Research Square

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Acute kidney injury is associated with less reversal of urinary metabolomic changes after coronary artery bypass grafting

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Abstract

Introduction: Urinary metabolomics can identify differences associated with acute kidney injury (AKI), but group comparisons do not show whether postoperative changes reverse within individual patients.

Objectives: We examined whether urinary profiles moved toward each patient's preoperative profile between approximately 20 and 44 h after coronary artery bypass grafting (CABG).

Methods: This secondary analysis used public data from 145 on-pump CABG patients (50 AKI and 95 non-AKI), sampled before surgery and approximately 6, 20 and 44 h afterward, with 4,048 features. Residual ratio measured the remaining distance from baseline relative to that at 20 h, reversal fidelity measured alignment toward baseline, and trajectory distance compared patients with a leave-one-patient-out cohort path; inference used patient-level permutations and bootstraps.

Results: AKI was associated with higher residual ratio (medians 1.035 versus 0.980; difference 0.0548; 95% confidence interval 0.0334–0.0790) and lower reversal fidelity (0.321 versus 0.413; difference −0.0927; 95% confidence interval −0.1206 to −0.0534; both one-sided $p = 1.00\times10^{-5}$). Trajectory distance was greater in AKI but closely tracked overall change magnitude; adjusted evidence was inconclusive, and separate urine and tissue datasets could not test longitudinal return.

Conclusion: AKI was associated with less reversal of urinary metabolomic changes from approximately 20 to 44 h after CABG. These profile changes do not establish kidney-function recovery and require independent longitudinal replication.

1. Introduction

Acute kidney injury (AKI) after cardiac surgery is associated with longer hospitalization, subsequent kidney dysfunction and mortality (Hoste et al., 2015; Kidney Disease: Improving Global Outcomes Acute Kidney Injury Work Group, 2012; Nadim et al., 2018; Ronco et al., 2019; Rosner & Okusa, 2006; Wang & Bellomo, 2017). Serum creatinine and urine output are used to diagnose AKI, but they do not describe the many molecular changes that occur during the first postoperative days. Urinary metabolomics offers a way to examine these changes alongside, rather than in place of, clinical measures.

Previous studies have identified urinary metabolites and other biomarkers associated with AKI, including changes that vary with time after surgery (Coca et al., 2008; Endre et al., 2011; Johnson & Zager, 2018; Lee et al., 2026b; Zeng et al., 2024; Zhao et al., 2025a). A different question is whether a patient's later urinary profile begins to resemble their own preoperative profile again. Comparing AKI and non-AKI groups at a single timepoint cannot answer this question: it requires repeated samples from the same patient and a direct comparison with that patient's starting values.

The public cohort reported by Zhao et al. (2025a) includes urine collected before on-pump coronary artery bypass grafting (CABG) and at approximately 6, 20 and 44 h after surgery. We used these repeated measurements to ask whether patients with AKI showed less reversal of the postoperative changes

between 20 and 44 h. We examined both the remaining difference from baseline and the direction of subsequent change. We then asked whether the 44-h profiles differed from the cohort's average postoperative trajectory. A separate early postoperative urine cohort and a kidney-tissue atlas provided additional observations in AKI, but neither contained the repeated urine samples needed to test the same return-to-baseline question.

2. Materials and Methods

2.1. Study Design and Data Sources

This secondary observational analysis used public, de-identified datasets and was reported with reference to STROBE (von Elm et al., 2007). The longitudinal analysis used the processed urine matrices in Zhao et al.'s Supporting Information Tables S1 and S2 (Zhao et al., 2025a, b). The associated PXD063754/IPX0009727000 record identifies the raw mass-spectrometry archive; raw files were not reprocessed (ProteomeXchange Consortium, n.d.). The independent urine analysis used the processed Supplementary Material 2 from Lee et al. (2026a, b). Kidney-tissue analyses used the source cell annotations and patient metadata in GSE183276 (Gene Expression Omnibus, n.d.; Lake et al., 2023). No new participants, specimens or molecular measurements were obtained.

2.2. Patients, Sampling Times and AKI Classification

The original CABG cohort contained 159 patients, classified by the source study as 55 AKI and 104 non-AKI. Samples were collected before surgery (T1) and at approximately 6 h (T2), 20 h (T3) and 44 h (T4) afterward. We included patients with exactly one sample at each of the four timepoints. This retained 145 patients (50 AKI and 95 non-AKI), 580 samples and 4,048 shared molecular features. Fourteen patients had incomplete series and were excluded (5 AKI and 9 non-AKI). No features or patients were selected on the basis of an AKI-associated molecular result.

The available source materials did not provide serum-creatinine measurements, urine-output criteria, AKI stages and diagnostic timing in a form that allowed us to independently reconstruct the AKI classification. We therefore used the source labels without reclassification. Complete patient-level clinical covariates were not available for confounder adjustment.

2.3. Measuring Return toward Each Patient's Preoperative Profile

We used T1, T3 and T4 to compare each patient with their own preoperative sample. T3 was the intermediate postoperative measurement and T4 was the final available measurement; these sampling labels do not establish when injury peaked or kidney function recovered. T2 was retained in the four-timepoint trajectory analysis.

For this within-patient analysis, features were processed using all 622 samples in the source matrices, including available samples from patients whose series were incomplete. A feature-specific

pseudocount equal to half the minimum positive value was added only to features containing zeros. Values were then $\log_2$-transformed, median-centered and scaled by the median absolute deviation (MAD). The source matrix contained no non-finite values, so no imputation was needed. Scale fallback rules are given in Online Resource 1.

Two measures summarized the same three samples. The residual ratio was the Euclidean distance between T4 and T1 divided by the distance between T3 and T1. A ratio below 1 means that the 44-h profile is closer to baseline than the 20-h profile; a ratio of 1 means that the two profiles are equally far from baseline. A ratio of 0 would indicate return to the preoperative profile.

Reversal fidelity measured direction rather than remaining distance. It was the cosine of the angle between the observed change from T3 to T4 and the direction from T3 back to T1. A value of 1 indicates exact alignment with the direction back to baseline, 0 indicates a perpendicular change, and a negative value indicates a change pointing away. The two measures describe related aspects of the same within-patient changes.

2.4. Comparing Patients with the Cohort's Postoperative Trajectory

To summarize the trajectory without letting a patient contribute to their own reference, we left out all four samples from one patient at a time. For each of the 145 repetitions, preprocessing parameters were estimated from the other 144 complete patients. Unlike the within-patient analysis above, the trajectory analysis added the training-derived half-minimum-positive pseudocount to every value before $\log_2$ transformation. Feature centers and robust scales were estimated in the training samples and then applied to both training and held-out samples.

For each training patient, we subtracted the preoperative profile from the postoperative profiles. We averaged these changes at 0, 6, 20 and 44 h and connected the four averages with straight-line segments. The held-out patient's changes were compared with the nearest point on this path in the full feature space. The distance to the path was termed off-trajectory distance. The interpolated time at the nearest point was termed molecular time in the figures. This time coordinate is restricted to 0–44 h and equals 0 at T1 by construction; it is a position on the fitted path, not a measured recovery time. Both AKI and non-AKI patients contributed to the reference path, without using their group labels.

The principal trajectory comparison was the AKI-minus-non-AKI mean difference in off-trajectory distance at T4. We repeated the calculation after replacing each sample's values with centered, unit-length ranks and after subtracting each sample's median before feature scaling. These analyses tested sensitivity to how the profiles were represented. We also assessed whether T4 profiles from patients with AKI were assigned earlier positions on the path, using 44 h minus molecular time as the lag measure.

Finally, we examined whether the distance from the path mainly reflected the size of the change from baseline. Using the previously calculated patient scores, we regressed log1p(off-trajectory distance) on log1p(T4-to-T1 distance), leaving out one patient at a time, and compared the held-out residuals between groups. This was a sensitivity analysis of overall profile-change magnitude, not adjustment for clinical confounders. Full details are in Online Resource 1.

2.5. Independent Urine Cohort and Kidney-Tissue Analyses

The independent urine dataset contained one sample collected within 4 h after surgery from each of 55 patients (29 AKI and 26 non-AKI), with 1,384 features (Lee et al., 2026a, b). We used the source "fill0.5min" worksheet. All features passed the stated missingness and variance checks, and all 76,120 values were finite. For each patient, we calculated the root-mean-square standardized difference from the median non-AKI reference profile. We termed this measure normative displacement. Each AKI patient was compared with all 26 non-AKI patients; each non-AKI patient was compared with the other 25. Because group membership defined the reference, the reference and scores were rebuilt for every label permutation. Bootstrap intervals resampled the fixed scores without rebuilding the reference. A secondary comparison used the source-defined severe and mild AKI labels. Detailed scaling rules and sensitivity analyses are in Online Resource 1.

In GSE183276, we used the original annotations for tubular epithelial cells from proximal, distal, collecting and intermediate tubules (Gene Expression Omnibus, n.d.; Lake et al., 2023). We calculated the fractions labeled degenerative, adaptive epithelial, transitioning, cycling and reference separately for each patient. The primary tissue comparison was the degenerative-cell fraction in 12 AKI versus 18 reference kidneys. Fifteen patients labeled chronic kidney disease (CKD) were excluded from this comparison. The remaining four cell-state comparisons were secondary. These tissue data were not paired with the urine samples.

2.6. Statistical Analysis and Software

The patient was the unit of analysis and resampling. For the two return-to-baseline measures, we reported median differences, Cliff's delta, one-sided rank-sum permutation tests with 100,000 label assignments, and 95% percentile intervals from 20,000 stratified patient bootstraps. The tests evaluated higher residual ratio and lower reversal fidelity in AKI. Benjamini–Hochberg correction was applied to this two-test family (Benjamini & Hochberg, 1995). Each patient was also omitted once to assess whether a single observation determined the effect direction.

For the trajectory-distance, independent-urine and primary tissue comparisons, we reported mean differences and Hedges g, with 100,000 one-sided label permutations and 10,000 stratified patient bootstraps. The four secondary tissue comparisons were two-sided and corrected together by Benjamini–Hochberg. Permutation p values were calculated as (1 + number of equally or more extreme results)/(1 + number of permutations); the smallest reportable value with 100,000 permutations was approximately 1.00×10^{-5}. Tests and intervals are identified throughout as one-sided or two-sided and as resampling-based where appropriate. The exploratory joint display of residual ratio and off-trajectory

distance is reported in Online Resource 1. Analyses used R 4.4.1 (R Core Team, 2024), readxl, openxlsx and Rcpp.

OpenAI ChatGPT and Codex assisted with analytical workflow development, code drafting, language editing, manuscript organization and formatting. They did not generate or alter primary data. The authors remain responsible for analytical decisions, code execution, numerical verification, interpretation and conclusions.

2.7. Analytical quality reporting and feature annotation

The reanalysis started from published processed matrices; no new mass-spectrometry acquisition, peak integration or compound identification was performed. The quality-control reporting checklist in Online Resource 3 distinguishes checks on these matrices from original laboratory quality assurance that was not independently reconstructed. Features were retained as source measurements, not newly confirmed metabolite identities. No compound-specific mechanism or pathway was inferred from an unverified annotation. A step-by-step computational protocol is supplied in Online Resource 5.

3. Results

3.1. Repeated Samples Were Available for 145 Patients

The analysis included 145 patients with complete four-timepoint sampling: 50 with source-defined AKI and 95 without AKI (Table 1; Fig. 1a). These patients contributed 580 urine profiles containing 4,048 shared features. The 14 excluded patients lacked at least one sample; their AKI group counts are shown in Fig. 1a.

The leave-one-patient-out trajectory broadly ordered the postoperative samples by collection time (Fig. 1b–d). Molecular time correlated with sampling time at Spearman $\rho = 0.898$ across postoperative samples; the correlation was 0.956 when the baseline samples, all fixed at zero, were included. Median absolute errors were 0.67 h at T2 and 1.76 h at T3. These results describe internal agreement with the sampling schedule, rather than validation of a biological recovery clock.

Table 1
Data sources, sampling structure and questions addressed.

Dataset	Analyzed patients	Samples and features	Question addressed
Longitudinal urine	145 patients: 50 AKI and 95 non-AKI	T1 before surgery; ~6, ~ 20 and ~ 44 h afterward; 4,048 shared features	Do later profiles become more similar to the same patient's baseline? How far are they from the cohort trajectory?
Independent urine	55 patients: 29 AKI and 26 non-AKI	One sample per patient within 4 h after surgery; 1,384 features	Are early profiles farther from a non-AKI reference in a separate cohort?
KPMP kidney tissue	45 metadata patients: 12 AKI, 18 reference and 15 CKD. Primary comparison: 30 patients (12/18); 15 CKD excluded.	79,336 eligible tubular cells across 45 patients; 39,756 cells in the 30-patient AKI–reference comparison	Does the sampled tubular-cell composition differ between AKI and reference kidneys?

AKI, acute kidney injury; CKD, chronic kidney disease; KPMP, Kidney Precision Medicine Project.

3.2. AKI Was Associated with Less Reversal between 20 and 44 h

The residual ratio was higher in AKI than in non-AKI patients (medians 1.035 and 0.980; median difference 0.0548; 95% bootstrap CI 0.0334 to 0.0790; Cliff's delta 0.424; one-sided $p = 1.00\times10^{-5}$; adjusted $q = 1.00\times10^{-5}$). Thus, relative to the change already present at 20 h, more of the difference from the preoperative profile remained at 44 h in patients with AKI (Fig. 2b,d). The non-AKI median of 0.980 indicates only a small reduction in distance from baseline over this interval: its 44-h distance was still about 98% of its 20-h distance.

The direction of the later change also differed. Reversal fidelity was lower in AKI (median 0.321 vs 0.413; difference − 0.0927; 95% bootstrap CI − 0.1206 to − 0.0534; Cliff's delta − 0.522; one-sided $p = 1.00\times10^{-5}$; adjusted $q = 1.00\times10^{-5}$). The change from 20 to 44 h was therefore less aligned with the direction back to the preoperative profile (Fig. 2c,d). Both group differences retained their direction in all 145 delete-one-patient analyses. Table S1 provides the full estimates.

3.3. The 44-h Profiles Were Farther from the Cohort Trajectory in AKI

We next compared each patient's final profile with the trajectory defined by the other patients. Mean off-trajectory distance at T4 was 98.524 in AKI and 73.544 in non-AKI patients (difference 24.980; 95% bootstrap CI 17.869 to 34.032; Hedges g = 1.268; one-sided $p = 1.00\times10^{-5}$; Fig. 3b,c). The difference was positive in all 145 delete-one analyses. It also remained positive using within-sample ranks and sample-median centering (Hedges g = 1.375 and 1.548, respectively; both $p = 1.00\times10^{-5}$; Fig. 3d; Table S2).

However, a larger distance from the path was strongly associated with a larger overall change from baseline (Spearman ρ ≈ 0.93). After accounting for that size, the remaining AKI contrast was small and uncertain (Hedges g = 0.265; p = 0.064; 95% CI − 0.004 to 0.032 on the residual scale). The unadjusted distance therefore cannot distinguish a change in profile direction from a larger change overall.

The time-position analysis did not show a greater lag in AKI: the AKI-minus-non-AKI mean lag difference was − 0.691 h (95% CI − 2.811 to 1.590; one-sided p = 0.7158; Fig. S3). The finding is therefore not evidence that patients with AKI simply moved more slowly along the same postoperative path. The exploratory two-measure display is reported in Fig. S1.

3.4. Separate Datasets Showed Early Urinary Differences and Altered Tubular-Cell Composition

In the independent early postoperative urine cohort, patients with AKI had a larger standardized distance from the non-AKI reference profiles (mean difference 5.384; 95% fixed-score bootstrap CI 2.619 to 8.218; Hedges g = 0.946; fully refitted one-sided permutation p = 0.0168; Fig. 4a). This supports an association between AKI and altered urinary profiles in a different cohort. Because there was only one sample per patient, it does not show whether those profiles later returned toward baseline. The secondary severe-versus-mild comparison was inconclusive (difference 4.265; 95% CI − 0.533 to 9.431; p = 0.0543; Table S3 and Fig. S4).

In the kidney-tissue atlas, the mean fraction of tubular epithelial cells labeled degenerative was 0.379 in 12 AKI kidneys and 0.267 in 18 reference kidneys (difference 0.113; 95% bootstrap CI 0.025 to 0.202; Hedges g = 0.874; one-sided p = 0.0116; Fig. 4b,c). The other source-defined cell-state fractions are reported in Table S4 and Fig. S5. These observations describe tissue changes in AKI, but the unpaired datasets cannot link those cells to the urinary features measured here.

4. Discussion

This reanalysis asked whether the urinary changes present at approximately 20 h after CABG were reversed by approximately 44 h in the same patient. Patients with AKI had a higher residual ratio and a lower reversal fidelity. In practical terms, their final profiles retained more of the earlier difference from baseline relative to the size of that earlier difference, and their later changes pointed less directly back toward the preoperative profile. The result concerns how the whole measured urinary profile changed over time, rather than which individual metabolite differed between groups.

Previous perioperative studies, including those by Zhao et al. (2025a) and Zeng et al. (2024), described time-dependent urinary changes and AKI-associated signals. Our analysis addresses a narrower within-patient question using a preoperative reference. This is useful because a difference between groups at 44 h alone does not reveal whether the profile has become more or less similar to its own baseline since 20 h. The residual ratio provides that comparison, while reversal fidelity describes the direction of the

intervening change. Both are calculated from the same three samples and should be read together, not counted as independent replications.

The size and meaning of the effects matter. The residual-ratio medians were close to 1 in both groups, and their difference was approximately 0.055. The results do not show broad restoration of preoperative profiles in patients without AKI, followed by complete failure of that process in patients with AKI. Instead, they show a between-group difference during an early interval in which both groups' final profiles remained approximately as far from baseline as their earlier postoperative profiles. Likewise, positive reversal-fidelity values indicate a component of change pointing toward baseline, but do not by themselves establish that the final profile is close to baseline. This is why both remaining distance and direction were examined.

The trajectory analysis adds a comparison with the other patients, but it does not establish a separate recovery mechanism. The path summarized the average changes of a mixture of AKI and non-AKI patients, not a healthy reference population. Patients with AKI were farther from this path at 44 h, but that distance closely tracked the total change from their own baseline. The magnitude-adjusted result was inconclusive, and the time-position analysis did not support a greater lag in AKI. Together, these findings support persistent differences in urinary profiles, not a demonstrated delay along a normal recovery trajectory or a distinct, magnitude-independent disease state.

The additional datasets address different parts of the clinical picture. The independent urine cohort showed larger differences from non-AKI reference profiles within 4 h after surgery. It therefore supports an early association with AKI, but cannot replicate a 20-to-44-h return-to-baseline pattern. The kidney atlas showed a greater fraction of cells carrying the source-defined degenerative label in AKI kidneys. Because the tissue and urine were obtained from different people, in different settings, these findings cannot identify the cellular origin of the urinary changes or establish a mechanism connecting them.

The clinical question left open is whether persistent urinary-profile changes identify patients whose kidney function will recover poorly. The present data do not answer it: the molecular measurements were not linked to a sufficiently detailed clinical recovery course. A study designed to answer that question would need repeated urine samples extending beyond 44 h, documented AKI onset and severity, serial kidney-function measurements and follow-up outcomes. It would also need to test whether the urinary measures add information beyond routine clinical data. Until then, these measures are research descriptions of postoperative change, not thresholds for diagnosis, prognosis or treatment.

Several limitations affect interpretation. The longitudinal finding comes from one complete-case on-pump CABG cohort and has not been independently reproduced with repeated urine sampling. Incomplete series were excluded, and missing clinical covariates prevented conventional adjustment for differences between AKI and non-AKI patients. We retained source AKI labels because the public materials did not allow independent diagnostic reconstruction; the relation between AKI onset and each urine sample could therefore not be resolved. The 4,048 measurements were molecular features with limited high-confidence structural identification, so they cannot be read as 4,048 identified metabolites

or assigned to specific pathways from this analysis. These constraints limit causal, mechanistic and clinical interpretation despite the consistent within-cohort differences.

5. Conclusions

Patients with AKI after on-pump CABG showed less reversal of urinary metabolomic changes between approximately 20 and 44 h. Their final profiles retained a larger relative difference from their own preoperative profiles, and the intervening changes were less aligned with the direction back to baseline. Whether these urinary changes track subsequent recovery of kidney function remains to be tested in an independent longitudinal cohort.

Abbreviations

AKI
acute kidney injury
CABG
coronary artery bypass grafting
CI
confidence interval
CKD
chronic kidney disease
CSA-AKI
cardiac surgery-associated acute kidney injury
FDR
false discovery rate
GEO
Gene Expression Omnibus
IQR
interquartile range
KPMP
Kidney Precision Medicine Project
MAD
median absolute deviation
T1
preoperative sample
T2
approximately 6 h after surgery
T3
approximately 20 h after surgery
T4
approximately 44 h after surgery.

Statements and declarations

Author contributions

Conceptualization, D.X. and Z.L.; methodology and software, D.X.; formal analysis, D.X. and Z.L.; data curation, D.X., Z.L., A.L. and Q.C.; validation, D.X., Z.L., A.L., Q.C. and J.L.; visualization, D.X.; writing—original draft preparation, D.X. and Z.L.; writing—review and editing, H.Z., A.L., Q.C., J.L. and H.S.; funding acquisition, project administration and supervision, H.S. H.Z. also contributed to interpretation of the findings. D.X. and Z.L. contributed equally. All authors have read and approved the manuscript.

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Competing interests

Donglin Xu, Zengkun Liu, Haixuan Zhao, Ang Li, Qiduo Chen, Jing Liu and Hourong Sun declare that they have no competing interests.

Data availability

The longitudinal analyses used the processed Zhao Supporting Information matrices: Table S1 (AKI; pr5c00113_si_002.xlsx) and Table S2 (non-AKI; pr5c00113_si_003.xlsx) (Zhao et al., 2025a, 2025b). The raw mass-spectrometry archive is recorded as PXD063754 and IPX0009727000; raw files were not analysis inputs (ProteomeXchange Consortium, n.d.). The independent urine analysis used Lee et al.'s processed Supplementary Material 2 (11306_2026_2423_MOESM2_ESM.xlsx) (Lee et al., 2026a, 2026b). The kidney-tissue analysis used patient-level metadata for GSE183276 (Gene Expression Omnibus, n.d.; Lake et al., 2023). Records were accessed on 7 October 2026. Detailed input filenames and archive identifiers are listed in Online Resource 1, Table S5. Source publications and data records are cited in the reference list.

Code availability

The R 4.4.1 analysis script and instructions are supplied in Online Resource 2 (ESM_2.zip). The script reads the cited public source files and produces patient-level scores and summary estimates. The

source matrices are not redistributed in this package. Online Resource 5 gives the computational steps and input requirements.

Compliance with ethical standards

Ethics approval

This secondary analysis used only lawfully obtained, publicly available, de-identified datasets and involved no new participant recruitment, intervention, biospecimen collection or access to identifiable personal information. No additional ethics approval was required for this secondary analysis. Ethics approvals for the original studies were those reported in their respective publications. No new studies involving human or animal participants were performed by the authors.

Consent to participate and consent for publication

No additional informed consent was required for this secondary analysis of public, de-identified data. Informed-consent procedures for the original studies were those reported in their respective publications. No individually identifying participant information or identifiable images are included. Consent for publication is not applicable to the non-identifying information reported here.

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