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ORIGINAL ARTICLE

Inflammatory Indices and Mortality in Acute Heart Failure Complicated by Acute Kidney Injury: A Cross-Database Replication and Missing-Data Analyses

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Abstract: **Introduction:** Acute heart failure (AHF) complicated by acute kidney injury (AKI) carries high short-term mortality. This study compared five inflammatory blood-count indices, the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), systemic inflammation response index (SIRI) and prognostic nutritional index (PNI), across two intensive care unit (ICU) databases with explicit missing-data analyses. **Methods:** In the Medical Information Mart for Intensive Care IV (MIMIC-IV; derivation), adults with AHF and AKI were analyzed for 28-day in-hospital mortality using Cox regression with a 48-hour landmark; the eICU Collaborative Research Database (eICU-CRD; replication) used in-hospital mortality and logistic regression. Each index (per standard deviation [SD], log-transformed) was adjusted for clinical covariates, with false-discovery-rate (FDR) correction across the five indices. Complete-case analysis and multiple imputation (m=100) were examined as complementary primary analyses. Sensitivity analyses addressed the time origin (including a 48-hour landmark in eICU-CRD), the outcome definition, SIRI extreme values and the missing-data mechanism. **Results:** MIMIC-IV included 5,764 ICU stays from 5,141 patients (28-day in-hospital mortality 15.0%; 1,478 with a differential count) and eICU-CRD 2,517 (in-hospital mortality 16.3%). Component missingness was 45–75%. After FDR correction and multiple imputation, SIRI was associated with mortality in both databases (MIMIC-IV hazard ratio [HR] 1.18, FDR-adjusted q=0.011; eICU-CRD odds ratio [OR] 1.51, q<0.001); NLR (HR 1.15, q=0.045; OR 1.39, q<0.001) and SII (both q≤0.032) also replicated, whereas PLR was significant only in MIMIC-IV and PNI was inconsistent. Associations were robust to the landmark choice (eICU-CRD 48-hour landmark HR: SIRI 1.50, NLR 1.39, SII 1.33; all q≤0.001), to counting post-discharge deaths and to SIRI extreme values; incremental discrimination was small (change in concordance index (C-index) or area under the curve ≤0.03). **Conclusion:** Across two independent ICU databases, SIRI showed the most consistent association with short-term mortality, and NLR and SII also replicated. Effect sizes were modest and incremental discrimination was limited; these inexpensive, routinely available indices may provide adjunctive prognostic information but should not be regarded as standalone prediction tools.

Keywords: Heart Failure; Acute Kidney Injury; Cardio-Renal Syndrome; Inflammation; Mortality

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1. Introduction

Acute heart failure (AHF) complicated by acute kidney injury (AKI), type 1 cardiorenal syndrome, is an exceptionally high-risk phenotype in the intensive care unit (ICU), with short-term mortality frequently exceeding 15–25% (1, 2). Systemic inflammation is increasingly implicated in the acute cardiorenal cycle (3, 4), and several composite indices derived from the routine complete blood count, the neutrophil-to-lymphocyte ratio (NLR) (5), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII) (6), systemic inflammation response index (SIRI) (7), and the albumin-based prognostic nutritional index (PNI) (8), have each been associated with mortality in heart-failure or kidney-disease cohorts when studied in isolation (9-12).

Two gaps motivate this work. First, most reports derive from a single database (13), so it is unclear which indices replicate across independent ICU populations. Second, these indices require a differential white-cell count, which in ICU practice is ordered selectively and is therefore frequently missing; analyses restricted to complete cases may be affected by this selection, yet the sensitivity of published associations to missing-data handling is rarely examined. This study aimed to compare five indices across two ICU databases with explicit missing-data analyses.

2. Methods

2.1. *Study design and setting*

This retrospective cohort study used two de-identified ICU databases: the Medical Information Mart for Intensive Care IV (MIMIC-IV) v3.1 (derivation) (14) and the eICU Collaborative Research Database (eICU-CRD v2.0; replication) (15). We compared the five indices across two independent ICU databases and, rather than relying on complete cases alone, examined complete-case and formally imputed analyses side by side, together with sensitivity analyses for the choice of time origin and for extreme values.

The secondary analysis was exempt from institutional review board review; data access followed the required training and data-use agreements. Analyses used R 4.6.0 (mice, survival) and Python 3.12; the random seed was fixed and analysis code,

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SQL, and imputation diagnostics are provided (see Data Availability). Reporting follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for cohort studies.

2.2. *Participants and definitions*

Adults (≥18 years) with concomitant AHF and AKI during the index ICU stay (first ICU stay of each hospital admission) were included. AHF was defined by acute/acute-on-chronic heart-failure International Classification of Diseases (ICD) codes (present at baseline). AKI was defined by the MIMIC-IV-derived Kidney Disease: Improving Global Outcomes (KDIGO) stage ≥1 (16) recorded within the first 48 hours after ICU admission; because eligibility is therefore determined over the first 48 hours, the primary time origin was a 48-hour landmark (patients alive and in the ICU at 48 h; follow-up measured from the landmark), which aligns the start of follow-up with the point at which case status is established. Exposures were taken from the first complete blood count within 24 hours of admission in MIMIC-IV; in eICU-CRD, in which laboratory results are time-stamped as offsets and repeated same-day values are common, the median of values within the first 24 hours was used. In eICU-CRD, AHF was operationalized from diagnosis strings, the APACHE admission diagnosis, or ICD codes recorded within 24 hours of unit admission, and AKI from an AKI diagnosis or a serum creatinine rise of ≥0.3 mg/dL (≥26.5 μmol/L) or ≥1.5-fold within 48 hours (a creatinine-based KDIGO criterion; urine output is not reliably available). Because eICU-CRD records vital status only until hospital discharge, the primary replication analysis used the full eligible cohort and in-hospital mortality; to align eligibility and time origin with MIMIC-IV, the same 48-hour landmark (alive and in the ICU at 48 hours) was applied in additional sensitivity analyses (Section 2.5).

2.3. *Study size*

No a priori sample-size calculation was performed: the study size was fixed by the number of eligible patients in each database, and all consecutive eligible ICU stays were included (Figure 1). Adequacy was judged from the number of outcome events per model parameter. In MIMIC-IV complete-case models, 132–231 deaths were available for 14 parameters (approximately 9–17 events per parameter; the lower value applies only to PNI, whose complete-case estimate is therefore interpreted cautiously), and in eICU-CRD complete-case models 77–97 deaths for 15 parameters (approximately 5–6 events per parameter, because lactate was missing in 70% of patients; the eICU-CRD complete-case estimates are therefore imprecise and are interpreted alongside the imputed analyses). With 231 events, a Cox model has 80% power at a two-sided α of 0.05 to detect a per- standard deviation (SD) hazard ratio (HR) of approximately 1.20. The multiple-imputation analyses retained the full landmark cohort (MIMIC-IV n=5,764, 864 deaths) and the full eICU-CRD cohort (n=2,517, 411 deaths), although the effective information is reduced in proportion to the fraction of missing information.

2.4. *Indices, outcomes, and covariates*

The five indices were computed from admission blood counts and albumin as neutrophils/lymphocytes ratio (NLR); platelets/lymphocytes ratio (PLR); platelets × neutrophils/lymphocytes (SII); neutrophils × monocytes/lymphocytes (SIRI); and albumin (g/L) + 5 × lymphocytes (PNI), with all cell counts expressed as absolute counts ($\times 10^9$/L), log(x+1)-transformed and standardized to unit standard deviation (SD) within each cohort independently (cohort-specific parameters; MIMIC-derived parameters were not applied to eICU-CRD).

The primary outcome was in-hospital death within 28 days of ICU admission in MIMIC-IV, analyzed from the 48-hour landmark (patients discharged alive before day 28 were regarded as event-free to day 28) or in-hospital mortality (eICU-CRD).

A pre-specified clinical covariate set was used comprising age, sex, illness severity (first-day Sequential Organ Failure Assessment [SOFA] score in MIMIC-IV; Acute Physiology and Chronic Health Evaluation [APACHE] IVa score in eICU-CRD), routine laboratory values (creatinine, urea nitrogen, hemoglobin, lactate) and comorbidities (MIMIC-IV: diabetes with and without complications, renal disease, malignancy, severe liver disease, from the Charlson components; eICU-CRD: diabetes, hypertension, coronary artery disease, chronic kidney disease, chronic obstructive pulmonary disease, liver disease, malignancy, from the past-history table). Maximum KDIGO stage within 48 hours was additionally included in MIMIC-IV; it is not available in eICU-CRD.

2.5. *Statistical analysis*

Baseline characteristics were summarized as mean ± SD, median (interquartile range) or n (%) and compared between survivors and non-survivors with the Mann–Whitney U test or Welch's t-test (continuous variables) and the χ^2 test (categorical variables); laboratory values are reported in SI units. Each index (per SD) was entered separately into a multivariable Cox (MIMIC-IV) or logistic (eICU-CRD) model; collinearity was quantified by variance inflation factors (VIF). Because the indices were highly missing, two analyses were carried out as complementary primary analyses under different missing-data assumptions: (i) complete-case analysis, and (ii) formal multiple imputation by chained equations (R mice (17); m=100; predictive mean matching of the log(x+1)-transformed raw blood-count components, absolute neutrophils, lymphocytes, monocytes, platelets, albumin, with the five indices derived passively within each completed dataset; the Cox imputation model included the event indicator and the Nelson–Aalen cumulative hazard (18)). In MIMIC-IV, absolute neutrophil, lymphocyte and monocyte counts are reported directly by the laboratory; in eICU-CRD, in which the differential is reported as percentages, absolute counts were first calculated as white-cell count × percentage/100. Only absolute counts were imputed; percentages and the indices themselves were never imputed directly. Estimates were pooled by Rubin's rules (19), reporting the fraction of missing information (FMI), relative efficiency, and Monte-Carlo error; multiplicity was controlled by the Benjamini–Hochberg false-discovery rate (FDR) (20) across the five indices within each analysis, and FDR-adjusted P values are reported as q-values. Multiple imputation relies on a missing-at-random assumption and, given the high FMI, is not assumed to be less biased than complete-case analysis; the two are reported side by side (19). Discrimination was summarized by the concordance index (C-index) (21) (MIMIC-IV) or area under the receiver operating characteristic (ROC) curve (AUC) (eICU-CRD), and calibration by the calibration slope and Brier score.

Additional sensitivity analyses. Analyses added after the primary analysis, and reported as sensitivity analyses rather than pre-specified, comprised: (i) alternative time origins (72-hour landmark and no landmark); (ii) SIRI extreme-value handling (99th-percentile winsorization, exclusion of the top 1%, and

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exclusion of high-influence observations by DFBETAs (standardized change in the coefficient when each observation is deleted)), with restricted cubic splines to check monotonicity; (iii) a comparison of patients with and without an available differential count to characterize the missing-data mechanism; (iv) in eICU-CRD, restriction to the 48-hour landmark cohort (alive and in the ICU at 48 hours), analyzed for in-hospital mortality (logistic regression) and, harmonized with the MIMIC-IV primary analysis, for in-hospital death within 28 days of ICU admission from the landmark (Cox regression), by multiple imputation with the same specification as the primary eICU-CRD analysis (identical covariates, m=100), with complete-case analysis as a secondary check; (v) a description of the deaths occurring among patients excluded by the landmark; (vi) in MIMIC-IV, all-cause death within 28 days of ICU admission, adding post-discharge deaths identified from the recorded date of death (patients.dod) to in-hospital deaths; and (vii) cluster-robust standard errors by patient, because some patients contributed more than one hospital admission.

3. Results

3.1. *Cohorts*

Participant flow is shown in Figure 1. Of 8,200 AHF–AKI ICU stays in MIMIC-IV (KDIGO stage 1, 2 and 3 within 48 hours in 2,918 [35.6%], 3,578 [43.6%] and 1,704 [20.8%], respectively), 2,436 died or were discharged from the ICU within 48 hours, leaving 5,764 ICU stays (5,141 patients) in the 48-hour landmark cohort (864 in-hospital deaths by day 28; 15.0%), who formed the multiple-imputation population; 1,478 (25.6%) had a computable differential count and contributed to complete-case models (analytic n 615–1,341 per index after complete covariates; 132–231 deaths).

The eICU-CRD cohort comprised 2,517 patients (411 in-hospital deaths; 16.3%; complete-case analytic n 292–397 per index; 77–97 deaths), of whom 1,260 (50.1%) had a differential count and 1,438 were alive and in the ICU at 48 hours.

Table 1 compares survivors and non-survivors in the MIMIC-IV landmark cohort and the eICU-CRD primary cohort. In both databases, non-survivors were older, had higher illness-severity scores, urea, lactate and white-cell count, lower lymphocyte counts and albumin, and higher NLR, SII and SIRI, and more often received invasive mechanical ventilation and vasopressors within the first 48 hours (all p<0.001). In MIMIC-IV, non-survivors also more often had KDIGO stage 3 AKI (39.1% vs 21.7%), higher creatinine, lower hemoglobin and more frequent renal disease, malignancy, severe liver disease and renal replacement therapy (14.1% vs 7.6%); in eICU-CRD, renal replacement therapy was used equally often (15.3% vs 15.5%), creatinine and hemoglobin were similar, malignancy was more frequent, and diabetes (39.2% vs 50.3%), hypertension and chronic kidney disease were less frequent among non-survivors. Missingness of the differential-derived indices was high (74–75% in MIMIC-IV, 45–51% in eICU-CRD), motivating the missing-data analyses below.

3.2. *Collinearity*

The blood-count indices were correlated: the variance inflation factor (VIF) of the log-transformed indices was 8.0 (SII), 5.8 (NLR), 4.0 (PLR) and 3.3 (SIRI) in MIMIC-IV and comparable in eICU-CRD, so indices were modeled separately rather than jointly.

3.3. *Associations with mortality: complete-case and multiple imputation*

In MIMIC-IV, after FDR correction, SIRI, PLR and NLR were associated with 28-day in-hospital mortality in complete cases, and SIRI, PLR, SII, PNI and NLR were associated under multiple imputation; the NLR association was at the significance boundary in the imputed analysis (q=0.045). All indices satisfied the proportional-hazards assumption and added little discrimination (change in C-index [ΔC-index] ≤0.014). Calibration was adequate (slope ≈1.0; Brier ≈0.13). Fractions of missing information were high (0.68–0.77), indicating that a large share of the uncertainty derives from missing data (Table 2).

3.4. *Cross-database replication (eICU-CRD)*

In eICU-CRD, SIRI, NLR and SII were associated with in-hospital mortality after FDR correction in both complete-case and imputed analyses, whereas PLR was not associated and PNI was at most borderline (Table 3). Across the two databases, SIRI retained statistical significance most consistently across databases and missing-data approaches; this description concerns replication consistency, not a formal head-to-head comparison of effect sizes. NLR showed the same direction of association in both databases, and SII replicated under multiple imputation. PLR replicated only in MIMIC-IV and PNI was inconsistent across databases and missing-data assumptions. Hazard ratios and odds ratios (ORs) were not compared quantitatively because they arise from different outcome models and time scales.

3.5. *Sensitivity analyses*

Associations were stable across time origins: MIMIC-IV complete-case hazard ratios were near-identical under 48-hour, 72-hour, and no-landmark definitions (e.g., SIRI 1.23, 1.26, 1.29; NLR 1.19, 1.24, 1.20; Table 4). The SIRI association was not driven by extreme values: hazard ratios were 1.23 unadjusted for extreme values, 1.22 with 99th-percentile winsorization, 1.23 excluding the top 1%, and 1.18 after excluding 222 high-influence observations (all p≤0.03), and the spline relationship was monotonic (P-nonlinear=1.00). Patients with an available differential count had higher illness severity (SOFA 6.5 vs 5.3), higher lactate (2.5 vs 2.3 mmol/L) and slightly higher 28-day mortality (16% vs 14%), and were younger (70.9 vs 73.1 years) (all p<0.01 versus those without), indicating that testing was associated with clinical condition; this does not establish that data are missing not at random or fix the direction of any complete-case bias.

In eICU-CRD, 1,079 of the 2,517 patients were excluded from the landmark cohort: 1,078 died or left the ICU within 48 hours of admission, and one had no follow-up after the landmark because in-hospital death was recorded at or before 48 hours. In total, 119 patients died within 48 hours (29.0% of all in-hospital deaths). The 48-hour landmark cohort comprised 1,438 patients (248 in-hospital deaths; 238 within 28 days of ICU admission). Using the same multiple-imputation specification as the primary eICU-CRD analysis (m=100; FMI 0.38–0.47), the associations were not attenuated by the landmark (Table 5): per-SD odds ratios for in-hospital mortality were 1.63 (95% confidence interval [CI] 1.34–1.98) for SIRI, 1.46 (1.19–1.78) for NLR and 1.37 (1.13–1.66) for SII (all q≤0.002), compared with 1.51, 1.39 and 1.31 in the full cohort (Table 3). In the harmonized Cox analysis of in-hospital death within 28 days from the landmark, the same time origin, outcome, and model as in MIMIC-IV, the hazard ratios were 1.50 (1.27–1.76) for SIRI, 1.39 (1.17–1.65) for NLR and 1.33 (1.13–1.58) for SII (all q≤0.001), whereas PLR and PNI were not associated. Complete-case landmark analyses, restricted to 257–280 patients mainly by missing lactate, gave similar point estimates (SIRI

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OR 1.84 [1.29–2.63]; NLR 1.39; SII 1.37), with only SIRI meeting the FDR threshold. In MIMIC-IV, counting all-cause deaths within 28 days added 326 post-discharge deaths (1,190 vs 864 events); complete-case associations were similar or stronger (per-SD HR: SIRI 1.24 [95% CI 1.10–1.40], NLR 1.23 [1.09–1.39], SII 1.19 [1.03–1.36], PLR 1.28 [1.14–1.45], PNI 0.58 [0.38–0.88]; all q≤0.016; Table 5). Accounting for repeat admissions (5,764 stays from 5,141 patients) with cluster-robust standard errors left all complete-case estimates and their significance unchanged.

4. Discussion

Across two independent ICU databases of AHF complicated by AKI, inflammatory blood-count indices were associated with short-term mortality, but the strength and consistency of the evidence differed by index. SIRI retained statistical significance most consistently across both databases and the two missing-data approaches. This wording denotes consistency of replication rather than a formal ranking or head-to-head comparison of effect sizes; such comparisons were deliberately avoided because the indices were highly collinear and were fitted in separate models. NLR was strongly associated in eICU-CRD and directionally consistent in MIMIC-IV, though at the significance boundary in the imputed MIMIC-IV analysis; SII also replicated under multiple imputation. PLR was associated only in MIMIC-IV, and PNI was inconsistent across databases and missing-data assumptions, in keeping with albumin behaving as an acute-phase reactant (22, 23) and being the most frequently missing component. The Cox hazard ratios and logistic odds ratios are not directly comparable, so cross-database interpretation is limited to direction and replication consistency.

Our findings are consistent with, and extend, previous single-database reports. In 3,964 elderly patients with heart failure from MIMIC-III, the highest SIRI tertile was associated with higher 90-day mortality (adjusted HR 1.41, 95% CI 1.18–1.68) and with a greater need for renal replacement therapy (24), and in 1,448 patients with acute decompensated heart failure in southern China, each SD increase in SIRI was associated with higher 30-day mortality (HR 1.21, 95% CI 1.02–1.44) (25), an effect of similar magnitude to the per-SD estimates observed here. For SII, Tang et al. reported an adjusted HR of 1.23 (95% CI 1.04–1.45) for 30-day mortality in the highest tertile among 4,606 critically ill patients with congestive heart failure (13), and Jia et al. described a J-shaped association between SII and in-hospital mortality in 10,764 critically ill patients with AKI from MIMIC-IV (26). A meta-analysis of NLR in heart failure reported pooled HRs of 1.12 per unit increase and 1.77 for high versus low NLR (9), in keeping with the NLR associations observed in both databases. By contrast, although a meta-analysis linked lower PNI to worse outcomes in heart failure (11), PNI was inconsistent in our analysis, plausibly because albumin was the most frequently missing component and behaves as an acute-phase reactant in critical illness (22, 23). Most previous studies examined a single index, in a single database, in patients with either heart failure or AKI, and relied on complete cases. By assessing five indices together in the combined AHF–AKI phenotype, replicating them in an independent multicenter database and testing robustness to missing data, the present study suggests that SIRI provides the most reproducible prognostic signal among these indices in type 1 cardiorenal syndrome, whereas the evidence for PLR and PNI did not replicate.

Two features distinguish this analysis from prior single-database reports. First, replication across MIMIC-IV and eICU-CRD, with different outcomes, case-mix, and coding, provides more information about generalizability than any single cohort, although the differing outcomes (28-day in-hospital vs in-hospital mortality) mean this is a cross-database replication rather than validation of one fixed model. We emphasize that the eICU-CRD analysis constitutes conceptual validation of the direction and consistency of the associations, not validation of a fixed model or of its predictive performance across databases. Notably, when eICU-CRD was restricted to the same 48-hour landmark and analyzed with the same outcome and model as MIMIC-IV, the associations of SIRI, NLR and SII persisted under multiple imputation, indicating that the absence of a landmark in the primary eICU-CRD analysis did not drive the replication. Second, because the indices were missing in a large majority of patients, we did not rely on complete cases alone: complete-case and formally imputed analyses were examined together. Reassuringly, the associations for SIRI, NLR and SII persisted under multiple imputation; however, the high fractions of missing information (up to ~0.8) show that a substantial part of the uncertainty is attributable to missing data, and multiple imputation rests on a missing-at-random assumption that cannot be verified. The observation that testing was associated with illness severity is consistent with, but does not prove, a non-random mechanism.

Clinically, these indices are inexpensive and immediately available, but their incremental discrimination over routine data was small (ΔC-index/ΔAUC ≤0.03). They may offer supplementary prognostic information but should not be treated as standalone prediction tools, and the modest effect sizes argue against strong claims of clinical utility.

4.1. *Limitations*

AHF and AKI were defined administratively/from derived KDIGO staging rather than by adjudication; AKI eligibility used the first 48 hours, and although the 48-hour landmark aligns follow-up with case ascertainment and results were robust to the landmark choice in both databases, residual time-related misclassification cannot be excluded. The etiology of AKI could not be adjudicated in either database; we therefore report KDIGO stage as a descriptive proxy only, and in eICU-CRD AKI was identified from diagnoses or creatinine alone, without urine-output criteria or formal staging. eICU-CRD records vital status only until hospital discharge, and the primary MIMIC-IV outcome likewise captured in-hospital deaths, so both endpoints may be influenced by discharge and transfer practices; the all-cause 28-day analysis in MIMIC-IV, which added 326 post-discharge deaths and yielded similar or stronger associations, partly addresses this, whereas post-discharge deaths could not be ascertained in eICU-CRD. Some patients contributed more than one admission, although cluster-robust standard errors did not change the results. Exposure timing differed slightly between databases (first value in MIMIC-IV versus the first-day median in eICU-CRD). Biomarker missingness was high and its mechanism uncertain; the two databases used different outcomes and severity scores; and the analysis is retrospective and observational, so residual confounding remains. Illness-severity scores and lactate may lie partly on a causal pathway linking systemic inflammation to mortality; consequently, the adjusted estimates should be interpreted as conditional associations rather than total causal effects. Discrimination and calibration statistics were apparent esti-

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mates without optimism correction or bootstrap internal validation because prediction-model development was not the primary objective. The findings are associational and hypothesis-generating and require prospective confirmation in cohorts with systematically collected differential counts.

5. Conclusions

Across two independent ICU databases, SIRI demonstrated the most consistent association with short-term mortality after multiple imputation and correction for multiple testing, while NLR and SII also showed cross-database replication. Effect sizes were modest, incremental discrimination was limited, and the high fractions of missing information warrant cautious interpretation. These routinely available indices may provide inexpensive adjunctive prognostic information but should not be regarded as standalone prediction tools.

6. Declarations

6.1. *Acknowledgments*

The author thanks the MIT Laboratory for Computational Physiology for developing and maintaining MIMIC-IV, the eICU Research Program and Philips Healthcare for making eICU-CRD available, and PhysioNet for hosting both databases. The author is grateful to the patients whose de-identified data made this study possible.

6.2. *Conflict of interests*

The author declares no competing interests.

6.3. *Funding and supports*

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6.4. *Authors' contributions*

X.Z. is the sole author and conceived the study, extracted and analyzed the data, and wrote the manuscript. Public extraction SQL, analysis code, aggregate results, and environment documentation are available at https://github.com/marcbunel31/acute-cardiorenal-inflammatory-indices.

6.5. *Ethical statement*

MIMIC-IV and eICU-CRD are de-identified, publicly available databases; this secondary analysis was exempt from institutional review board review.

6.6. *Informed consent*

Not applicable. The requirement for informed consent was waived because MIMIC-IV and eICU-CRD contain only de-identified data.

6.7. *Availability of supporting data*

MIMIC-IV and eICU-CRD are available to credentialed users via PhysioNet under their respective data-use agreements. Extraction SQL, analysis scripts, the fixed random seed, software versions, aggregate results, and multiple-imputation diagnostics are publicly available at https://github.com/marcbunel31/acute-cardiorenal-inflammatory-indices; the extraction add-ons and scripts for the revision analyses are provided in Supplementary File 1. Patient-level data and imputed patient-level datasets are not distributed.

6.8. *Using artificial intelligence chatbots statement*

Generative AI was used to assist with language editing and code debugging. All statistical code, outputs, and interpretations were independently reviewed and verified by the author. No AI tool was used to generate or modify the study data.

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Table 1: Baseline characteristics by vital status in the MIMIC-IV 48-hour landmark cohort (in-hospital death within 28 days of ICU admission) and the eICU-CRD primary replication cohort (in-hospital death)

Characteristic	MIMIC-IV, 48-h landmark cohort (n=5,764)			eICU-CRD, eligible cohort (n=2,517)		
	Survivors n=4,900	Non-survivors n=864	P	Survivors n=2,106	Non-survivors n=411	P
Age, years	71.2 ± 13.6	75.8 ± 11.9	<0.001	68.8 ± 14.2	73.0 ± 14.2	<0.001
Male	2,713 (55.4)	497 (57.5)	0.255	1,104 (52.4)	236 (57.4)	0.071
SOFA (MIMIC-IV) / APACHE IVa (eICU-CRD)	5 (3–8)	7 (5–10)	<0.001	61 (48–73)	78 (64–104)	<0.001
KDIGO stage within 48 h, †						
Stage 1	1,538 (31.4)	189 (21.9)		1,022 (48.5)	221 (53.8)	
Stage 2	2,297 (46.9)	337 (39.0)		76 (3.6)	22 (5.4)	
Stage 3	1,065 (21.7)	338 (39.1)	<0.001	472 (22.4)	74 (18.0)	0.016
Creatinine criterion not met (AKI by diagnosis)	—	—		495 (23.5)	81 (19.7)	
Insufficient creatinine measurements	—	—		41 (1.9)	13 (3.2)	
Comorbidities, ‡						
Hypertension	3,896 (79.5)	689 (79.7)	0.911	1,459 (69.3)	256 (62.3)	0.006
Diabetes	2,211 (45.1)	387 (44.8)	0.886	1,060 (50.3)	161 (39.2)	<0.001
Chronic kidney/renal disease	2,188 (44.7)	460 (53.2)	<0.001	470 (22.3)	66 (16.1)	0.006
Myocardial infarction / coronary artery disease	1,845 (37.7)	364 (42.1)	0.014	440 (20.9)	98 (23.8)	0.204
Chronic pulmonary disease	1,925 (39.3)	317 (36.7)	0.160	523 (24.8)	100 (24.3)	0.878
Cerebrovascular disease	618 (12.6)	155 (17.9)	<0.001	370 (17.6)	83 (20.2)	0.231
Malignancy	438 (8.9)	135 (15.6)	<0.001	248 (11.8)	72 (17.5)	0.002
Liver disease (MIMIC-IV: severe)	125 (2.6)	50 (5.8)	<0.001	40 (1.9)	9 (2.2)	0.846
Laboratory values (first 24 h), median (IQR)						
Creatinine, µmol/L	115 (88–194)	159 (106–256)	<0.001	183 (124–304)	188 (132–283)	0.767
Urea, mmol/L	10.4 (6.8–16.8)	14.6 (9.3–22.5)	<0.001	12.9 (8.9–19.3)	15.2 (10.6–21.9)	<0.001
Lactate, mmol/L	1.7 (1.2–2.6)	2.0 (1.4–3.1)	<0.001	1.40 (1.00–2.27)	2.20 (1.48–5.03)	<0.001
Hemoglobin, g/L	102 (86–120)	99 (85–114)	<0.001	103 (88–118)	104 (88–121)	0.202
White blood cells, $\times 10^9$/L	10.9 (7.9–15.2)	12.0 (8.5–17.0)	<0.001	9.40 (7.00–12.60)	11.82 (8.08–17.30)	<0.001
Neutrophils, $\times 10^9$/L	10.1 (6.9–14.7)	10.7 (6.9–15.9)	0.175	7.43 (5.13–10.34)	10.28 (6.87–14.19)	<0.001
Lymphocytes, $\times 10^9$/L	1.10 (0.66–1.85)	0.81 (0.49–1.34)	<0.001	0.84 (0.54–1.26)	0.71 (0.41–1.10)	<0.001
Monocytes, $\times 10^9$/L	0.72 (0.44–1.07)	0.77 (0.49–1.15)	0.076	0.60 (0.35–0.86)	0.70 (0.43–1.02)	0.002
Platelets, $\times 10^9$/L	195 (145–259)	197 (135–258)	0.339	189 (144–244)	183 (128–242)	0.082
Albumin, g/L	32 (29–36)	30 (26–35)	<0.001	30.0 (26.0–34.0)	28.0 (23.0–33.0)	<0.001
Organ support (first 48 h), §						
Invasive mechanical ventilation	2,332 (47.6)	491 (56.8)	<0.001	682 (32.4)	232 (56.4)	<0.001
Vasopressor	2,011 (41.0)	456 (52.8)	<0.001	326 (15.5)	191 (46.5)	<0.001

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Characteristic	MIMIC-IV, 48-h landmark cohort (n=5,764)			eICU-CRD, eligible cohort (n=2,517)		
	Survivors n=4,900	Non-survivors n=864	P	Survivors n=2,106	Non-survivors n=411	P
Inotrope	561 (11.5)	139 (16.1)	<0.001	248 (11.8)	85 (20.7)	<0.001
Any renal replacement therapy	371 (7.6)	122 (14.1)	<0.001	326 (15.5)	63 (15.3)	0.998
CRRT	139 (2.8)	80 (9.3)	<0.001	20 (0.9)	15 (3.6)	<0.001
Inflammatory indices						
NLR	8.6 (5.0–15.7)	12.1 (6.5–26.8)	<0.001	8.46 (5.11–15.17)	12.61 (7.30–23.33)	<0.001
PLR	165 (80–294)	221 (113–403)	<0.001	224 (140–355)	249 (144–437)	0.056
SII	1483 (757–3224)	2246 (986–5072)	<0.001	1635 (844–3238)	2298 (1155–4636)	<0.001
SIRI	5.8 (2.6–13.2)	9.3 (4.3–19.9)	<0.001	4.58 (2.31–8.91)	8.52 (4.61–19.39)	<0.001
PNI	37.0 (32.5–41.5)	35.2 (30.4–39.6)	0.004	34.9 (30.6–39.8)	32.4 (27.0–36.9)	<0.001

Data are presented as mean ± standard deviation, frequency (%), or median (interquartile range [IQR]). P values: Welch's t-test for age, Mann–Whitney U test for other continuous variables, and χ^2 test for categorical variables. Laboratory values are in SI units. Missing data: MIMIC-IV albumin 65%, lactate 24%, differential-derived values 74–75% (PNI 88%); eICU-CRD albumin 47%, lactate 70%, differential-derived values 45–51% (PNI 66%), APACHE IVa 14%; other variables ≤11%. Summaries use available values. †eICU-CRD: approximation from serum creatinine only (pairs of values from 24 h before to 48 h after unit admission; stage 3 by the ≥4.0 mg/dL criterion only with an acute rise), with patients who met the AKI definition by diagnosis alone or had fewer than two creatinine values shown separately. §MIMIC-IV: any ventilation, vasoactive-agent or renal replacement therapy episode overlapping the first 48 h of the ICU stay; eICU-CRD: treatment, infusion or ventilation records within the first 48 h (ventilation started from 24 h before unit admission, to capture ongoing ventilation). ‡MIMIC-IV: Charlson comorbidity components (ICD codes); hypertension was identified from ICD-9/10 diagnosis codes and is not part of the Charlson score. eICU-CRD: past-history table; cerebrovascular disease was identified using stroke, cerebrovascular disease, CVA, TIA and transient ischemic attack terms, and stays without a matching past-history record were coded as absent. —, not applicable (all MIMIC-IV stays met KDIGO criteria by design). CRRT: continuous renal replacement therapy. Abbreviations: MIMIC-IV: Medical Information Mart for Intensive Care IV; eICU-CRD: eICU Collaborative Research Database; SD: standard deviation; SOFA: Sequential Organ Failure Assessment; APACHE: Acute Physiology and Chronic Health Evaluation; KDIGO: Kidney Disease: Improving Global Outcomes; AKI: acute kidney injury; COPD: chronic obstructive pulmonary disease; CVA: cerebrovascular accident; TIA: transient ischemic attack; ICD: International Classification of Diseases; SI: International System of Units; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; SII: systemic immune-inflammation index; SIRI: systemic inflammation response index; PNI: prognostic nutritional index.

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Table 2: MIMIC-IV: adjusted per-SD associations with 28-day in-hospital mortality (Cox), complete-case and multiple imputation, with FDR-adjusted q-values

Index	CC HR (95% CI)	CC q	MI HR (95% CI)	MI q	FMI
SIRI	1.23 (1.08–1.40)	0.005	1.18 (1.05–1.33)	0.011	0.68
PLR	1.24 (1.09–1.42)	0.005	1.22 (1.07–1.39)	0.011	0.73
SII	1.17 (1.00–1.37)	0.055	1.16 (1.03–1.32)	0.032	0.69
PNI	0.74 (0.51–1.09)	0.127	0.75 (0.58–0.97)	0.033	0.72
NLR	1.19 (1.04–1.36)	0.021	1.15 (1.00–1.32)	0.045	0.77

CC: complete-case (n=615–1,341; 132–231 deaths); MI: multiple imputation (n=5,764; m=100); FMI: fraction of missing information. Models adjusted for the covariates listed in Section 2.4. MIMIC-IV: Medical Information Mart for Intensive Care IV; HR: hazard ratio; CI: confidence interval; SD: standard deviation; q: Benjamini–Hochberg false-discovery-rate (FDR)-adjusted P value; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; SII: systemic immune-inflammation index; SIRI: systemic inflammation response index; PNI: prognostic nutritional index.

Table 3: eICU-CRD: adjusted per-SD associations with in-hospital mortality (logistic), complete-case and multiple imputation, with FDR-adjusted q-values

Index	CC OR (95% CI)	CC q	MI OR (95% CI)	MI q	FMI
SIRI	1.75 (1.29–2.38)	0.002	1.51 (1.28–1.78)	<0.001	0.48
NLR	1.51 (1.13–2.03)	0.014	1.39 (1.18–1.64)	<0.001	0.48
SII	1.44 (1.07–1.94)	0.029	1.31 (1.12–1.54)	0.001	0.40
PNI	0.92 (0.67–1.25)	0.59	0.84 (0.71–0.99)	0.050	0.43
PLR	1.22 (0.93–1.61)	0.19	1.12 (0.96–1.31)	0.135	0.40

CC: complete-case (n=292–397; 77–97 deaths), and the covariate set listed in Section 2.4; MI: multiple imputation (n=2,517; m=100); FMI: fraction of missing information; eICU-CRD: eICU Collaborative Research Database; OR: odds ratio; CI: confidence interval; SD: standard deviation; q: Benjamini–Hochberg false-discovery-rate (FDR)-adjusted P value; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; SII: systemic immune-inflammation index; SIRI: systemic inflammation response index; PNI: prognostic nutritional index.

Table 4: MIMIC-IV time-origin sensitivity (complete-case hazard ratios)

Index	48-h (primary)	72-h	No landmark
NLR	1.19	1.24	1.20
PLR	1.24	1.26	1.23
SII	1.17	1.22	1.18
SIRI	1.23	1.26	1.29
PNI	0.74	0.67	0.76

Values are complete-case hazard ratios per standard deviation (SD) of the log-transformed index. 48-h (primary) and 72-h: follow-up starting from a landmark 48 or 72 hours after ICU admission; No landmark: follow-up from ICU admission. MIMIC-IV: Medical Information Mart for Intensive Care IV; ICU: intensive care unit; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; SII: systemic immune-inflammation index; SIRI: systemic inflammation response index; PNI: prognostic nutritional index.

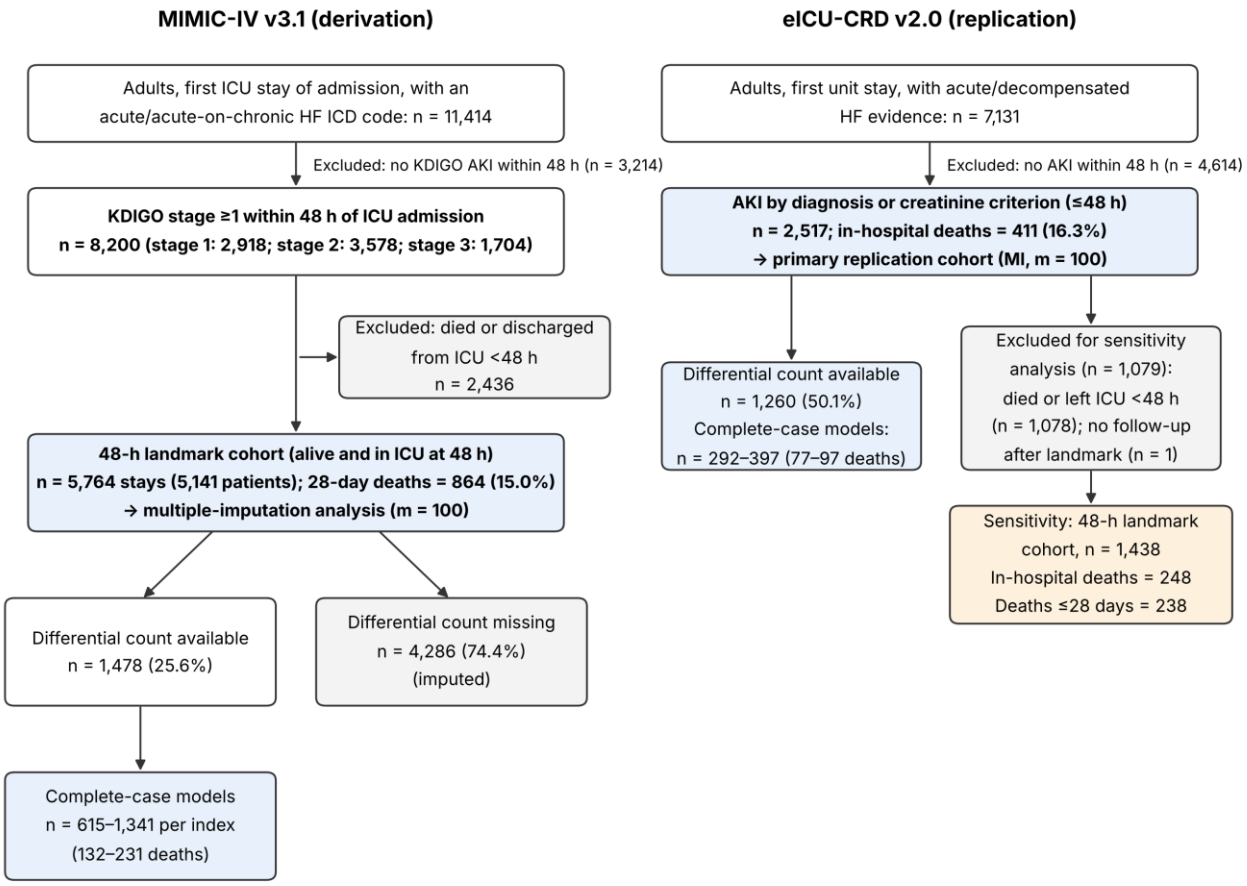
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Table 5: Additional sensitivity analyses: 48-hour landmark and harmonized outcome in eICU-CRD (multiple imputation), and all-cause 28-day mortality in MIMIC-IV (complete-case); adjusted estimate per SD, 95% CI, FDR q

Cohort / outcome	SIRI	NLR	SII	PLR	PNI
eICU-CRD 48-h landmark in-hospital death, MI (OR)	1.63	1.46	1.37	1.13	0.83
	(1.34–1.98); <0.001	(1.19–1.78); <0.001	(1.13–1.66); 0.002	(0.93–1.37); 0.22	(0.68–1.02); 0.089
n (deaths); FMI	1,438 (248); 0.41	1,438	1,438	1,438	1,438
		(248); 0.45	(248); 0.38	(248); 0.46	(248); 0.44
eICU-CRD 48-h landmark in-hospital death ≤28 days, MI (HR, harmonized)	1.50	1.39	1.33 (1.13–1.58);	1.11	0.88
	(1.27–1.76); <0.001	(1.17–1.65); <0.001	0.001	(0.94–1.32); 0.23	(0.74–1.05); 0.21
n (deaths); FMI	1,438 (238); 0.41	1,438	1,438	1,438	1,438
		(238); 0.47	(238); 0.39	(238); 0.45	(238); 0.47
MIMIC-IV 48-h landmark all-cause death ≤28 days, CC (HR)	1.24	1.23	1.19	1.28	0.58
	(1.10–1.40); 0.001	(1.09–1.39); 0.002	(1.03–1.36); 0.016	(1.14–1.45); <0.001	(0.38–0.88); 0.012
n (deaths)	1,313 (296)	1,336 (298)	1,336 (298)	1,341 (298)	615 (174)

Each cell: estimate (95% CI); Benjamini–Hochberg q across the five indices within each analysis. eICU-CRD models used the same covariates and imputation specification as Table 3 (MI); the 48-hour landmark cohort comprised 1,438 patients alive and in the ICU at 48 hours. Harmonized: same time origin, outcome (in-hospital death within 28 days of ICU admission) and model (Cox) as the MIMIC-IV primary analysis. MIMIC-IV: same covariates as Table 2; all-cause deaths include post-discharge deaths identified from the recorded date of death (patients.dod). OR: odds ratio (logistic); HR: hazard ratio (Cox); MI: multiple imputation (m=100); CC: complete-case; FMI: fraction of missing information; MIMIC-IV: Medical Information Mart for Intensive Care IV; eICU-CRD: eICU Collaborative Research Database; ICU: intensive care unit; CI: confidence interval; SD: standard deviation; q: Benjamini–Hochberg false-discovery-rate (FDR)-adjusted P value; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; SII: systemic immune-inflammation index; SIRI: systemic inflammation response index; PNI: prognostic nutritional index.

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AHF/HF, (acute) heart failure; AKI, acute kidney injury; KDIGO, Kidney Disease: Improving Global Outcomes; MI, multiple imputation.

Figure 1: Flow diagram of patient selection in MIMIC-IV and eICU-CRD (STROBE). The MIMIC-IV 48-hour landmark cohort formed the multiple-imputation population; patients with an available differential count contributed to complete-case models. In eICU-CRD, the full eligible cohort was analyzed, with the 48-hour landmark applied as a sensitivity analysis. AKI: acute kidney injury; MIMIC-IV: Medical Information Mart for Intensive Care IV; eICU-CRD: eICU Collaborative Research Database; STROBE: Strengthening the Reporting of Observational Studies in Epidemiology; HF: heart failure; KDIGO: Kidney Disease: Improving Global Outcomes; ICU: intensive care unit; MI: multiple imputation.

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