

Persistent Cardiac Surgery-Associated Acute Kidney Injury Identifies a High-Risk Phenotype after Pediatric Congenital Heart Surgery

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Research Article

Keywords: congenital heart disease, cardiac surgery-associated acute kidney injury, persistent acute kidney injury, vasoactive-inotropic score, fluid accumulation, machine learning

Posted Date: September 30th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10939031/v1>

Abstract

Background

Cardiac surgery-associated acute kidney injury (CS-AKI) is heterogeneous, and persistence may define a clinically important postoperative phenotype. We examined early CS-AKI phenotypes, their perioperative associations and clinical outcomes, and exploratory discrimination of persistent CS-AKI.

Methods

This retrospective single-center cohort included 219 eligible patients from 288 consecutively screened children aged ≤ 18 years who underwent congenital heart surgery in 2023–2024. Early CS-AKI was classified as transient CS-AKI if it had resolved by postoperative day 3 and as persistent CS-AKI if it remained present on postoperative day 3 or if therapeutic renal replacement therapy precluded valid creatinine-based assessment. The primary CatBoost model used preoperative, intraoperative, and first-24-hour postoperative variables while excluding postoperative creatinine and was evaluated using nested cross-validation.

Results

Early CS-AKI occurred in 69 patients (31.5%): 40 had transient CS-AKI and 29 had persistent CS-AKI. Short-term in-hospital mortality was 0.7%, 5.0%, and 44.8% in the no early CS-AKI, transient CS-AKI, and persistent CS-AKI groups, respectively. In the multivariable model, persistent CS-AKI remained associated with younger age, Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery (STAT) category 4–5 procedures, a vasoactive-inotropic score (VIS) > 15 , and POD0 fluid accumulation. The primary exploratory model achieved a cross-validated area under the receiver operating characteristic curve of 0.85 (95% confidence interval, 0.77–0.93), with a calibration slope of 0.87 and a Brier score of 0.073.

Conclusions

Persistent CS-AKI, rather than transient, identified a high-risk postoperative phenotype associated with substantially worse short-term outcomes than transient CS-AKI. Routine perioperative variables showed promising exploratory discrimination of persistence after the first postoperative day, but prospective multicenter external validation is required before clinical use.

Introduction

Acute kidney injury (AKI) is common after pediatric congenital heart surgery; in this context, it is termed cardiac surgery-associated acute kidney injury (CS-AKI) and is associated with prolonged mechanical

ventilation, longer intensive care unit and hospital stays, and higher mortality [1]. A meta-analysis estimated an incidence of approximately 34% [2], whereas a multicenter neonatal cohort reported an incidence of 53.8%, with AKI occurring most frequently on postoperative day 1 (POD1) [3]. Early postoperative serum creatinine changes may be difficult to interpret because they can reflect hemodilution and fluid shifts in addition to kidney dysfunction [4]. Beyond the occurrence of AKI alone, subsequent resolution or persistence may therefore provide additional clinically relevant information, because transient and persistent CS-AKI phenotypes have been defined by duration [5] and have been associated with different clinical outcomes [6]. In neonates undergoing the Norwood procedure, persistent CS-AKI combined with marked fluid accumulation was associated with particularly poor outcomes [7]. Pediatric consensus frameworks similarly emphasize distinguishing evolving AKI phenotypes by timing, severity, and recovery [8, 9].

The renal angina index (RAI) predicts subsequent severe AKI in critically ill children [10, 11], and cardiac-specific adaptations have been evaluated after pediatric heart surgery [12]. More recently, a cardiac RAI nomogram predicted a composite of POD2-4 AKI or prolonged ventilation, with a small absolute gain in discrimination (AUROC 0.82 to 0.84) after adding urinary neutrophil gelatinase-associated lipocalin [13]. These observations suggest that persistence may identify a particularly high-risk phenotype. We therefore examined the incidence and clinical course of early CS-AKI phenotypes, their perioperative associations, and the exploratory discrimination of persistent CS-AKI using routinely available perioperative variables.

Materials and Methods

Study Design and Participants

This retrospective single-center cohort study was conducted at a tertiary pediatric cardiac center and was reported in accordance with the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis plus Artificial Intelligence (TRIPOD + AI) and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [14, 15]. A completed TRIPOD + AI checklist is provided in Table S11 of Online Resource 1. Consecutive patients aged ≤ 18 years who underwent surgery for congenital heart disease between 1 January 2023 and 31 December 2024 were screened. Postoperative day 0 (POD0) was defined as the first 24 h after completion of surgery. The prespecified perioperative CS-AKI ascertainment window extended through POD6; short-term mortality was defined as in-hospital death occurring before POD90. Patients were excluded for preoperative AKI ($n = 12$), AKI first detected after POD6 ($n = 7$), sepsis-related death ($n = 1$), death after POD90 ($n = 1$), and incomplete required analysis data because urine-output records were of insufficient quality for reliable extraction ($n = 48$). Reliable urine-output data were required for fluid-balance derivation and other prespecified analyses. Available characteristics and outcomes of the 48 patients excluded because of incomplete data were compared with the analytic cohort in Table S2. The final analytic cohort comprised 219 patients (Fig. 1). Detailed eligibility criteria, time-window rationale, and data-completeness procedures are provided in the Supplementary Methods.

AKI Definitions and Phenotypes

CS-AKI was defined according to KDIGO serum creatinine criteria [16], using the most recent preoperative creatinine value as baseline, as in prior NEPHRON work [5]. Based on the available urine-output data, no patient was assigned a higher AKI stage than by serum creatinine criteria. Early CS-AKI was defined by onset during POD0-2. Transient CS-AKI was defined as resolution below the AKI threshold on POD3, whereas persistent CS-AKI continued to meet AKI criteria on POD3 [5]. Patients receiving therapeutic, non-prophylactic renal replacement therapy (RRT) were classified as having persistent CS-AKI because RRT could lower serum creatinine and preclude valid creatinine-based assessment on POD3. Prophylactic peritoneal dialysis alone did not determine AKI stage; these patients were staged according to serum creatinine criteria. Complete staging rules, handling of early deaths and late-onset AKI, and creatinine-only sensitivity analyses are detailed in the Supplementary Methods and Tables S3-S4.

Variables and Outcomes

Demographic, clinical, operative, laboratory, hemodynamic, fluid-balance, and medication-exposure variables were abstracted from the medical records. Anthropometric z-scores were calculated using World Health Organization growth standards and the WHO growth reference for school-aged children and adolescents [17, 18]. Weight-for-age z-score and malnutrition (z-score <-2) were evaluated in children aged < 10 years; body mass index (BMI)-for-age was used only for older patients in machine-learning analyses. Surgical complexity was represented by Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery (STAT) category 4–5 in regression analyses and by the continuous STAT mortality score in discrimination analyses. Maximum vasoactive-inotropic score (VIS) during POD0 was calculated according to Gaies et al. [19]. Fluid accumulation for POD0, POD1, and POD2 was calculated independently for each 24-h interval as net fluid balance relative to baseline body weight and expressed as a percentage [20]; no cumulative fluid-overload measure across postoperative days was available. Perioperative exposure to prespecified nephrotoxic or kidney-relevant medications was assessed from the day before surgery through POD6; the complete agent list is provided in Supplementary Methods S3. Agent-specific analyses focused on aminoglycosides, vancomycin, and nonsteroidal anti-inflammatory drugs (NSAIDs). Principal clinical outcomes were short-term in-hospital mortality and ventilator-free days through day 28 (VFD28); extracorporeal membrane oxygenation (ECMO) was reported as a co-occurring marker of circulatory failure. Additional variable definitions, formulas, and secondary outcomes are provided in Supplementary Methods S3-S4.

Statistical Analysis and Machine Learning

Continuous variables were summarized as median [interquartile range (IQR)] and categorical variables as n (%). Group comparisons used the Kruskal-Wallis, chi-square, or Fisher's exact tests, as appropriate. For descriptive summaries and univariable association analyses, cardiopulmonary bypass and aortic

cross-clamp durations were restricted to recipients, and nonrecipients were not assigned a duration of 0 min. In the multivariable model, aortic cross-clamp was entered as two terms: receipt (binary) and, among recipients, duration per 30 min centered at the recipient median (60 min). Benjamini-Hochberg correction was applied within prespecified 22-comparison families, separately for the descriptive comparisons and for each univariable-regression outcome [21]. Univariable logistic regression evaluated associations with any early CS-AKI and persistent CS-AKI; continuous variables were modeled continuously, whereas selected thresholds were examined separately as exploratory analyses (Fig. S3). Age was modeled continuously in regression analyses and was additionally examined descriptively in clinically interpretable age groups because the crude grouped pattern suggested nonlinearity (Fig. S2). Multivariable models used Firth-penalized logistic regression because of sparse events and the potential for separation [22]. Discrimination was summarized by the area under the receiver operating characteristic curve (AUC); pairwise between-model AUC comparisons used the DeLong test [23] and, because information sets and validation schemes differed, were treated as descriptive.

To assess the feasibility of identifying persistent CS-AKI from widely available variables, CatBoost classifiers were developed with persistent CS-AKI as the binary outcome (29/219) [24]. Three nested predictor sets were evaluated: ML-1 used preoperative and intraoperative variables; ML-2 added creatinine-free POD0 hemodynamic/perfusion variables (maximum VIS, lactate, and fluid accumulation); and ML-3 added the renal angina index (RAI) to ML-2. ML-2 was the primary model because it added POD0 clinical variables while excluding postoperative creatinine; ML-1 and ML-3 served as benchmarks. Given the limited number of events, feature selection and hyperparameter tuning were restricted to the training data within a nested cross-validation framework comprising 10 outer folds and five inner folds. Out-of-fold predictions were used to assess discrimination, calibration, and the Brier score; SHapley Additive exPlanations (SHAP) values were used to describe model behavior [25], and exploratory decision-curve performance was also assessed [26]. Full candidate-variable, feature-selection, hyperparameter, and software details are provided in Supplementary Methods S5. Statistical analyses and figure preparation were performed in R 4.5.3, whereas machine-learning analyses, model interpretation, and associated visualizations used Python 3.12.11.

Results

Cohort and AKI Phenotypes

Of 288 screened patients, 219 comprised the analytic cohort: 150 had no early CS-AKI, 40 had transient CS-AKI, and 29 had persistent CS-AKI (Fig. 1). Median age was 27 months (IQR, 5-96), and 60 patients (27%) underwent STAT category 4-5 procedures. Patients with persistent CS-AKI were younger and more often cyanotic, had weight-for-age-defined malnutrition, received preoperative respiratory support, and underwent STAT category 4–5 procedures (Table 1). The 48 patients excluded because of incomplete data were broadly similar to the analytic cohort for the available clinical outcomes and categorical complexity measures, although standardized differences were larger for age and the continuous STAT

mortality score (Table S2). Full cohort characteristics, operation-specific proportions, KDIGO stage distributions, and sensitivity analyses of the AKI definition are reported in Tables S1a-S1b and S3-S4.

Clinical Outcomes

Short-term in-hospital mortality was 0.7%, 5.0%, and 44.8% in the no early CS-AKI, transient CS-AKI, and persistent CS-AKI groups, respectively; ECMO use was 2.0%, 5.0%, and 44.8%, respectively. Median ventilator-free days through day 28 (VFD28) were 27, 26, and 0 days, respectively; 55.2% of patients with persistent CS-AKI had VFD28 = 0 (Table 2). All 10 patients who received therapeutic RRT were classified as having persistent CS-AKI; details are provided in Supplementary Methods S2 and Table S4.

Perioperative Associations

Younger age, lower weight-for-age z-score, cyanosis, single-ventricle physiology, greater surgical complexity, higher VIS, and greater POD0 fluid accumulation were associated with any early CS-AKI and persistent CS-AKI in univariable analyses (Table S5 and Fig. S3). Among recipients, longer cardiopulmonary bypass duration was associated with both any early CS-AKI and persistent CS-AKI, and longer aortic cross-clamp duration with any early CS-AKI (Tables S5 and S6). The crude positive associations for aminoglycoside and vancomycin exposure and the inverse association for NSAID exposure attenuated after adjustment for age and STAT category 4-5 (Table S7). Patients with persistent CS-AKI showed higher median VIS values across POD0 and POD1 and greater POD0 fluid accumulation; median POD0 fluid accumulation was 3.5%, compared with 1.3% in transient CS-AKI and 0.6% in patients with no early CS-AKI (Fig. 2).

Multivariable and Machine-Learning Analyses

In Firth models, younger age remained associated with any early CS-AKI; the association with cyanosis was attenuated and no longer reached significance (OR, 1.80; 95% CI, 0.88-3.67; $p = 0.11$) once aortic cross-clamp was entered as receipt plus recipient duration. For persistent CS-AKI, younger age remained associated (OR, 0.99 per month; 95% CI, 0.97-1.00; $p = 0.010$), as did STAT category 4-5 (OR, 3.42; 95% CI, 1.09-11.1; $p = 0.035$), VIS >15 (OR, 4.37; 95% CI, 1.38-13.80; $p = 0.013$), and POD0 fluid accumulation (OR, 1.42 per percentage point; 95% CI, 1.21-1.72; $p < 0.001$) (Table 3). The complete persistent CS-AKI model coefficients and optimism-corrected internal performance are reported in Table 4.

The primary ML-2 model achieved a nested cross-validated AUC of 0.85 (95% CI, 0.77-0.93), versus 0.80 (0.70-0.89) for ML-1 and 0.89 (0.82-0.97) for the benchmark ML-3. Directly calculated benchmark AUCs were 0.72 for the continuous STAT mortality score, 0.68 for the Risk Adjustment for Congenital Heart Surgery version 1 (RACHS-1) category, and 0.89 for the post hoc modified RAI. Because information sets and validation schemes differed, these comparisons and the exploratory pairwise DeLong tests are

descriptive rather than head-to-head evaluations (Tables S9 and S10). Age, POD0 lactate, baseline creatinine, POD0 fluid accumulation, and POD0 maximum VIS ranked among the features with the highest SHAP importance in the ML-2 analysis (Fig. 3). ML-2 showed a calibration slope of 0.87 and a Brier score of 0.073, and exploratory decision-curve analysis showed positive net benefit across part of the evaluated threshold range (Fig. S4). Age-group and severity-persistence analyses are provided in Fig. S2 and Table S8.

Discussion

Not all postoperative AKI is the same: persistence identifies a particularly high-risk phenotype after pediatric congenital heart surgery. In this cohort, early CS-AKI occurred in approximately one third of children, but persistent CS-AKI carried a markedly greater short-term clinical burden than transient CS-AKI. Younger age, greater surgical complexity, higher vasoactive support, and greater early fluid accumulation were independently associated with persistent CS-AKI. These findings are consistent with pediatric meta-analytic risk-factor data [2] and a contemporary congenital-heart-surgery cohort [27], although the multicenter neonatal cohort did not confirm age or complexity as independent predictors [3]. The principal contribution is the POD3-based characterization of transient and persistent CS-AKI phenotypes rather than a deployable score, complemented by an exploratory model using routinely available perioperative variables and nested internal cross-validation.

VIS and fluid accumulation are readily available but nonspecific markers of postoperative physiological stress. VIS quantifies the intensity of cardiovascular support [19], whereas fluid accumulation may reflect resuscitation, capillary leak, oliguria, or a combination of these processes. Prior pediatric cardiac studies have associated early fluid overload with subsequent AKI and morbidity [28], day-of-surgery fluid overload with mortality and low cardiac output [20], and delayed achievement of negative fluid balance with greater resource use [29]. The Neonatal and Pediatric Heart and Renal Outcomes Network (NEPHRON) Norwood cohort likewise reported especially poor outcomes among patients with both persistent CS-AKI and marked fluid accumulation [7]. We observed the same pattern in a broader congenital heart surgery cohort. These relationships may be bidirectional, and the observational associations do not establish that vasoactive therapy or fluid management drove AKI; VIS may instead reflect the severity of underlying circulatory dysfunction. Prospective studies are needed to determine whether protocolized hemodynamic or fluid strategies improve kidney outcomes [30].

AKI was more frequent among infants and young children, consistent with developmental renal physiology and the limitations of serum creatinine in this population [4]. This association may also partly reflect differences in disease complexity, surgical exposure, and physiological reserve across age groups. Grouped age results are presented descriptively in Fig. S2 because crude proportions varied nonlinearly, while continuous age was retained in modeling. Creatinine-only ascertainment can miss urine-output-defined AKI in neonatal and pediatric critical care [31, 32], although urine output did not result in a higher recorded AKI stage in this cohort.

Perioperative medication results also require caution. The predefined exposure window from the day before surgery through POD6 standardized ascertainment but included doses given after AKI onset, so the reported estimates represent perioperative exposure associations rather than antecedent or causal drug effects. Confounding by indication and severity-dependent treatment selection remain plausible; nephrotoxin-surveillance programs developed in non-critically-ill inpatients support careful monitoring but do not establish causality of these associations [33].

The model should be interpreted as a tool for early persistence stratification rather than pre-AKI prediction, because some patients already met creatinine-based AKI criteria during POD0. ML-2 was the primary model after completion of POD0; ML-1 and the creatinine-containing ML-3 and modified RAI served as benchmarks [10–13], whereas the RACHS-1 and STAT systems were developed for operative risk and case-mix adjustment rather than kidney-specific outcomes [34, 35]. Previous pediatric cardiac machine-learning studies have reported strong performance in single- or limited-center cohorts [36–38], including one with favorable external validation across two additional centers [36], but a recent multicenter validation showed substantial between-center variation [39]. The intended future use is therefore clinician-facing stratification after the first postoperative day, contingent on prospective workflow testing, external validation, and, if necessary, site-specific recalibration; the exploratory decision-curve findings support further evaluation rather than immediate implementation. SHAP values describe model behavior within this dataset and do not establish biological importance or causality.

Persistence may capture clinically relevant information beyond a binary AKI label, although its prognostic contribution could not be fully separated from peak AKI severity in this cohort. The persistent CS-AKI group had substantially greater mortality, more frequent co-occurring ECMO use, and fewer ventilator-free days, whereas transient CS-AKI had lower event rates. The small number of deaths precluded a reliable comparison between transient CS-AKI and no early CS-AKI. Large pediatric cohorts have linked increasing AKI severity to mortality [32], and progression from AKI to acute kidney disease is associated with later chronic kidney disease [40]. Because all stage-3 cases were persistent, duration could not be disentangled from peak severity. Incorporating therapeutic RRT into the definition of persistence was pragmatic, because dialysis may lower creatinine despite ongoing dysfunction. The observed severity-persistence pattern was qualitatively consistent with kidney-recovery phenotypes reported by LoBasso et al. [6] and with pediatric consensus recommendations to distinguish evolving AKI phenotypes [8, 9].

Biomarker-defined phenotypes and functional kidney assessments were unavailable in this cohort, so the present model reflects routinely measured clinical physiology rather than direct evidence of structural kidney injury; whether adding such measures improves discrimination of persistent CS-AKI warrants study [41, 42]. Pediatric AKI-prevention trials remain limited and generally inconclusive [43], so improved risk stratification does not yet translate into a specific preventive intervention.

Several limitations should be considered. This was a retrospective single-center study; 48 patients were excluded because urine-output records were of insufficient quality for reliable extraction of all required analysis data, and no imputation was performed. These excluded patients were broadly similar to the

analytic cohort with respect to STAT category 4–5, CS-AKI phenotype, ECMO use, therapeutic RRT, and in-hospital mortality before POD90, although modest differences in age and the continuous STAT mortality score were present (Table S2). Accordingly, some degree of selection bias related to complete-case inclusion cannot be excluded. The POD0-POD6 AKI and pre-POD90 mortality windows were study-specific operational definitions. Seven patients whose AKI was first detected after POD6, one sepsis-related death, and one death after POD90 were excluded, which may also have introduced selection bias; these excluded events were not proven unrelated to surgery. Four patients who first met AKI criteria during POD3-POD6 remained in the no early CS-AKI reference group, potentially attenuating differences between the reference and early-AKI groups.

Although 55 of 69 early CS-AKI cases (79.7%) began on POD0, persistence was assessed at a fixed POD3 landmark; therefore, the elapsed duration of AKI before classification varied depending on whether AKI began on POD0, POD1, or POD2, and the phenotype did not represent an identical duration of injury in every patient. Daily protocol creatinine collection ended at POD6, precluding standardized assessment of renal recovery, acute kidney disease, and major adverse kidney events at 30 days (MAKE30). Retrospective urine-output data may have missed mild oliguria, neonatal baseline creatinine may partly reflect maternal values, deep hypothermia was approximated using minimum intraoperative temperature because circulatory-arrest status was unavailable, and nephrotoxin dose and timing were not modeled.

The persistent CS-AKI subgroup included only 29 events; both Firth and CatBoost analyses remain susceptible to overfitting and statistical instability despite penalization and nested cross-validation, calibration was imprecise, and no external validation was performed, so the reported performance is exploratory rather than evidence of clinical readiness.

Conclusions

Persistent, rather than transient, CS-AKI identifies a particularly high-risk postoperative phenotype in children undergoing congenital heart surgery. Younger age, greater surgical complexity, higher vasoactive support, and early fluid accumulation were associated with persistence, and routinely available perioperative variables through POD0 provided promising exploratory discrimination. These findings support prospective multicenter validation of persistence-based CS-AKI phenotyping and early risk stratification.

Declarations

Funding

This research received no external funding.

Ethics Approval

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Hacettepe University Health Sciences Research Ethics Committee (protocol SBA 25/793; approved on 23 September 2025).

Consent to Participate

The requirement for informed consent was waived by the ethics committee because of the retrospective design and use of de-identified data.

Data Availability

The data presented in this study are available on reasonable request from the corresponding author because they contain patient-level clinical information subject to privacy and institutional restrictions. The data are not publicly available. Dedicated analysis scripts are not available for sharing; derived summary results are reported in the article and Supplementary Information.

Use of Generative Artificial Intelligence

Generative artificial intelligence was used solely for language editing and clarity and was not used to generate scientific content or to design, conduct, or interpret the analyses. The machine-learning analyses reported in the study were performed by the authors using the software specified in the Methods. All authors reviewed and approved the final manuscript and take responsibility for its content.

Competing Interests

The authors declare no conflict of interest.

Author Contributions

Conceptualization, MAD and SK; Methodology, MAD and SK; Formal Analysis, ITA; Investigation, MAD and SG; Data Curation, MAD and SG; Software, ITA; Validation, MAD; Visualization, MAD and ITA; Writing - Original Draft Preparation, MAD and ITA; Writing - Review and Editing, SK, SA, MC, and BB; Supervision, SK, SA, MC, and BB; Project Administration, SK. All authors have read and approved the final version of the manuscript.

Acknowledgments

Not applicable.

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Tables

Tables 1 to 4 are available in the Supplementary Files section.

Figures

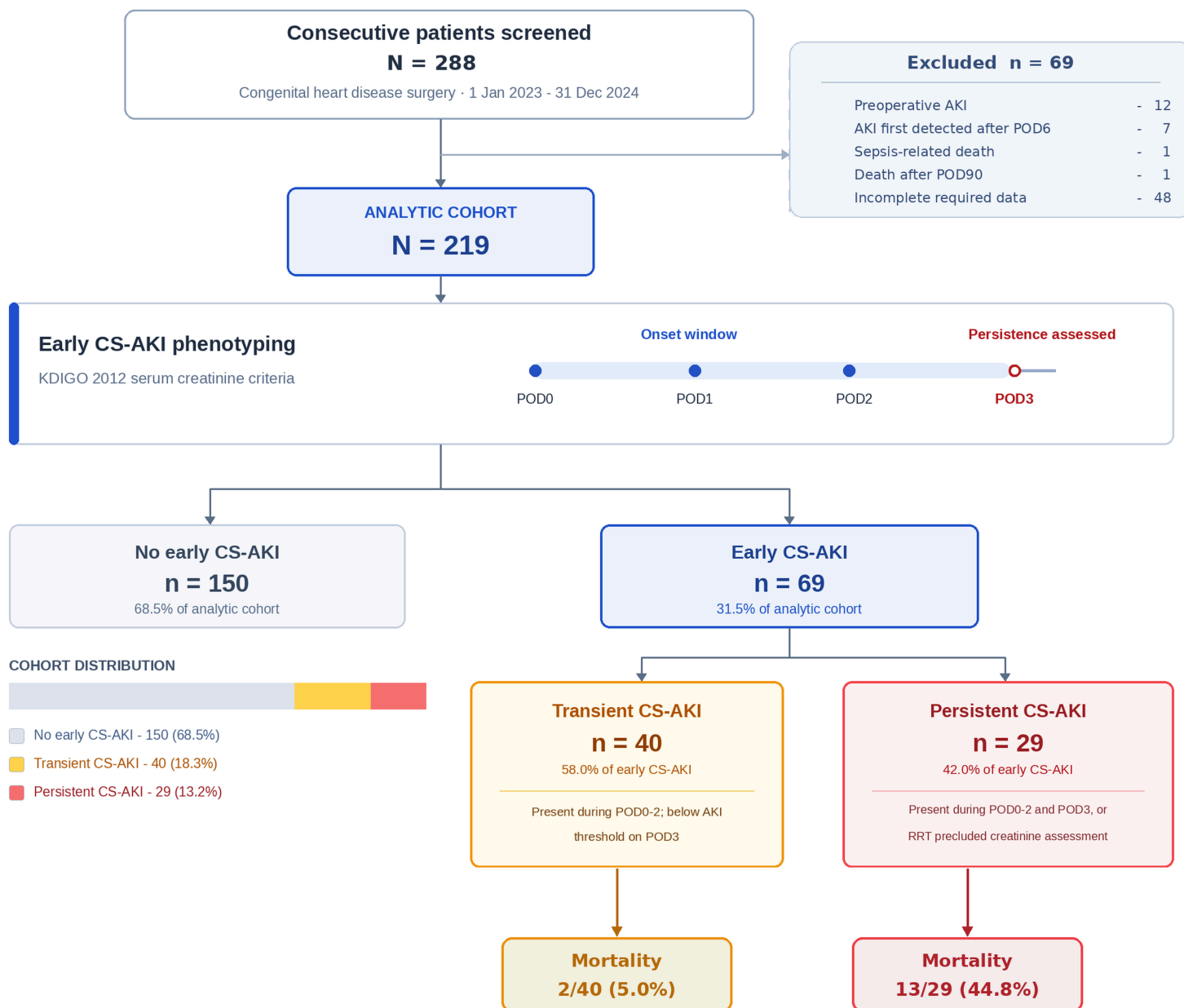
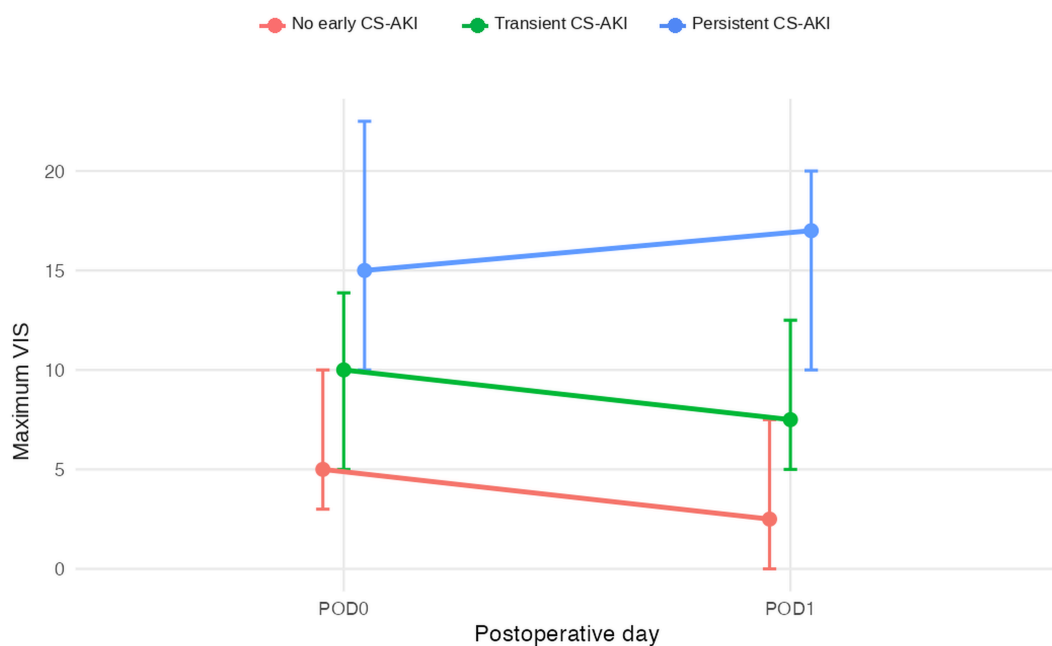


Figure 1

Participant flow and early CS-AKI phenotyping, presented according to the STROBE flow diagram format. Percentages are calculated within the analytic cohort (N = 219) for the no early CS-AKI and early CS-AKI groups, and within the early CS-AKI group (n = 69) for the transient CS-AKI and persistent CS-AKI phenotypes. Mortality boxes indicate in-hospital death before POD90 within the transient and persistent CS-AKI groups. AKI, acute kidney injury; CS-AKI, cardiac surgery-associated AKI; KDIGO, Kidney Disease: Improving Global Outcomes; POD, postoperative day; RRT, renal replacement therapy.

a



b

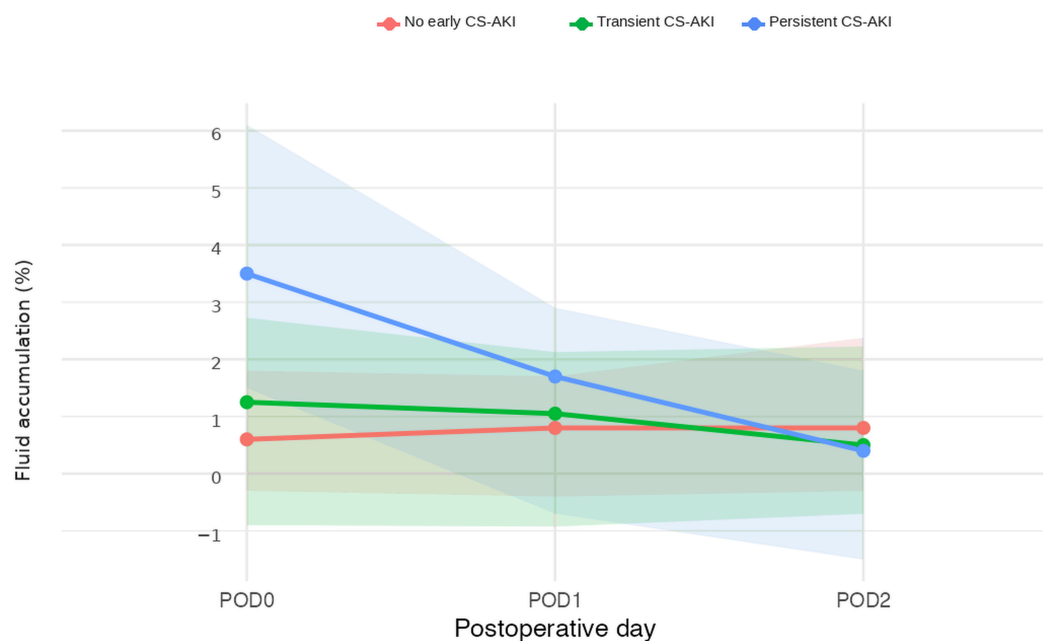


Figure 2

Early postoperative physiological trajectories by phenotype. (a) Maximum vasoactive-inotropic score (VIS) during POD0 and POD1; points are medians and bars are IQRs. (b) Daily fluid accumulation during POD0-POD2; values were calculated independently for each 24-h interval, and lines are medians and shaded bands are IQRs.

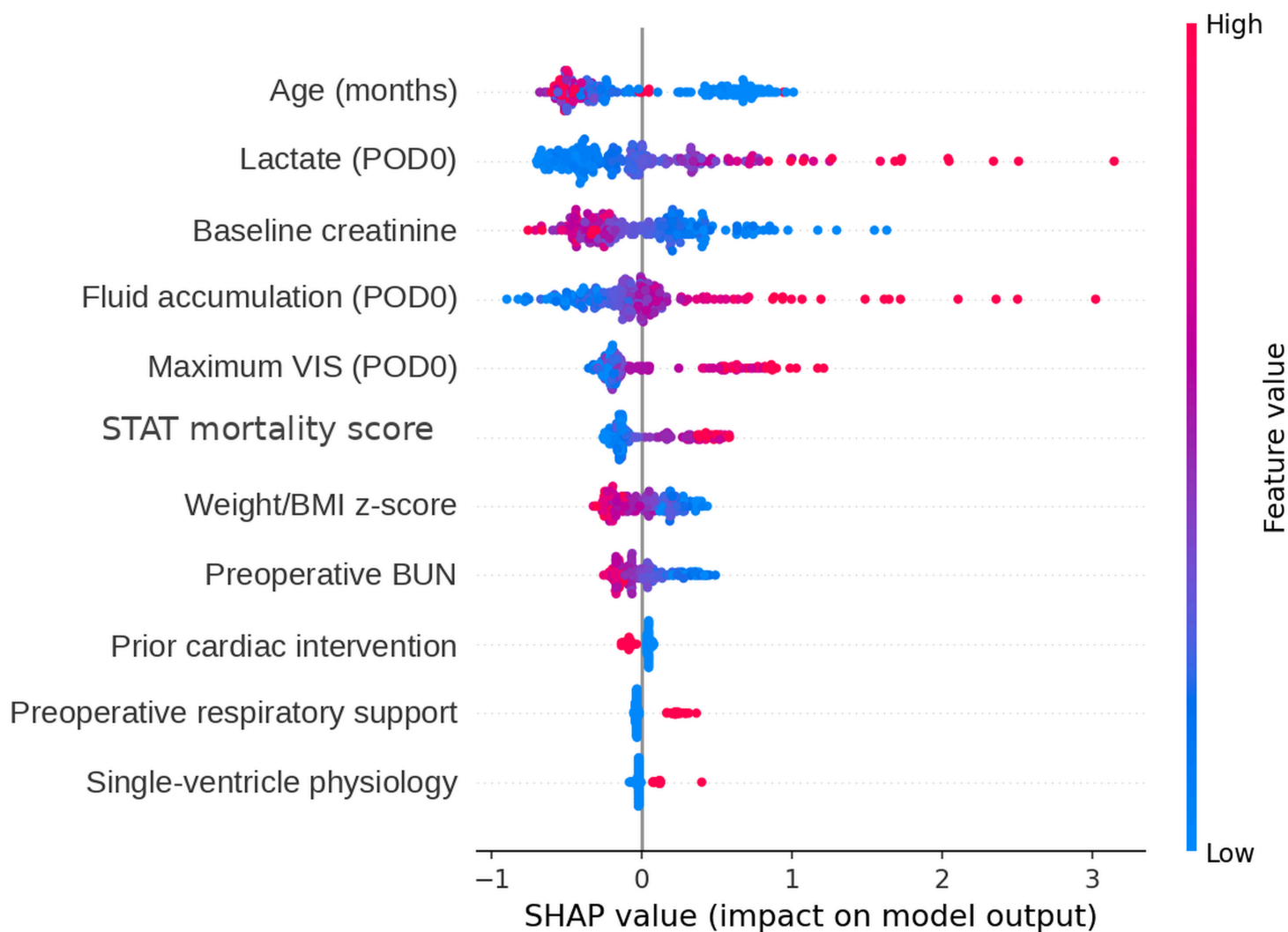


Figure 3

SHAP summary for the exploratory ML-2 CatBoost model for persistent CS-AKI. ML-2 used the continuous STAT mortality score. Each dot represents one patient; horizontal position indicates the contribution to the model output, and color indicates the observed feature value. SHAP values explain the fitted model and do not establish causal importance.

Supplementary Files

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