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Early Shock-Index Change and a Short Renal-Surveillance Window After Acute Myocardial Infarction: Contemporary-Cohort Findings With Secondary Transportability Analyses

Shuting Kong
Jinhua Central Hospital of Zhejiang University (Jinhua Central Hospital)
Yibin Pan
zqwen628@163.com

Jinhua Central Hospital of Zhejiang University (Jinhua Central Hospital)

Research Article

Keywords: acute myocardial infarction, acute kidney injury, shock index, landmark analysis, critical care, electronic health records

Posted Date: November 19th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11558127/v1

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Additional Declarations: No competing interests reported.

Abstract

Background

Acute kidney injury (AKI) after acute myocardial infarction (AMI) is usually recognized only after serum creatinine has risen. Clinicians need an earlier, low-burden signal that can focus renal surveillance while the patient is still in the first hours of critical care. We examined whether early change in routinely recorded shock index (SI) marks such a window.

Methods

We conducted a retrospective 6-hour landmark cohort study. MIMIC-IV and eICU-CRD were the contemporary core cohorts; MIMIC-III and SICdb were secondary transportability analyses. ΔSI was the median SI at 4–6 hours minus the median at 0–2 hours. The outcome was the first recorded fulfillment of creatinine-defined AKI after the landmark, defined by the Kidney Disease: Improving Global Outcomes creatinine criteria as an increase of at least 0.3 mg/dL within 48 hours or at least 1.5 times the lowest creatinine in the preceding 7 days; urine-output criteria were unavailable. Database-specific cause-specific Cox models adjusted for early SI and prespecified clinical covariates.

Results

The contemporary cohorts included 876 MIMIC-IV and 4,052 eICU patients. Per 0.1 higher ΔSI—equivalently, a higher 4–6-hour SI conditional on the 0–2-hour SI—the adjusted hazard of subsequent recorded AKI was 10% higher in the prespecified MIMIC-IV hospital-boundary analysis (hazard ratio [HR], 1.100; 95% confidence interval [CI], 1.011–1.197) and 23% higher as an average linear summary in eICU (HR, 1.230; 95% CI, 1.137–1.331), where the association was nonlinear ($P < 0.001$). At 6.75 days, cumulative AKI incidence was 44.8% versus 41.4% in MIMIC-IV and 14.4% versus 11.9% in eICU for increasing versus non-increasing SI. The MIMIC-IV estimate crossed the null under the common ICU-transfer boundary, and secondary transportability analyses were null. Delaying risk-set entry to hour 24 attenuated both contemporary-cohort estimates. Stand-alone discrimination gain in MIMIC-IV was small (ΔC-index = 0.0040).

Conclusions

Early ΔSI identified a short period in which routinely recorded heart rate and blood pressure carried information about the next recorded creatinine-defined AKI event in two contemporary cohorts. Because the calculation requires no new laboratory test, it may help target when clinicians review perfusion, congestion, urine output, nephrotoxic exposure, and the need for renal-function reassessment. The

signal is not a universal threshold or stand-alone alarm; prospective silent-mode studies should test its local lead time, workload, and clinical benefit.

Clinical trial registration

Not applicable.

Introduction

Acute kidney injury (AKI) after acute myocardial infarction (AMI) is common, prognostically important, and often recognized only after creatinine has already risen.[1–4] The bedside problem is therefore temporal: clinicians need an inexpensive signal of unresolved circulatory stress while there is still time to review perfusion, congestion, nephrotoxic exposure, fluid balance, and the frequency of renal-function monitoring.[5–7]

Shock index (SI), calculated as heart rate divided by systolic blood pressure, is available whenever routine vital signs are recorded. Since its original description,[8] higher admission SI has been linked to mortality, cardiogenic shock, myocardial damage, heart failure, and other adverse outcomes after AMI or acute coronary syndrome.[9–13,35–38] Dynamic SI studies have examined cumulative abnormal exposure or change during emergency care,[14–16] and kidney-focused AMI studies have linked hemodynamic impairment or SI-based scores to AKI risk.[17,18] However, most of this evidence begins with a single admission value, a threshold-derived exposure, a mortality outcome, or a predictor that already contains renal function.

What remained unclear was whether a within-patient change in SI during the first ICU hours precedes the first later *recorded* fulfillment of creatinine-based AKI criteria. This question requires three safeguards that earlier studies rarely combined: the exposure window must end before follow-up starts, patients who already meet AKI criteria must be removed using specimen or chart time, and the result must be tested across different monitoring systems. It also requires restraint, because recorded criterion fulfillment is not the biological onset of kidney injury and creatinine sampling is part of care.[19,30]

We therefore constructed an AKI-free 6-hour landmark cohort in four critical-care databases. MIMIC-IV was the prespecified primary cohort; eICU-CRD was a parallel multicenter analysis under a different outcome boundary, MIMIC-III was a historical and technical comparison, and SICdb was an exploratory European comparison. We tested whether ΔSI from 0–2 to 4–6 hours—equivalently, the 4–6-hour SI contrast conditional on the starting SI—was associated with subsequent recorded creatinine-defined AKI, and whether the association survived different endpoint boundaries and later risk-set entry. The intended contribution was a clinically interpretable answer about when a routine vital-sign contrast may support further renal-surveillance research—and where that answer fails to transport—not a new cutoff or treatment target.

Methods

Study design and reporting

This was a retrospective, multicohort observational cohort study with a prespecified 6-hour landmark. The landmark ensured that both SI windows were complete before follow-up began and excluded patients who had already fulfilled creatinine-defined AKI criteria. This design establishes the order of recorded exposure and outcome measurements but does not establish the biological onset of kidney injury or causal effects.[30]

The study was reported with reference to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) and REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statements.[33,34] The project analysis plan, variable definitions, cohort roles, covariates, and stop rules were documented before the final association models and redrafting. We did not change the exposure windows or outcome, search for an outcome-derived SI cutoff, or add unplanned subgroups in response to null cross-database results.

Data sources and cohort roles

We used MIMIC-IV version 3.1 (Beth Israel Deaconess Medical Center, Boston, United States; 2008–2022),[20,21] eICU Collaborative Research Database version 2.0 (multiple United States hospitals; 2014–2015),[22,23] MIMIC-III version 1.4 (Beth Israel Deaconess Medical Center; 2001–2012),[24,25] and Salzburg Intensive Care database (SICdb) version 1.0.8 (four ICUs at University Hospital Salzburg, Austria; 2013–2021).[26–28] These are the source-database collection periods represented by the eligible records used in this study. MIMIC-IV was the development and primary-analysis cohort; its database-provided anchor-year groups were 2008–2010, 2011–2013, 2014–2016, 2017–2019, and 2020–2022. eICU was a parallel multicenter cohort under an ICU-transfer outcome boundary; the final patient-level cohort represented 152 hospitals, and inference accounted for hospital clustering. MIMIC-III came from the same health-system lineage as MIMIC-IV and was treated as a historical and technical comparison, not independent external validation. SICdb was an independent European exploratory comparison. Its evidentiary weight was limited by 42 AKI events and incomplete observability of chronic dialysis and kidney-transplant history. Database-specific phenotype definitions are summarized in Supplementary Table S1.

Participants

We included adults with AMI and retained one qualifying ICU stay per patient. AMI was identified from the principal hospital diagnosis in MIMIC-IV, the Acute Physiology and Chronic Health Evaluation (APACHE) ICU admission diagnosis in eICU, a principal International Classification of Diseases, Ninth Revision (ICD-9) code beginning with 410 in MIMIC-III, and a principal Tenth Revision (ICD-10) I21 or I22

diagnosis in SICdb. Patients had to be alive and still observable at six hours after ICU admission, have at least two valid SI observations in both the 0–2-hour and 4–6-hour windows, and have creatinine data sufficient to establish landmark status and post-landmark follow-up. In eICU, after unit-level deduplication, one qualifying hospital stay was retained per unique patient using the earliest recorded discharge year and, within year, the smallest stay identifier. This deterministic rule removed 39 additional stays but does not establish verified longitudinal ordering within a deidentified year.

Where reliable fields were available, we excluded end-stage kidney disease or chronic dialysis, kidney transplant, and renal replacement therapy by the landmark. We also excluded AKI occurring before or at six hours. SICdb allowed exclusion of early continuous renal replacement therapy but did not provide reliable chronic dialysis and transplant fields; this limitation was retained rather than imputed. Figure 1 shows the cohort flow, and detailed counts are provided in Supplementary Table S9.

Shock-index exposure

SI was calculated as heart rate divided by systolic blood pressure. Heart rates from 20 to 250 beats/min and systolic pressures within database-specific physiologic ranges were retained. MIMIC-IV heart rate and systolic pressure measurements were matched as mutually nearest pairs no more than five minutes apart; both results also had to be available by the landmark. eICU used concurrent invasive observations or the closest periodic heart rate to a noninvasive pressure within five minutes. MIMIC-III used harmonized CareVue and MetaVision item mappings and paired heart rate and systolic pressure recorded at the same chart time. SICdb minute-level signals were decoded using the published data structure, aligned to ICU offset, and paired within five minutes.

For each patient, early SI was the median valid SI from 0–2 hours and late SI was the median from 4–6 hours. The primary exposure was ΔSI = late SI minus early SI; positive values indicated an increase in the heart-rate-to-pressure ratio. ΔSI was analyzed continuously per 0.1 increase, with early SI included in every model. Because early SI plus ΔSI is algebraically equivalent to early SI plus late SI, the ΔSI coefficient represents the late-window contrast conditional on the early value. It does not demonstrate that change is intrinsically more informative than the late level. No category or clinical threshold was derived from the outcome.

Kidney outcome and follow-up

The outcome was first recorded fulfillment of creatinine-defined AKI criteria after the 6-hour landmark. Event and landmark eligibility were determined from specimen or chart time, not later storage time; six MIMIC-IV records with pre-landmark sample-time AKI but post-landmark storage were excluded. The event time denotes when the available record first met the electronic phenotype, not when biological renal injury began. The phenotype followed the creatinine component of Kidney Disease: Improving Global Outcomes (KDIGO): an increase of at least 0.3 mg/dL from the lowest observed creatinine in the

preceding 48 hours or a value at least 1.5 times the lowest observed creatinine in the preceding seven days.[19] Urine-output criteria were not used. Creatinine values outside 0.1–20 mg/dL were excluded. The most recent creatinine available by six hours was used to calculate landmark estimated glomerular filtration rate (eGFR) with the 2021 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation.[29] Because acute illness may violate steady-state assumptions, landmark eGFR was treated as a creatinine-derived risk-adjustment measure rather than direct measurement of steady-state filtration.

The prespecified MIMIC-IV primary endpoint followed patients from the six-hour landmark to the earliest of AKI, hospital death or discharge, or ICU-admission day 7. This retained AKI events diagnosed after ICU transfer but during the same hospitalization. A harmonized MIMIC-IV sensitivity endpoint ended at ICU death or transfer, matching eICU, MIMIC-III, and SICdb. Death and discharge or ICU transfer before AKI and before day 7 were competing events. Patients still observed and event-free at day 7 were administratively censored rather than assigned a later discharge or transfer as a competing event. In SICdb, a known observation end before day 7 with unknown non-AKI discharge status was classified as a combined non-AKI exit, whereas unknown status at day 7 was administratively censored.

Covariates

The common core model included early SI, age, sex, and landmark acute-phase eGFR as a creatinine-derived risk-adjustment measure; eGFR was not interpreted as steady-state filtration. The prespecified MIMIC-IV primary model additionally included diagnosis-code indicators for diabetes, hypertension, chronic heart failure, chronic kidney disease (CKD), and the database-provided anchor-year group. eICU and MIMIC-III extended models added diabetes, hypertension, heart failure, and CKD to the common core. MIMIC-III also included a CareVue-versus-MetaVision source sensitivity analysis. SICdb was limited to the core model because only 42 AKI events were available. Covariates were selected from clinical reasoning and prior evidence, not univariable P values.

Missing data

The exposure and all common-core variables were complete in the analytic cohorts; primary models therefore used complete records without imputation. A stricter renal-function measure based on the latest pre-ICU creatinine or the first 0–2-hour creatinine was available for 738 MIMIC-IV, 3,796 eICU, 916 MIMIC-III, and 242 SICdb patients. This measure was used only in a complete-case sensitivity analysis. Lactate was missing in 45.8% of the original MIMIC-IV risk set and was not introduced into the main model. Treatment variables were not included because they could be both consequences of hemodynamic deterioration and determinants of subsequent AKI.

Statistical analysis

Continuous variables are described as median (interquartile range [IQR]) and categorical variables as number (percentage). Means and standard deviations were not used because several continuous variables were skewed. Baseline P values were not calculated across databases because these cohorts differed in phenotype, era, monitoring system, and outcome boundary and were not samples from one exchangeable population.

The primary association in each database was estimated with a cause-specific Cox proportional-hazards model. Death and discharge or ICU transfer before AKI were treated as competing events and were censored in the cause-specific analysis. eICU models used hospital-cluster robust standard errors. Effect estimates are reported as hazard ratios (HRs) with 95% confidence intervals (CIs) per 0.1 higher ΔSI. Covariates were chosen before modeling from clinical reasoning, prior evidence, and database availability rather than univariable P values. An unadjusted ΔSI model was not reported because the prespecified estimand was the 4–6-hour SI contrast conditional on the 0–2-hour SI; omitting early SI would answer a different question and would not estimate within-person change conditional on its starting value. We did not pool estimates because cohort roles, monitoring systems, independence, and outcome observability differed; MIMIC-III was also not independent of MIMIC-IV.

Prespecified sensitivity analyses used Fine–Gray subdistribution-hazards models,[31,32] a stricter early-eGFR complete-case definition, and the harmonized MIMIC-IV ICU boundary. The eICU Fine–Gray model could not represent hospital clustering and was interpreted as an unclustered sensitivity analysis. Departure from linearity was assessed with a hospital-cluster robust 2-df Wald test of the nonlinear components of a 3-df natural spline in eICU; the spline was not used to select a cutoff.

To examine the observation process, post-landmark creatinine-test counts were compared between ΔSI ≤ 0 and ΔSI > 0 with the Wilcoxon rank-sum test. Proportions with at least two tests were compared with the χ^2 test or Fisher exact test when expected counts were small, and the association between continuous ΔSI and test count was summarized with Spearman's rank correlation. Cause-specific Cox models were then repeated among patients with at least two and at least three post-landmark creatinine tests. Because these restrictions condition on post-exposure care, they were interpreted only as sensitivity analyses.

Additional analyses delayed risk-set entry to ICU hours 12 and 24; used 3-df natural splines for early SI, age, and eGFR; replaced acute-phase eGFR with log landmark creatinine; and repaired identified proportional-hazards violations with time-varying coefficients and, for the MIMIC-IV full model, era-stratified baseline hazards. Proportional hazards were assessed with Schoenfeld residual tests. After repair, residual time dependence was checked with joint Wald tests of covariate-by-log(time/1 day) interactions; the eICU test used hospital-cluster robust covariance. Influence on the ΔSI coefficient was assessed with standardized DFBETAS and the threshold $2/\sqrt{N}$, followed by a leave-one-out refit after removing the single most influential observation. In MIMIC-IV, incremental fit was assessed with a likelihood-ratio test and change in Harrell's C-index; 500 bootstrap samples estimated optimism in the full-model C-index.

The exposure and core covariates were complete in the analytic cohorts, so primary models used complete records and no multiple imputation. All eligible records were used, and no a priori power calculation was performed. The ΔSI coefficient in the prespecified MIMIC-IV full cause-specific Cox model was the single primary test. A two-sided $P < 0.05$ indicated statistical significance for that test. Parallel-cohort, competing-risk, diagnostic, and sensitivity P values were two-sided and nominal without multiplicity adjustment; effect sizes and 95% CIs were emphasized. Analyses used R version 4.6.1 (survival 3.8-6, cmprsk 2.2–12, ggplot2 4.0.3). Python 3 with pandas, NumPy, and pyarrow was used for phenotype harmonization and audit outputs.

Data-quality audit

Duplicate patients, nonpositive follow-up, missing core variables, exposure distributions, event coding, result-time ordering, and influential observations were audited before redrafting. Six MIMIC-IV records were removed because sample time showed AKI by the landmark although storage occurred later; no retained MIMIC-IV creatinine exceeded the prespecified 20 mg/dL upper bound. In eICU, limiting to the first ICU unit did not ensure one record per patient; patient-level deduplication removed 39 additional hospital stays. Administrative day-7 censoring was corrected so that later exits were not misclassified as competing events. One MIMIC-IV record had an impossible early hospital-discharge timestamp despite valid later ICU, creatinine, AKI, and death timestamps; the invalid timestamp was ignored under a time-order rule and both endpoints were reconstructed from valid later timestamps.

Ethics

All four source databases contain deidentified routinely collected clinical data. MIMIC-IV data sharing was approved by the Beth Israel Deaconess Medical Center Institutional Review Board with informed consent waived; MIMIC-III was approved by the Beth Israel Deaconess Medical Center and Massachusetts Institute of Technology review boards with consent waived.[20,21,24,25] eICU data were deidentified to Health Insurance Portability and Accountability Act safe-harbor standards and are available to credentialed researchers under a data-use agreement.[22,23] SICdb was approved by the ethics committee of Land Salzburg, Austria (EK 1115/2021), with individual consent waived.[26–28] This secondary analysis used only deidentified controlled-access research databases in an authorized local environment and involved no participant contact. The ethics department of Jinhua Central Hospital determined that this secondary analysis used only deidentified public-database resources and required no additional ethics review or approval; no determination number was issued. No additional participant consent was required for this analysis.

Results

Cohort construction and clinical context

The contemporary core cohorts included 876 MIMIC-IV patients with 380 subsequent AKI events and 4,052 eICU patients with 536 events (Fig. 1 and Table 1). MIMIC-IV began with AMI/acute-coronary-

syndrome candidates; 879 met the sample-time-consistent landmark and measurement criteria, and three ACS-only records were removed by the final AMI restriction. The secondary transportability cohorts included 1,003 MIMIC-III patients with 266 events and 265 SICdb patients with 42 events. Their complete flow and baseline characteristics are reported in Supplementary Tables S1 and S9 and Supplementary Figure S1. Keeping these roles separate prevented historical and exploratory cohorts from being presented as equivalent contemporary replications.

Table 1
Baseline characteristics of the two contemporary core cohorts

Characteristic	MIMIC-IV (n = 876)	eICU-CRD (n = 4,052)
Age, years	70.0 (61.0–79.0)	65.0 (55.0–75.0)
Female sex, n (%)	301 (34.4)	1343 (33.1)
Early shock index, 0–2 h	0.688 (0.578–0.807)	0.607 (0.510–0.735)
ΔShock index, 4–6 h minus 0–2 h	0.020 (-0.056–0.095)	0.006 (-0.049–0.065)
Landmark eGFR, mL/min/1.73 m²	74.6 (51.9–95.8)	78.2 (57.5–96.0)
Diabetes, n (%)	343 (39.2)	1243 (30.7)
Hypertension, n (%)	683 (78.0)	2280 (56.3)
Heart failure, n (%)	432 (49.3)	601 (14.8)
Chronic kidney disease/renal dysfunction code, n (%)	195 (22.3)	266 (6.6)
Creatinine-defined AKI, n (%)	380 (43.4)	536 (13.2)
Competing death/discharge or ICU transfer, n (%)	385 (43.9)	3452 (85.2)
Follow-up, hours	67.9 (31.9–116.4)	28.5 (17.8–44.3)

Values are median (interquartile range) for continuous variables and n (%) for categorical variables. No between-cohort P value was calculated because MIMIC-IV and eICU differed in phenotype, monitoring system, and outcome boundary and were not samples from one exchangeable population. Full four-database characteristics are reported in Supplementary Table S1. AKI, acute kidney injury; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ICU, intensive care unit; SI, shock index. The MIMIC-IV event proportion uses the prespecified hospital-discharge/day-7 boundary; eICU uses the ICU-transfer/day-7 boundary.

Early ΔSI and subsequent AKI

In the prespecified MIMIC-IV hospital-boundary model, each 0.1 higher ΔSI was associated with a 10.0% higher cause-specific hazard of subsequent recorded AKI-criterion fulfillment (HR, 1.100; 95% CI, 1.011–1.197; P = 0.027). A parallel multicenter eICU analysis across 152 hospitals gave an average linear HR of 1.230 (95% CI, 1.137–1.331; P < 0.001); extended adjustment gave HR 1.223 (95% CI, 1.131–1.324; P < 0.001) (Fig. 2 and Table 2). These findings place the signal within the first six ICU hours and use measurements already collected in routine care. Because eICU used an ICU-transfer outcome boundary

and showed nonlinearity, it is a clinically supportive parallel analysis rather than strict external replication of the MIMIC-IV estimand.

Table 2
Contemporary-cohort association of early shock-index change with later creatinine-defined acute kidney injury

Analysis	Measure	N	AKI events	Estimate per 0.1 increase in ΔSI (95% CI)	P value
MIMIC-IV primary, prespecified full model	Cause-specific HR	876	380	1.100 (1.011–1.197)	0.027
MIMIC-IV, harmonized ICU-boundary core model	Cause-specific HR	876	285	1.066 (0.973–1.168)	0.168
eICU, core model with hospital-cluster robust SE	Cause-specific HR	4052	536	1.230 (1.137–1.331)	< 0.001
eICU, extended model with hospital-cluster robust SE	Cause-specific HR	4052	536	1.223 (1.131–1.324)	< 0.001
MIMIC-IV, delayed risk set: icu hour 12	Cause-specific HR	828	333	1.094 (0.998–1.199)	0.056
MIMIC-IV, delayed risk set: icu hour 24	Cause-specific HR	745	255	1.026 (0.922–1.142)	0.642
eICU, delayed risk set: icu hour 12	Cause-specific HR	3958	470	1.211 (1.118–1.312)	< 0.001
eICU, delayed risk set: icu hour 24	Cause-specific HR	2995	319	1.107 (0.998–1.228)	0.055
MIMIC-IV primary, competing-risk sensitivity	Subdistribution HR	876	380	1.098 (1.008–1.196)	0.032
MIMIC-IV harmonized, competing-risk sensitivity	Subdistribution HR	876	285	1.124 (1.024–1.234)	0.014
eICU, unclustered competing-risk sensitivity	Subdistribution HR	4052	536	1.226 (1.122–1.341)	< 0.001

Effect estimates are per 0.1 higher ΔSI and are shown with 95% confidence intervals and nominal two-sided P values unless identified as the single prespecified primary test. The MIMIC-IV primary cause-specific Cox model used the hospital-discharge/day-7 boundary and adjusted for early SI, age, sex, landmark acute-phase eGFR, diabetes, hypertension, heart failure, CKD, and era. Harmonized models used the ICU-transfer/day-7 boundary and common-core adjustment. eICU cause-specific models used hospital-cluster robust standard errors; its Fine-Gray sensitivity was unclustered. Historical and exploratory transportability estimates are reported in Supplementary Tables S2 and S12. AKI, acute kidney injury; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; ICU, intensive care unit; P, two-sided probability value; SE, standard error; SHR, subdistribution hazard ratio; SI, shock index; ΔSI, median SI at 4–6 hours minus median SI at 0–2 hours.

The clinical window depended on how long renal outcomes remained observable. Ending MIMIC-IV follow-up at ICU transfer rather than hospital discharge attenuated the estimate to 1.066 (95% CI, 0.973–1.168; P = 0.168), with 95 of 380 primary events occurring after ICU transfer. Secondary MIMIC-III and SICdb transportability estimates were also null. These negative checks are retained in Supplementary Tables S2 and S12 and Supplementary Figure S3 because they define where the contemporary-cohort finding should not be assumed to apply.

Competing-risk sensitivity analyses supported the direction of the two contemporary findings: Fine–Gray estimates were 1.098 (95% CI, 1.008–1.196; P = 0.032) for the MIMIC-IV primary boundary and 1.226 (95% CI, 1.122–1.341; P < 0.001) for eICU (Table 2). The eICU Fine–Gray model was unclustered and was not used to support multicenter inference; all secondary estimates are reported in the supplement.

Shape and absolute-risk description

The linear functional form was adequate in MIMIC-IV. In eICU, the hospital-cluster robust nonlinear Wald test supported departure from linearity (χ^2=25.02; P < 0.001). Relative to ΔSI = 0, the adjusted curve reached approximately 1.11 at + 0.05, 1.24 at + 0.10, and 1.67 at + 0.20 (Fig. 3). These are descriptive points on a continuous curve, not candidate diagnostic thresholds; complete secondary-cohort shape analyses are reported in the supplement.

Descriptive Aalen–Johansen curves made the contemporary findings clinically tangible (Fig. 4 and Supplementary Table S10). At 6.75 days, cumulative AKI incidence for increasing versus non-increasing SI was 44.8% versus 41.4% in MIMIC-IV and 14.4% versus 11.9% in eICU. These post hoc groups were not compared inferentially, and zero was not proposed as a clinical cutoff. Secondary-cohort absolute-risk results are retained in Supplementary Table S10.

Observation process and sensitivity analyses

Creatinine-test counts were similar between the two direction groups in the contemporary cohorts: 6 (IQR, 4–10) versus 7 (4–10) in MIMIC-IV (Wilcoxon P = 0.638) and 1 (1–2) versus 1 (1–2) in eICU (P = 0.655) (Supplementary Table S11 and Supplementary Figure S2). Requiring at least two or three post-landmark tests preserved positive estimates in both cohorts, although eICU estimates attenuated (Supplementary Table S12 and Supplementary Figure S3). These restrictions do not remove observation-process bias because testing is part of post-exposure care.

The strict early-eGFR complete-case estimate in MIMIC-IV was directionally consistent but crossed the null (HR, 1.093; 95% CI, 0.998–1.196; nominal P = 0.055), whereas eICU remained positive (HR, 1.231; 95% CI, 1.134–1.337; nominal P < 0.001) (Supplementary Table S3). Flexible covariate functions and direct landmark-creatinine adjustment preserved the primary MIMIC-IV and eICU estimates (Supplementary Table S12).

Time mattered. With risk-set entry delayed to ICU hour 12, HRs were 1.094 (95% CI, 0.998–1.199) in MIMIC-IV and 1.211 (95% CI, 1.118–1.312) in eICU. At hour 24, they attenuated to 1.026 (95% CI, 0.922–

1.142) and 1.107 (95% CI, 0.998–1.228), supporting a short surveillance window rather than a durable risk label (Supplementary Table S12 and Supplementary Figure S3).

Diagnostics and incremental value

The ΔSI proportional-hazards test was nonsignificant in MIMIC-IV, eICU, and MIMIC-III but not in SICdb (P = 0.036). PH-repaired estimates were similar in MIMIC-IV, eICU, and MIMIC-III; time-specific SICdb estimates varied and remained imprecise. Post-repair joint residual time-interaction tests were nonsignificant in all five repaired models (Supplementary Tables S4, S5, S13, S14, and S15). Standardized DFBETAS exceeded 2/√N in 54 MIMIC-IV, 234 eICU, 58 MIMIC-III, and 18 SICdb observations, but removal of the single most influential record from each model did not change the overall pattern (Supplementary Tables S6 and S6b).

In MIMIC-IV, adding ΔSI improved likelihood fit (likelihood-ratio P = 0.029) but increased the C-index only from 0.6557 to 0.6596, an absolute gain of 0.0040. After 500 successful bootstrap replications, the optimism-corrected full-model C-index was 0.6455 (Supplementary Table S8). Thus, the association alone did not produce a clinically useful stand-alone prediction model.

Discussion

Principal findings

This study addressed a practical gap in AMI care: vital signs are available continuously, whereas creatinine-based AKI is recognized intermittently and usually later. In MIMIC-IV and eICU, a higher 4–6-hour SI conditional on its 0–2-hour value was associated with the next recorded creatinine-defined AKI event. The finding is clinically useful because it is available within six hours, requires no new laboratory measurement, and points to a short period when clinicians could reassess perfusion, congestion, urine output, nephrotoxic exposure, and the timing of renal-function testing.

The study also defines how this signal should be developed. Its value lies in timing surveillance, not in replacing clinical assessment or creating another bedside score. The association weakened when outcome observation ended at ICU transfer and when risk-set entry moved to hour 24. Historical and exploratory analyses were null. These checks do not erase the contemporary-cohort finding; they show that any electronic implementation must be local, time-specific, and evaluated within the actual ICU-to-ward pathway.

Relation to previous studies

Previous AMI studies have linked admission SI with mortality, myocardial damage, cardiogenic shock, and longer-term events.[9–13,35–38] Dynamic-SI studies have examined emergency-department change or cumulative exposure,[14–16] while kidney-focused studies have related hemodynamic impairment, admission SI, or SI combined with creatinine clearance to AKI.[17,18] Those studies did not answer the present bedside question: after two early SI windows have been observed and before AKI is recorded,

does the later value relative to the starting value identify a near-term renal-surveillance window? Our landmark design completed the exposure before follow-up and excluded patients who had already fulfilled creatinine criteria. Because early SI plus ΔSI is algebraically equivalent to early plus late SI, the result supports a conditional late-window contrast rather than proving that a change score is intrinsically superior.

Potential mechanisms

A rising SI can reflect tachycardia, falling systolic pressure, or both. After AMI, these changes may accompany ventricular dysfunction, arrhythmia, reduced forward flow, venous congestion, sympathetic activation, inflammation, or responses to fluids, vasopressors, analgesia, sedation, ventilation, and reperfusion care.[5–7] Several of these pathways can reduce renal perfusion or increase renal venous pressure. The nonlinear eICU curve is compatible with greater risk at larger positive changes, although the data cannot distinguish among mechanisms.

ΔSI should therefore be treated as an integrated record-based signal, not a direct measure of renal blood flow and not a modifiable treatment target. Interventions can move SI in opposite directions without necessarily improving kidney physiology. The observational models cannot show that lowering SI prevents AKI, and the hour-24 attenuation suggests that the usable lead time, if real, may be short.

Why the association did not transport uniformly

Outcome boundaries changed both event capture and the risk set. In MIMIC-IV, 95 AKI events occurred after ICU transfer; ending follow-up at transfer removed this surveillance interval and selected a different remaining population. This finding has direct clinical relevance: an ICU-only alert may miss renal events that become visible after transfer to the ward. Monitoring systems, creatinine ordering, heart-rate/pressure pairing, and discharge practices can also change exposure precision and outcome detection.

The secondary cohorts served as boundary tests rather than equivalent replications. MIMIC-III shared a health-system lineage with MIMIC-IV, and SICdb contributed only 42 events. We therefore did not pool the estimates. The supplement reports these results in full so that the contemporary findings are interpreted with their limits rather than selectively.

Clinical implications

The most useful next step is prospective silent-mode evaluation. A hospital could calculate ΔSI automatically from existing monitor data without displaying an alert, then test whether it identifies patients whose perfusion, congestion, urine output, nephrotoxic exposure, and creatinine schedule deserve earlier review. This design would preserve clinician judgment while measuring usable lead time, ICU-to-ward continuity, management changes, and patient benefit.

The immediate clinical value is operational. ΔSI can be calculated without another blood draw, and the hour-24 attenuation suggests that any useful lead time is concentrated early rather than lasting throughout the admission. It should trigger a structured review hypothesis, not an automatic test order or treatment. A silent-mode study should therefore measure false alerts and additional testing burden alongside lead time and clinical benefit.

Strengths and limitations

The main strengths were temporal and practical. The AKI-free landmark separated two SI windows from later follow-up; specimen-time auditing prevented delayed storage timestamps from creating false temporal order; starting SI was retained in every model; no outcome-derived cutoff was created; and competing events, endpoint boundaries, creatinine observation, later risk-set entry, nonlinearity, proportional hazards, and influence were examined. The two contemporary cohorts also provided complementary evidence: one offered detailed hospital-boundary follow-up and the other multicenter breadth.

The study remains observational and cannot remove confounding by infarct severity, ventricular function, congestion, treatment, or workflow. The outcome was the first *recorded* creatinine-criterion event, not biological injury onset; urine-output AKI, AKI severity and persistence, and a harmonized lead-time measure were unavailable. Requiring repeated vital signs and creatinine selected closely monitored ICU patients, and database phenotypes and follow-up boundaries were not identical. These limitations restrict direct deployment but do not change the central finding that the first six hours contain a low-cost, testable renal-surveillance signal in the contemporary cohorts.

Conclusions

Among selected ICU patients with database-defined AMI who remained free of recorded creatinine-defined AKI at six hours, higher early ΔSI was associated with the next recorded event in MIMIC-IV and eICU. The calculation uses existing vital signs and defines a short window for testing whether renal surveillance can be better timed without adding a new biomarker. Its effect depended on outcome boundary and prediction time, so it should be evaluated prospectively in silent mode rather than deployed as a universal alert or treatment target.

Abbreviations

AKI, acute kidney injury; AMI, acute myocardial infarction; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; ICU, intensive care unit; IQR, interquartile range; PH, proportional hazards; SI, shock index; SHR, subdistribution hazard ratio.

Declarations

Ethics approval and consent to participate

This study used deidentified controlled-access research databases made available to eligible users and involved no participant contact. The original database teams obtained ethics approvals and informed consent or consent waivers as applicable under their source protocols.[20–28] The ethics department of Jinhua Central Hospital determined that this secondary analysis used only deidentified public-database resources and required no additional ethics review or approval; no determination number was issued.

Consent for publication

Not applicable.

Clinical trial registration

Not applicable.

Availability of data and materials

MIMIC-IV, eICU-CRD, MIMIC-III, and SICdb are available through PhysioNet to eligible users under their respective credentialing, training, contributor-approval, and data-use requirements.[21,23,25,28] Patient-level source and derived data cannot be redistributed. The accompanying non-patient-level reproducibility archive contains the analysis scripts, aggregate model outputs and figure-source data, variable-harmonization documentation, execution logs without record identifiers, an executable run-order guide, and Python/R version manifests. The scripts require authorized users to supply the controlled-access source data at locally configured paths. The archive is supplied with this submission and may also be provided by the corresponding author, subject to the source databases' data-use requirements.

Funding

This work was supported by the Jinhua Traditional Chinese Medicine Science and Technology Research Program (Award No. 2023KY05; grant recipient: Shuting Kong). The funder had no role in study design, data extraction, analysis, interpretation, manuscript preparation, or the decision to submit.

Competing interests

The authors declare no competing interests.

Author contributions

SK: Data curation, Formal analysis, Investigation, Writing – original draft. YP: Conceptualization, Supervision, Writing – review and editing. Both authors interpreted the findings, approved the final manuscript, and agree to be accountable for the work.

Acknowledgments

The authors thank the patients and study populations whose deidentified data made this work possible. We also thank the investigators, participating hospitals, data stewards, and PhysioNet team who created,

curated, and maintain MIMIC-IV, eICU-CRD, MIMIC-III, and SICdb.

Use of artificial intelligence-assisted technologies

OpenAI Codex was used as an AI-assisted tool for local code generation and execution support, statistical workflow checks, figure preparation, manuscript structuring, and language editing. The authors reviewed the source data, analysis code and logs, numerical outputs, references, interpretations, figures, and final text; made all scholarly decisions; and take full responsibility for the accuracy and integrity of the work. The tool is not listed as an author.

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Figures

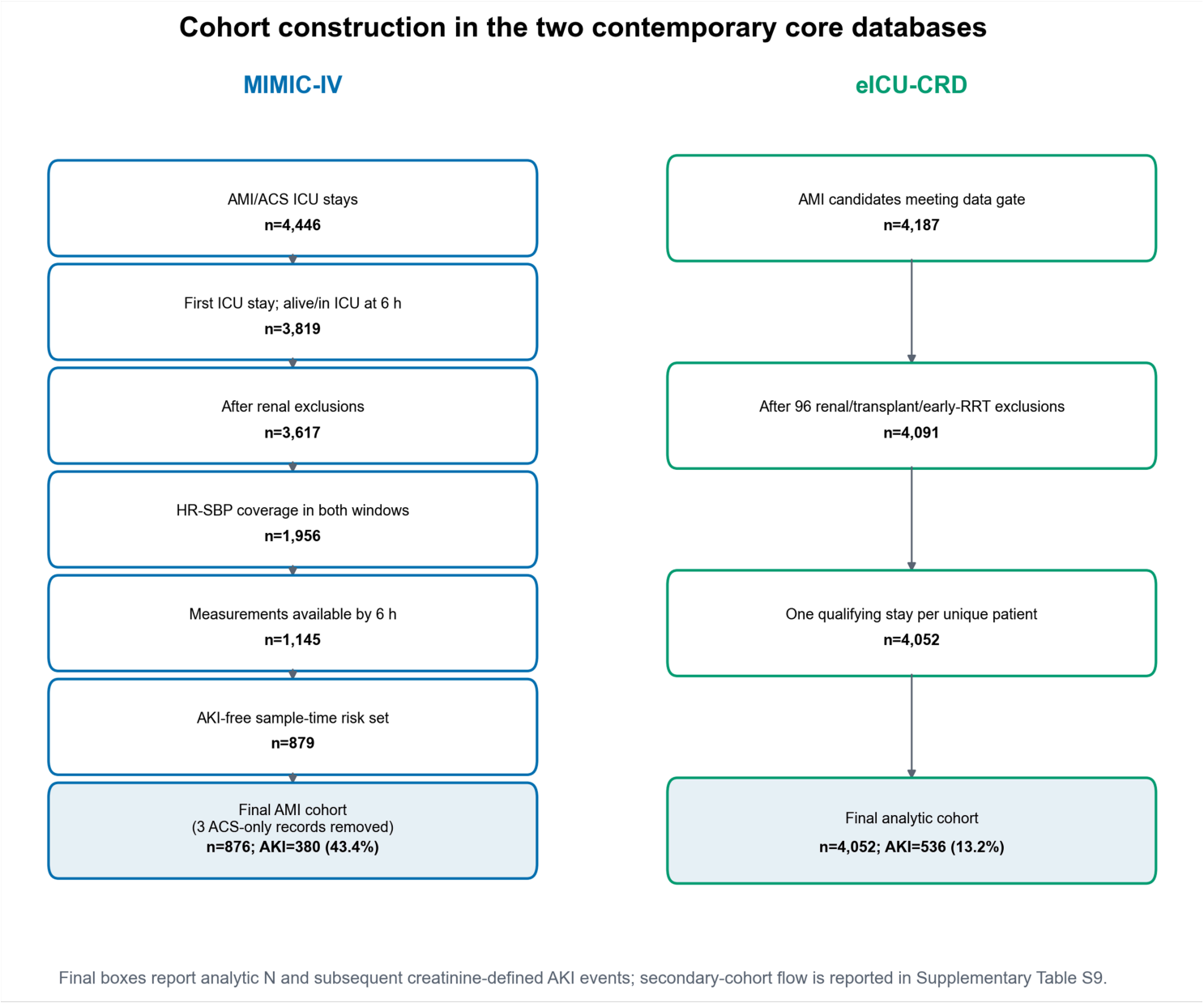
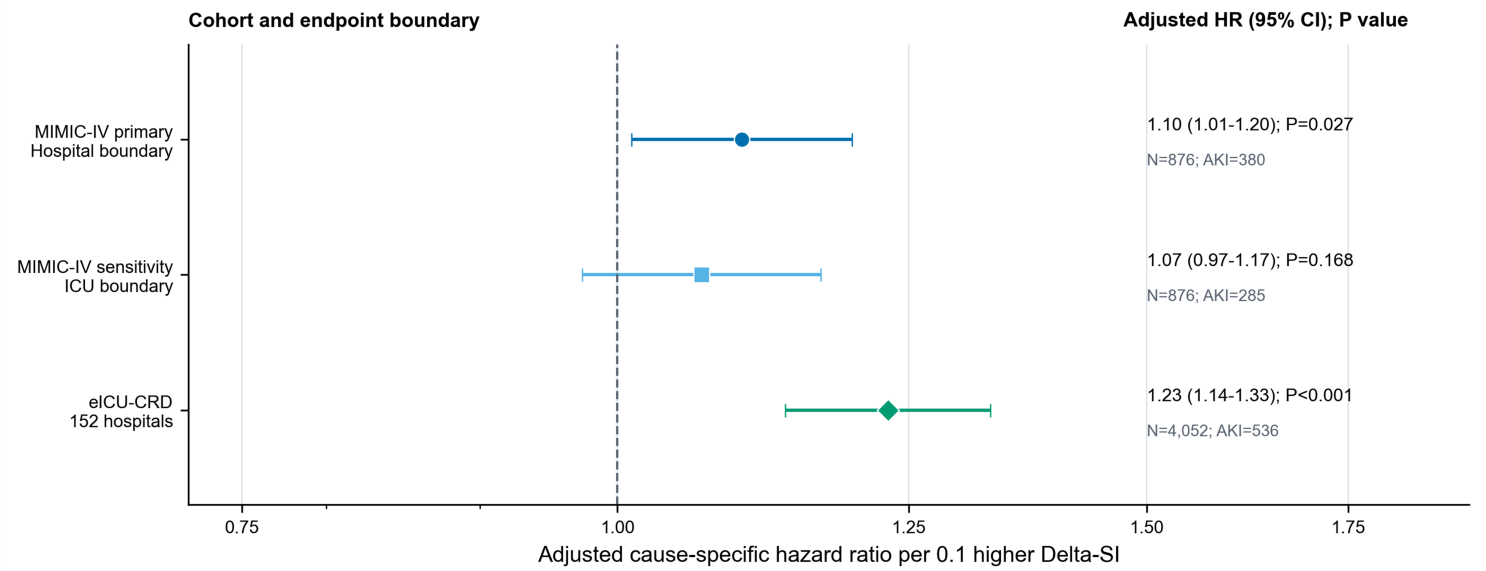


Figure 1

Cohort construction in the two contemporary core databases. Final boxes show analytic sample size and subsequent creatinine-defined AKI events, with percentages calculated within each final cohort. Intermediate counts are sequential numbers remaining after each gate and are not mutually exclusive exclusion totals. In MIMIC-IV, 879 records reached the AKI-free sample-time risk set and three ACS-only records were then removed by the final AMI restriction, leaving 876. The 6-hour landmark required patients to be alive, observable, and free of creatinine-defined AKI by specimen or chart time. Secondary MIMIC-III and SICdb flow is reported in Supplementary Table S9. ACS, acute coronary syndrome; AKI, acute kidney injury; AMI, acute myocardial infarction; CRRT, continuous renal replacement therapy; eICU-CRD, eICU Collaborative Research Database; ESRD, end-stage renal disease; HR, heart rate; ICU, intensive care unit; N or n, number of patients; RRT, renal replacement therapy; SBP, systolic blood pressure; SI, shock index.



Models were fitted separately; historical and exploratory transportability estimates are reported in Supplementary Figure S3.

Figure 2

Contemporary-cohort association of early shock-index change with subsequent creatinine-defined AKI. Points and horizontal lines show adjusted cause-specific HRs and 95% CIs per 0.1 higher ΔSI; the numeric column reports the two-sided P value, analytic N, and AKI events. MIMIC-IV primary used the prespecified hospital-discharge/day-7 boundary and full adjustment. The MIMIC-IV sensitivity used the harmonized ICU-transfer/day-7 boundary and common-core adjustment. eICU used hospital-cluster robust standard errors. Secondary transportability estimates are shown in Supplementary Figure S3. AKI, acute kidney injury; CI, confidence interval; eICU-CRD, eICU Collaborative Research Database; HR, hazard ratio; ICU, intensive care unit; N, number of patients; P, two-sided probability value; SI, shock index; ΔSI, median SI at 4–6 hours minus median SI at 0–2 hours.

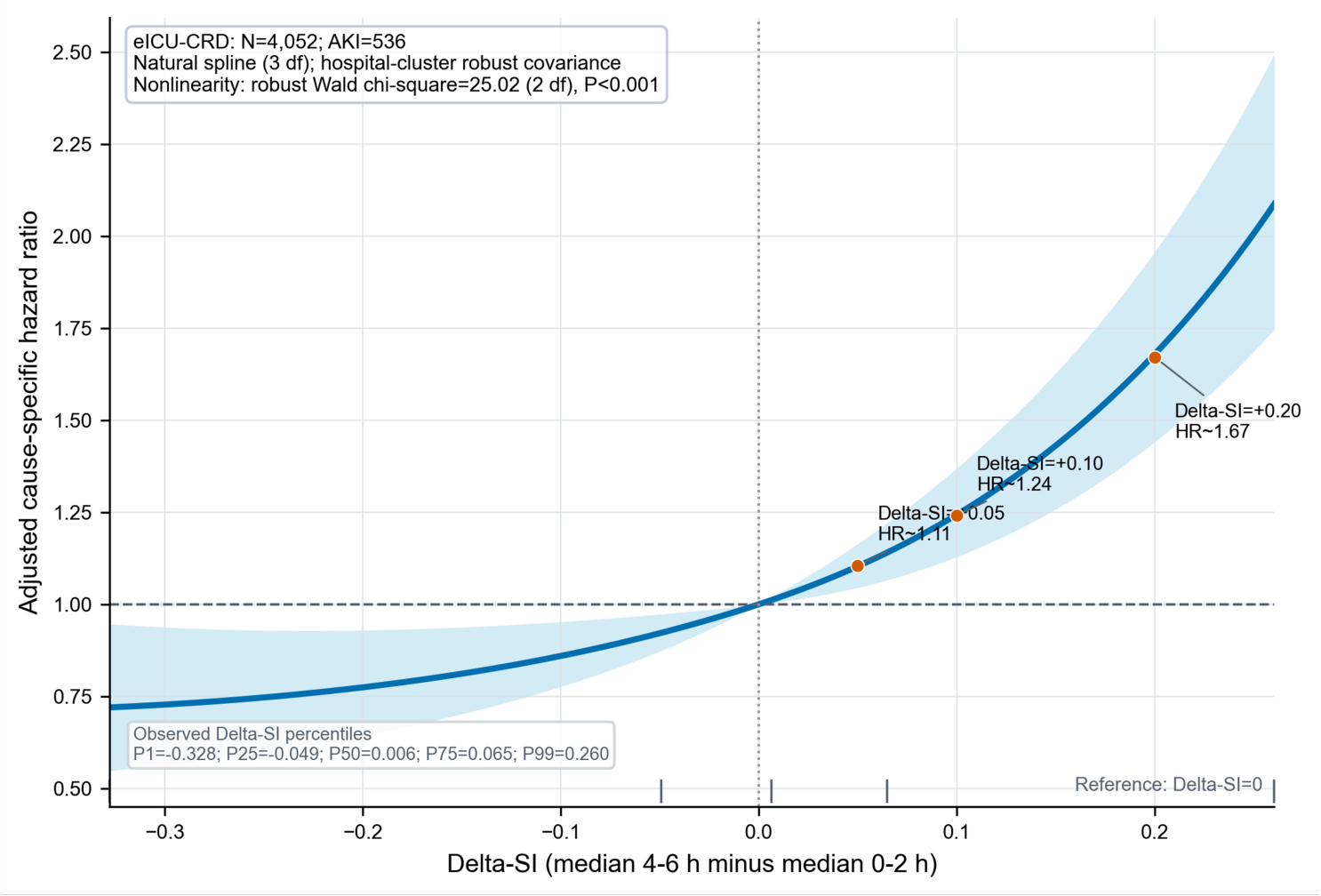


Figure 3

Continuous association of early shock-index change with creatinine-defined AKI in eICU-CRD. The curve and shaded 95% CI were estimated with a 3-df natural spline adjusted for early SI, age, sex, and landmark eGFR using hospital-cluster robust covariance (N=4,052; 536 AKI events). ΔSI=0 is the reference. The robust 2-df Wald test of nonlinear components gave χ^2=25.02 (P<0.001). Annotated HRs at +0.05, +0.10, and +0.20 are descriptive points on the continuous curve, not diagnostic thresholds. Rug marks and on-figure labels show the observed 1st, 25th, 50th, 75th, and 99th percentiles of ΔSI, clarifying where data support is densest. AKI, acute kidney injury; CI, confidence interval; df, degrees of freedom; eGFR, estimated glomerular filtration rate; eICU-CRD, eICU Collaborative Research Database; HR, hazard ratio; N, number of patients; P, two-sided probability value; SI, shock index; χ^2, chi-square statistic; ΔSI, median SI at 4–6 hours minus median SI at 0–2 hours.

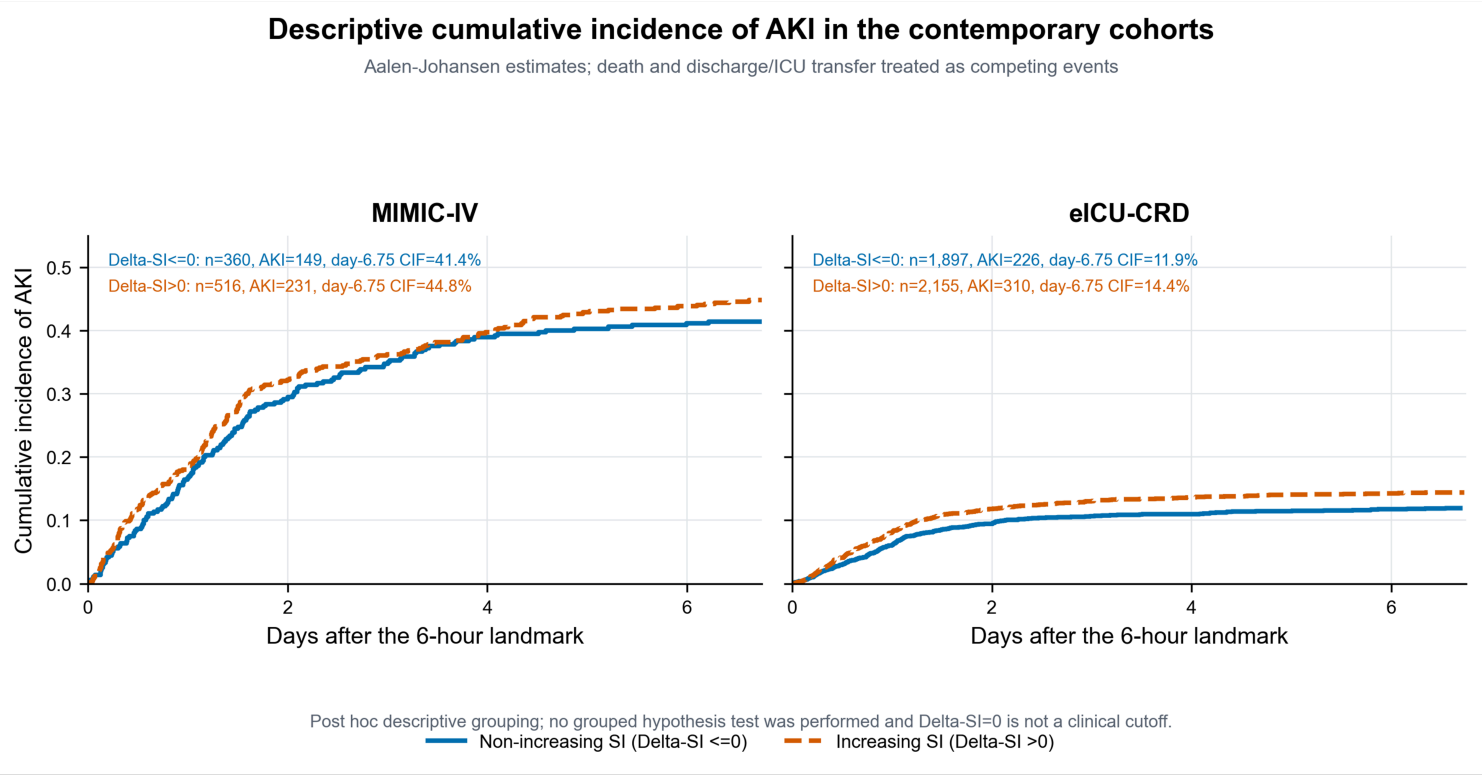


Figure 4

Descriptive cumulative incidence of AKI by shock-index change direction in the contemporary cohorts. Aalen–Johansen curves treat death and discharge or ICU transfer before day 7 as competing events. Each panel reports group-specific N, AKI events, and cumulative incidence at 6.75 days for ΔSI≤0 and ΔSI>0. The grouping was post hoc and zero was not chosen from the outcome. No grouped hypothesis test was performed; continuous adjusted models remain the inferential analyses. AKI, acute kidney injury; CIF, cumulative incidence function; eICU-CRD, eICU Collaborative Research Database; ICU, intensive care unit; N or n, number of patients; SI, shock index; ΔSI, median SI at 4–6 hours minus median SI at 0–2 hours.

Supplementary Files

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