was heterogeneity among clusters in both baseline characteristics, AKI patterns and outcomes. Patients with severe persistent AKI had the highest mortality rate and MAKE28.

The current KDIGO consensus criteria defined and staged AKI by maximum SCr and/or minimum urine output.[5] However, AKI is a syndrome with dynamic changes in stages, duration and aetiologies. The severity can be influenced by inherent factors, such as the severity of illness or receipt of therapy. Refining classification could aid studies evaluating the pathophysiology and molecular mechanisms of aetiology-specific AKI.[18] Identifying subphenotypes is important to designing personalised management strategies and informing appropriate monitoring and follow-up.[19-21]

Previous studies have demonstrated different AKI trajectories and associations with outcomes. Kellum et al. used a priori approach to determine 5 categories based on AKI reversal, relapse and recovery status at hospital discharge.[6] Bhatraju et al. divided critically ill patients with AKI into non-resolving and resolving AKI based on SCr in the first 72 hours of ICU stay.[22] Abdel-Nabey et al. defined 3 patterns of AKI staging trajectory in 350 critically ill patients, 50% of whom had sepsis.[23] Andrew et al. identified 12 SCr trajectory-based subphenotypes in patients who underwent nonemergent coronary artery bypass grafts.[9] Takkavatrakarn et al. identified 8 distinct clusters in critically ill patients with SA-AKI who developed AKI within the first 48 h based on SCr in the first 4 days.[8] Horie et al. recently classified trajectory patterns based on changes in urine liver-type acid-binding protein (uL-FABP).[10] Chaudhary et al. routinely collected vital signs, health information, and laboratory parameters from electronic health records (EHRs) and used deep learning to identify SA-AKI subphenotypes.[24] These studies were able to demonstrate differing subphenotypes associated with different prognoses. However, these data were from resource-sufficient settings, used early trajectories and excluded patients who received RRT. Therefore, only a minority of patients were classified into the most severe and persistent form of AKI.

In our study, 15-20% were in the most severe cluster. We could differentiate subphenotypes based on AKI severity, duration and recovery. Our data stem from resource-limited settings where a significant proportion of patients had community-acquired AKI and often required RRT early. This stresses the importance of early recognition, early referral and the role of community-based preventive strategies. In patients who did not require RRT in the first week, the peak SCr was after day 4, suggesting AKI progression after ICU admission. This might be explained by other factors such as haemodynamic optimisation, nephrotoxic agents, fluid balance, glucose control, etc. Our study also demonstrated a high prevalence of AKD, which is associated with the development of CKD, ESKD, and higher mortality.[25] Therefore, identification of high-risk patients might inform targeted therapies to alleviate the onset and severity of AKD, thereby reducing long-term adverse consequences.[26]

These findings support that SA-AKI is a complex syndrome with heterogeneous trajectories and outcomes. For clinical applications, risk prediction models could be developed and embedded in EHRs to identify subphenotypes early and allocate resources appropriately. In addition, biomarkers may aid in differentiation between subphenotypes and potentially show heterogeneity in treatment effects.[27]

There are several limitations to this study. First, we did not include urine output in the models. However, there may be heterogeneity in the recordings of urine output. Second, baseline SCr concentrations were available in only 22.1% of the development cohort, which limits our ability to perform sensitivity analyses with subjects containing baseline SCr. However, longitudinal follow-up of SCr could inform the diagnosis of AKI, AKI on CKD, or CKD, and might bypass the need for baseline SCr. Due to the small sample size, trajectory modeling might miss small trajectory classes, such as recurrent AKI, and a prospective study is required to confirm these findings.

There may also be inherent confounders not included in the multivariable models. In addition, several factors can affect SCr concentrations, making subphenotyping by SCr alone insufficient. Therefore, additional biomarkers may be needed for improved risk stratification. Nevertheless, SCr is widely available and can be easily measured, making the model practical and applicable in clinical practice. Despite these limitations, this is one of the first studies using a prospectively collected database from resource-limited settings. We used 7-day data to visualize the trajectories in one week. The models were externally validated; therefore, these findings could serve as the basis for larger studies using subphenotyping for risk stratification and interventions.

Conclusions

We identified 3 distinct AKI staging trajectories based on SCr changes within the 1st week after ICU admission. These clusters were different regarding AKI and AKD characteristics. The risk stratification was independently associated with outcomes and validated in an external cohort. Further studies are needed to identify the therapeutic implications of these subphenotypes towards personalised medicine.

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