

Early KDIGO trajectories after sepsis-associated acute kidney injury onset: an exploratory retrospective cohort study using MIMIC-IV

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Article

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Abstract

Sepsis-associated acute kidney injury (SA-AKI) is common in critically ill patients, but early post-onset evolution is often summarized by static KDIGO staging. We performed a retrospective landmark cohort study using MIMIC-IV to identify KDIGO trajectory phenotypes during the first 96 hours after SA-AKI onset and to compare them with a prespecified simplified rule-based classification. Adults with SA-AKI who remained alive and under observation through 96 hours after AKI onset and had sufficient data to define four consecutive 24-hour KDIGO windows were included. Latent class mixed modeling identified four trajectory phenotypes among 7,737 patients: mild rapidly resolving, severe early improving, persistent/fluctuating moderate, and persistent severe. Higher-burden trajectories were associated with greater risks of 30-day mortality after the landmark time and day-7 persistent AKI or death. Compared with the simplified rule-based classification, the four-class model showed better fit and modestly better discrimination. The AUCs for 30-day mortality were 0.6751 and 0.6661, respectively; those for day-7 persistent AKI or death were 0.7238 and 0.7046. These findings support early KDIGO trajectories as an exploratory phenotyping framework rather than a definitive prognostic model.

Introduction

Sepsis-associated acute kidney injury (SA-AKI) is one of the most frequent and clinically important organ dysfunction syndromes in critical care. Prior studies have linked SA-AKI to higher mortality, longer intensive care unit (ICU) stay, worse renal recovery, and greater long-term kidney risk ^[1, 2]. Improving early risk stratification remains an important goal in SA-AKI research and clinical practice.

The early course of SA-AKI is heterogeneous. Patients with the same KDIGO stage at presentation may follow different paths over the next few days, including rapid recovery, persistent instability, or further deterioration. Static staging reflects severity at a single time point but does not capture direction of change or pace of recovery. In SA-AKI, initial severity and early evolution may both carry prognostic information, and focusing on only one time point may miss clinically meaningful variation ^[1–3].

Interest in AKI subphenotypes and trajectory-based approaches has increased in recent years. Prior work suggests that AKI subgroups can differ in inflammatory profiles, endothelial injury, outcomes, and treatment response ^[4–7]. Trajectory phenotypes have shown prognostic gradients after cardiac surgery ^[8], and early creatinine trajectory analysis in septic critically ill patients has suggested distinct short-term kidney risks ^[9]. Related work on SOFA score, urine output, body temperature, and anion gap further supports the idea that longitudinal patterns may provide information that single measurements do not capture ^[10–13].

However, many prior trajectory studies have been anchored at ICU admission rather than AKI onset, making it difficult to separate timing of disease onset from subsequent evolution. In addition, few studies have directly compared a data-driven trajectory model with a simple, clinically interpretable rule-based framework. We therefore examined the first 96 hours after AKI onset using a landmark design,

identified early KDIGO trajectory phenotypes with LCMM, and compared them with a prespecified simplified rule-based four-group classification. Given the limited incremental discrimination and the temporal proximity between the 96-hour trajectory window and the day-7 kidney-related endpoint, this study was framed as an exploratory phenotyping analysis rather than as the development of a definitive prognostic model.

Methods

Study design and data sources

This was a retrospective cohort study using MIMIC-IV, a large publicly available, de-identified critical care database derived from the electronic health record system of Beth Israel Deaconess Medical Center ^[14]. The study was reported in accordance with the STROBE framework for observational studies. Because the database is de-identified, informed consent was waived. The eICU Collaborative Research Database was used for a supplementary transportability analysis ^[15].

Study population and 96-hour landmark framework

Adult patients with sepsis were first identified in MIMIC-IV according to Sepsis-3 criteria, and AKI was then ascertained using KDIGO definitions ^[16, 17]. To reduce immortal-time bias and differential-observation bias, we adopted a 96-hour landmark framework after AKI onset. Eligible patients had an ascertainable AKI onset time, remained alive and under observation through 96 hours, and had sufficient data to construct four consecutive 24-hour KDIGO staging windows. This study therefore represents a landmark-defined subgroup of patients with SA-AKI rather than all ICU patients with SA-AKI.

Trajectory construction and LCMM

The first 96 hours after AKI onset were divided into four consecutive 24-hour windows: 0–24 hours, 24–48 hours, 48–72 hours, and 72–96 hours. The KDIGO stage for each window was extracted to form a repeated sequence. Trajectory phenotypes were identified with the `lcmm` package in R ^[18]. KDIGO stage was treated as an ordered severity sequence for empirical phenotype identification rather than as a strictly continuous biological process. Model selection considered log-likelihood, AIC, BIC, convergence, minimum class size, average posterior probability, and clinical interpretability. Details are provided in Supplementary Table S10.

Simplified rule-based comparator

A prespecified simplified rule-based four-group classification was constructed using the same four 24-hour KDIGO windows. The four rule-based groups were rapidly resolving, persistent mild-to-moderate, worsening/fluctuating, and persistent severe. This framework was designed as a clinically intuitive

comparator rather than as an optimal simplified model. Detailed rules are provided in Supplementary Table S9.

Covariates and outcomes

Prespecified covariates were age, sex, chronic kidney disease, baseline serum creatinine, non-renal SOFA proxy within 24 hours after AKI onset, maximum KDIGO stage within 24 hours, vasopressor use, invasive mechanical ventilation, septic shock proxy, and first lactate value within 24 hours after AKI onset. The primary outcome was 30-day all-cause mortality measured from the 96-hour landmark time. The exploratory kidney-related endpoint was day-7 persistent AKI or death before day 7. Persistent AKI on day 7 was operationally defined as a maximum KDIGO stage of at least 1 within the day-7 assessment window, representing delayed early kidney recovery rather than a full replacement for formal consensus definitions of persistent AKI or acute kidney disease.

Missing data and statistical analysis

Complete-case analysis was used as the main analysis, and multiple imputation by chained equations was performed as a robustness analysis^[19, 20]. Baseline serum creatinine and first lactate within 24 hours after AKI onset were imputed using predictive mean matching. Multivariable logistic regression was used to examine associations between trajectory classes and outcomes, using the mild rapidly resolving class as the reference. Model performance was evaluated with AIC, BIC, and AUC. Likelihood ratio tests were used for nested-model comparisons, and DeLong tests were used to compare AUCs^[21, 22]. A three-class LCMM was fitted as a sensitivity analysis. Because the LCMM derivation process could not be fully replicated in eICU, the external analysis was treated as a supplementary transportability analysis rather than formal external validation.

Results

A total of 21,163 candidate patients with SA-AKI were identified in MIMIC-IV. Under the prespecified 96-hour landmark framework, 1,910 patients who died before 96 hours after AKI onset, 11,486 who were no longer under observation at the 96-hour landmark, and 30 without sufficient data to construct four complete 24-hour KDIGO windows were excluded. The final main analysis cohort included 7,737 patients (Fig. 1).

The four LCMM-derived trajectory classes were labeled mild rapidly resolving ($n = 2,652$), severe early improving ($n = 1,023$), persistent/fluctuating moderate ($n = 1,886$), and persistent severe ($n = 2,176$). The four-class model converged well; the smallest class comprised 1,023 patients (13.2% of the cohort), and the average maximum posterior probability was 0.876. Figure 2 shows mean trajectory patterns over the first 96 hours after AKI onset, and Table 1 summarizes baseline and early clinical characteristics by class. To help readers judge selection introduced by the landmark framework, Supplementary Table S13 compares included and excluded audit groups.

Table 1
Baseline and early clinical characteristics by the four-class LCMM trajectories.

Characteristic	Mild rapidly resolving N = 2,652	Severe early improving N = 1,023	Persistent/fluctuating moderate N = 1,886	Persistent severe N = 2,176	P value
Demographics and early severity					
Age, years	64.0 (52.0, 75.0)	68.0 (57.0, 78.0)	66.0 (55.0, 77.0)	65.0 (54.0, 75.0)	< 0.001
Male	1608 (60.6%)	593 (58.0%)	1083 (57.4%)	1223 (56.2%)	0.015
Female	1044 (39.4%)	430 (42.0%)	803 (42.6%)	953 (43.8%)	
Non-renal SOFA proxy within 24 h after AKI onset	2.0 (1.0, 3.0)	1.0 (0.0, 2.0)	1.0 (0.0, 3.0)	1.0 (0.0, 3.0)	< 0.001
Maximum KDIGO stage within 24 h after AKI onset					< 0.001
Stage 1	1357 (51.2%)	1 (0.1%)	543 (28.8%)	61 (2.8%)	
Stage 2	1245 (46.9%)	632 (61.8%)	1291 (68.5%)	637 (29.3%)	
Stage 3	50 (1.9%)	390 (38.1%)	52 (2.8%)	1478 (67.9%)	
Chronic kidney disease	433 (16.3%)	221 (21.6%)	398 (21.1%)	724 (33.3%)	< 0.001
Kidney function and biomarkers					
Baseline serum creatinine, mg/dL	1.0 (0.8, 1.4)	1.1 (0.8, 1.7)	1.0 (0.8, 1.4)	1.5 (1.0, 2.7)	< 0.001
Baseline serum creatinine missing	7	2	3	4	
Lactate within 24 h, mmol/L	1.5 (1.1, 2.3)	1.7 (1.2, 2.8)	1.7 (1.2, 2.6)	2.2 (1.4, 3.7)	< 0.001
Lactate missing	1122	319	708	387	
Organ support within 24 h after AKI onset					
<i>Note: Continuous variables are presented as median (interquartile range), and categorical variables as number (%). P values were derived from the Kruskal-Wallis test or the chi-square test, as appropriate.</i>					

Characteristic	Mild rapidly resolving N = 2,652	Severe early improving N = 1,023	Persistent/fluctuating moderate N = 1,886	Persistent severe N = 2,176	P value
Demographics and early severity					
Vasopressor use	1037 (39.1%)	531 (51.9%)	809 (42.9%)	1268 (58.3%)	< 0.001
Invasive mechanical ventilation	1806 (68.1%)	761 (74.4%)	1299 (68.9%)	1611 (74.0%)	< 0.001
Septic shock proxy within 24 h after AKI onset	309 (11.7%)	212 (20.7%)	247 (13.1%)	656 (30.1%)	< 0.001
<i>Note: Continuous variables are presented as median (interquartile range), and categorical variables as number (%). P values were derived from the Kruskal-Wallis test or the chi-square test, as appropriate.</i>					

Using the mild rapidly resolving class as the reference, the complete-case adjusted model showed higher 30-day mortality in the persistent/fluctuating moderate class and the persistent severe class, with odds ratios of 1.64 (95% CI 1.36–1.98) and 2.75 (95% CI 2.21–3.42), respectively. The severe early improving class showed a weaker association in complete-case analysis (OR 1.24, 95% CI 0.97–1.59; $P = 0.083$). In the multiply imputed model, the severe early improving class reached statistical significance, whereas the effect sizes for the persistent/fluctuating moderate and persistent severe classes remained stable (Table 2).

For day-7 persistent AKI or death, all three higher-risk LCMM classes were associated with worse outcomes in both complete-case and multiply imputed analyses. In the multiply imputed model, the odds ratios were 1.63 (95% CI 1.37–1.94) for severe early improving, 2.64 (95% CI 2.32–3.01) for persistent/fluctuating moderate, and 5.82 (95% CI 4.91–6.91) for persistent severe. Because this kidney-related endpoint was temporally close to the 96-hour trajectory window, these findings should be interpreted as exploratory evidence of short-term kidney status rather than as definitive prediction of an independent downstream outcome.

Table 2

Associations of the four-class LCMM trajectories with 30-day mortality and day-7 persistent AKI or death.

Trajectory class	Complete-case OR (95% CI)	P value	Multiply imputed OR (95% CI)	P value
Panel A. 30-day mortality				
Mild rapidly resolving	1.00 (reference)	—	1.00 (reference)	—
Severe early improving	1.24 (0.97–1.59)	0.083	1.28 (1.06–1.58)	0.010
Persistent/fluctuating moderate	1.64 (1.36–1.98)	< 0.001	1.59 (1.38–1.85)	< 0.001
Persistent severe	2.75 (2.21–3.42)	< 0.001	2.53 (2.12–3.03)	< 0.001
Panel B. Day-7 persistent AKI or death				
Mild rapidly resolving	1.00 (reference)	—	1.00 (reference)	—
Severe early improving	1.48 (1.20–1.83)	< 0.001	1.63 (1.37–1.94)	< 0.001
Persistent/fluctuating moderate	2.52 (2.14–2.97)	< 0.001	2.64 (2.32–3.01)	< 0.001
Persistent severe	5.87 (4.78–7.21)	< 0.001	5.82 (4.91–6.91)	< 0.001
<i>Note: All models were adjusted for age, sex, non-renal SOFA proxy within 24 hours after AKI onset, maximum KDIGO stage within 24 hours after AKI onset, chronic kidney disease, baseline serum creatinine, vasopressor use, invasive mechanical ventilation, septic shock proxy, and lactate within 24 hours after AKI onset.</i>				

Compared with the baseline covariate model alone, adding either the simplified rule-based classification or the four-class LCMM improved model fit and discrimination. For 30-day mortality after the landmark time, the AUCs were 0.6487 for the baseline model, 0.6661 for the baseline plus simplified rule-based classification, 0.6751 for the baseline plus four-class LCMM, and 0.6764 for the combined model. For day-7 persistent AKI or death, the corresponding AUCs were 0.6618, 0.7046, 0.7238, and 0.7264 (Table 3 and Supplementary Table S2). The incremental discrimination of LCMM over the simplified rule-based framework was therefore modest, especially for 30-day mortality.

Table 3

Predictive performance of the simplified rule-based four-group classification and the four-class LCMM trajectories.

Outcome	Model	AIC	BIC	AUC
30-day mortality after the landmark time	Baseline covariate model	6009.129	6087.801	0.6487
30-day mortality after the landmark time	Baseline covariate model + simplified rule-based four-group classification	5942.014	6040.355	0.6661
30-day mortality after the landmark time	Baseline covariate model + four-class LCMM	5904.992	6003.332	0.6751
30-day mortality after the landmark time	Combined model	5899.744	6017.752	0.6764
Day-7 persistent AKI or death	Baseline covariate model	6794.883	6873.555	0.6618
Day-7 persistent AKI or death	Baseline covariate model + simplified rule-based four-group classification	6548.648	6646.988	0.7046
Day-7 persistent AKI or death	Baseline covariate model + four-class LCMM	6402.398	6500.738	0.7238
Day-7 persistent AKI or death	Combined model	6392.582	6510.591	0.7264
<i>Note: Exact likelihood ratio test and DeLong test P values are provided in Supplementary Table S2.</i>				

Cross-tabulation between LCMM classes and simplified rule-based groups showed substantial heterogeneity within the rule-based categories (Supplementary Table S3). The rapidly resolving rule-based group contained both the mild rapidly resolving LCMM class and the severe early improving class, whereas the worsening/fluctuating rule-based group spanned all four LCMM classes. A three-class LCMM sensitivity analysis reproduced the overall risk gradient but provided less clinical granularity (Supplementary Figure S1 and Supplementary Table S5). The eICU analysis showed partial but discordant findings and was interpreted as supplementary transportability evidence rather than external validation (Supplementary Table S4).

Discussion

In this exploratory retrospective cohort study, early KDIGO trajectories after SA-AKI onset identified four clinically interpretable dynamic phenotypes associated with different short-term risks. The findings suggest that AKI onset-anchored trajectory information may complement static severity measures. However, the incremental discrimination over a simplified rule-based classification was modest, and the study should not be interpreted as establishing a definitive prognostic model.

The most important interpretive issue is the temporal relationship between the trajectory window and the day-7 kidney-related endpoint. Because the trajectory window extended through 96 hours after AKI onset, part of the association with day-7 persistent AKI or death likely reflects persistence of kidney injury status across adjacent time periods. We therefore interpret this endpoint as an exploratory marker of short-term kidney status and delayed early recovery, rather than as a fully independent downstream prognostic outcome.

Compared with the simplified rule-based four-group classification, the LCMM provided more detailed phenotyping but only modest gains in model discrimination. Its main value may therefore lie in describing heterogeneity within clinically intuitive groups rather than in substantially improving prediction. The severe early improving class illustrates this point: although these patients showed a declining KDIGO trajectory, their risk remained higher than that of the mild rapidly resolving class, suggesting that a favorable direction of change does not fully offset the prognostic burden of a higher initial stage.

These findings are broadly consistent with prior studies of AKI subphenotypes and trajectory-based stratification. Previous work has suggested that AKI subgroups can differ in outcome risk and may reflect distinct clinical or biological states ^[4–9]. Our study extends this literature by anchoring trajectory construction at AKI onset and by directly comparing a data-driven trajectory framework with a simple rule-based comparator. At the same time, the modest gain in AUC underscores the need for cautious interpretation, especially when the intended application is clinical risk prediction rather than descriptive phenotyping.

The eICU analysis did not provide confirmatory external validation. Differences in database structure, monitoring density, variable generation, and landmark cohort construction may have contributed to this discordance. Consequently, the present findings should be regarded as hypothesis-generating and require further validation in independent cohorts before broader application.

This study has several strengths. The 96-hour landmark design restricted exposure definition to a prespecified and comparable early observation window. Early kidney injury burden was characterized using four consecutive 24-hour KDIGO windows rather than a single time point or peak stage alone. In addition, the data-driven LCMM and the clinically interpretable rule-based grouping were evaluated within the same analytic framework.

Several limitations should be acknowledged. First, the main analysis included only patients who survived and remained under observation through 96 hours after AKI onset, so the findings do not apply to patients with earlier death or shorter observation. Second, residual confounding and phenotype-construction bias cannot be excluded in an observational study. Third, KDIGO stage is an ordinal severity measure, whereas LCMM is more commonly applied to approximately continuous longitudinal measures. Fourth, the simplified rule-based classifier was only one prespecified comparator, and alternative simplified frameworks might perform differently. Finally, the external analysis provides limited evidence regarding transportability.

Overall, early KDIGO trajectories after SA-AKI onset identified dynamic phenotypes associated with different short-term risks. The results support early KDIGO trajectories as an exploratory phenotyping framework rather than a definitive prognostic model.

Conclusions

Early KDIGO trajectories after SA-AKI onset identified clinically interpretable dynamic phenotypes associated with different short-term risks. The incremental discrimination over a simplified rule-based classification was modest, and the kidney-related short-term endpoint should be interpreted cautiously because of its temporal proximity to the trajectory window. These findings support early KDIGO trajectories as an exploratory phenotyping framework that requires further validation.

Declarations

Data availability

The datasets used in this study are publicly available through PhysioNet. The MIMIC-IV database is available at <https://physionet.org/content/mimiciv/3.1/> and the eICU Collaborative Research Database is available at <https://physionet.org/content/eicu-crd/2.0/>. Access to these databases requires completion of the required training and approval of the relevant data use agreements. No additional individual-level data were generated in this study.

Ethics declarations

This study used publicly available de-identified data. The source MIMIC-IV database was approved by the institutional review boards of Beth Israel Deaconess Medical Center and the Massachusetts Institute of Technology, and the requirement for informed consent was waived because protected health information had been removed before release. The supplementary transportability analysis using the eICU Collaborative Research Database likewise relied on publicly available de-identified data.

Competing interests

The authors declare no competing interests.

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Author Contribution

ZL conceived and designed the study. ZL drafted the manuscript and prepared the figures and tables. ZL and YC verified data integrity and analytical accuracy. NZ supervised the study and critically revised the manuscript. All authors read and approved the final manuscript.

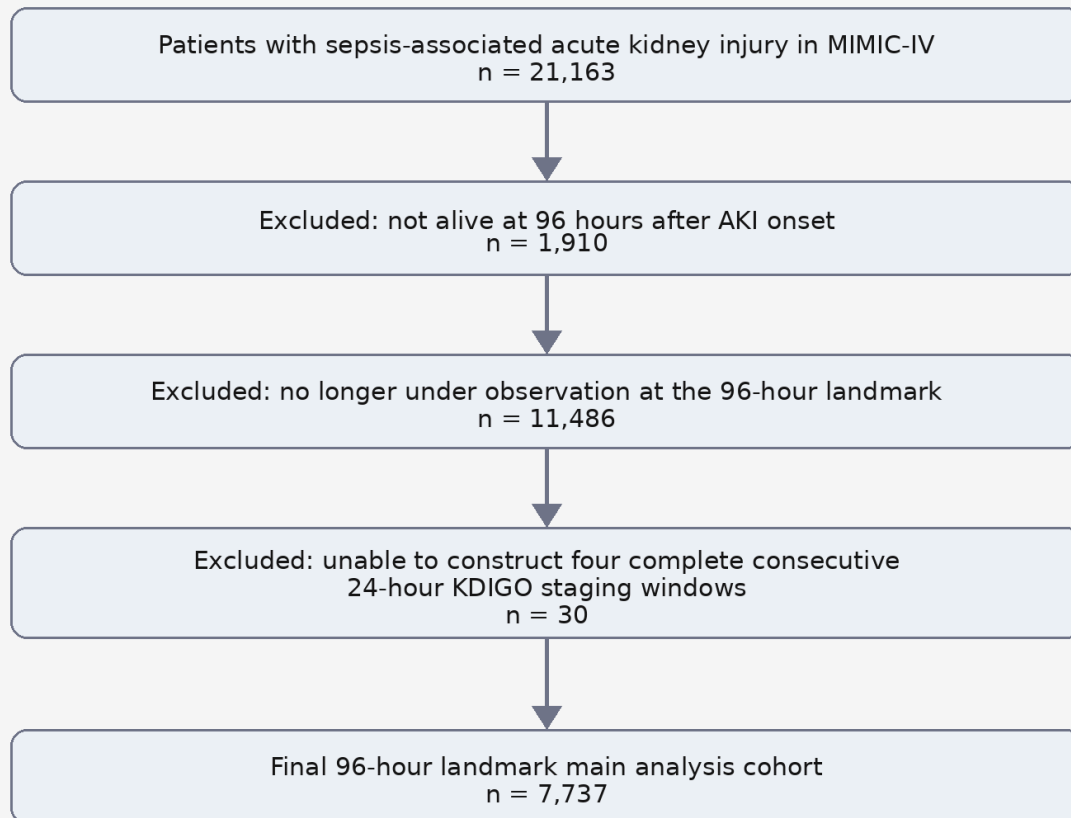
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Figures



Exclusion reasons were applied hierarchically.

Figure 1

Study flowchart.

Figure 2. Mean four-class LCMM trajectories

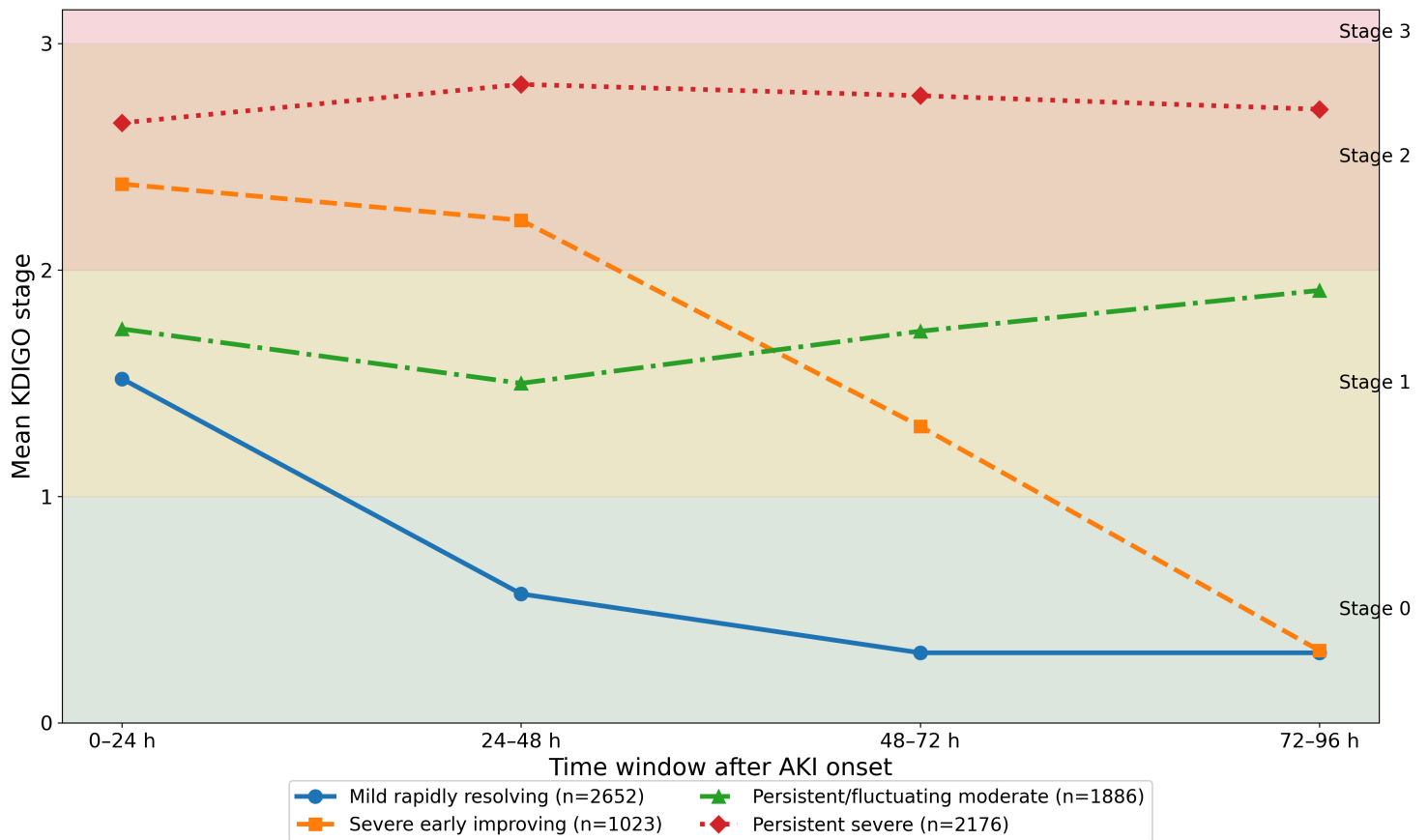


Figure 2

Mean four-class LCMM trajectories during the first 96 hours after AKI onset.

Supplementary Files

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