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From Potassium Snapshots to Time in Range During Diabetic Ketoacidosis: A Three-Cohort Study

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Abstract

Background

Potassium management during diabetic ketoacidosis (DKA) is inherently dynamic, yet observational studies commonly characterize potassium exposure using isolated values or discrete episodes of dyskalemia. Whether time spent within the guideline-recommended potassium range captures reproducible clinical information during early DKA treatment is uncertain.

Methods

We conducted a multicohort observational study using MIMIC-IV, eICU, and NWICU. Adults with DKA were eligible if they had at least three serum potassium measurements during the first 24 hours of ICU care and at least 12 hours between the first and last eligible measurement. Potassium time in target range (K-TIR) was the proportion of the observed monitoring interval in which linearly interpolated serum potassium was within the prespecified guideline-anchored range of 4.0–5.0 mmol/L. The primary outcome was ICU length of stay of at least 72 hours. The same prespecified multivariable model was fitted independently in each database, and adjusted effects per 10-percentage-point increase in K-TIR were synthesized by random-effects meta-analysis. Restricted cubic splines assessed nonlinearity.

Results

The final cohorts comprised 1,672 ICU stays; primary complete-case models included 1,639 stays and 381 prolonged-stay events. Adjusted odds ratios (ORs) per 10-percentage-point increase in K-TIR were below 1.0 in all three databases: 0.977 (95% CI, 0.932–1.025) in MIMIC-IV, 0.935 (95% CI, 0.811–1.079) in eICU, and 0.929 (95% CI, 0.853–1.010) in NWICU. The pooled OR was 0.963 (95% CI, 0.925–1.002; P = 0.062; I2 = 0.0%), indicating directional concordance across cohorts but statistical uncertainty around the magnitude of association. Restricted cubic splines showed no evidence of nonlinearity. For invasive mechanical ventilation, the pooled OR was 0.956 (95% CI, 0.912–1.002; P = 0.062; I2 = 0.0%). A cross-database adjusted mortality estimate was not estimable because of sparse events and incomplete outcome availability.

Conclusions

Guideline-defined K-TIR can be operationalized as a longitudinal phenotype of early potassium management in DKA. Its association with prolonged ICU stay was directionally consistent across three independent critical-care databases, but the pooled estimate remained compatible with no association. These findings support further evaluation of K-TIR as a measurement framework while leaving unresolved whether it is a marker of recovery or a modifiable treatment target.

Introduction

Potassium management during diabetic ketoacidosis (DKA) is inherently longitudinal. Total-body potassium depletion can coexist with normal or elevated serum potassium at presentation, while insulin administration, correction of acidosis, volume expansion, and ongoing urinary losses can rapidly alter extracellular potassium during treatment (1–3). Current international guidance accordingly describes potassium management as a process over time: replacement is initiated as serum potassium falls and treatment aims to maintain concentrations within approximately 4.0–5.0 mmol/L with repeated biochemical monitoring (1–3). A potassium value at ICU admission therefore captures only a snapshot of a treatment process that is intrinsically dynamic.

Most observational studies nevertheless reduce potassium exposure to snapshots or extrema. Severe treatment-associated hypokalemia has been associated with higher in-hospital mortality, deviations from potassium replacement protocols with longer DKA treatment, and admission potassium or subsequent hypokalemia with time to metabolic recovery or hospital stay (4–7). These findings establish the clinical relevance of potassium, but they also expose a measurement mismatch: potassium is managed as a range that should be maintained during treatment, whereas it is often analyzed as one value, one extreme, or one dyskalemic episode.

Time in range offers a way to align measurement with that clinical process by integrating both concentration and duration. In general ICU populations, potassium variability and time outside reference ranges have been associated with adverse outcomes (8–10), and potassium time in target range has recently been evaluated in heart failure using linear interpolation between serial measurements (11, 12). However, a clinically intuitive longitudinal metric is not necessarily clinically informative. Whether guideline-defined potassium time in target range (K-TIR) captures reproducible information during the rapidly changing physiology of DKA treatment remains uncertain, particularly across clinical data environments with different monitoring practices, case mix, and data structures.

We therefore evaluated early K-TIR across three independent ICU databases using a common prespecified exposure definition and adjustment framework. Rather than pooling patient-level data, we estimated associations separately in MIMIC-IV, eICU, and NWICU and synthesized database-specific effects, using cross-cohort concordance as a test of reproducibility. We hypothesized that a greater proportion of observed time with serum potassium within the guideline-anchored 4.0–5.0 mmol/L range during the first 24 hours of ICU care would be associated with lower odds of an ICU stay of at least 72 hours. Secondary analyses examined invasive mechanical ventilation, in-hospital mortality, and potential nonlinearity.

Materials and methods

Study design and data sources

We conducted a multicohort observational study using three independent critical-care databases: MIMIC-IV, eICU, and NWICU. MIMIC-IV contains deidentified electronic health record data from a large academic medical center, and eICU is a multicenter US critical-care database (13, 14). The purpose of the multicohort design was not simply to increase sample size, but to apply the same scientific question independently across distinct clinical data environments. Patient-level data were therefore not pooled; each database was analyzed under a common prespecified framework and database-specific effect estimates were synthesized after model fitting.

Database-specific variable mappings were harmonized to a common analytic definition while retaining the source-specific data structure. The final analysis specification, exposure definition, covariate set, and outcomes were fixed before cross-database synthesis.

Study population

The study population consisted of adults with DKA admitted to an ICU. The first eligible ICU stay per patient was retained. To ensure that K-TIR represented a longitudinal exposure rather than an isolated laboratory value, inclusion required at least three eligible serum potassium measurements during ICU hours 0–24 and at least 12 hours between the first and last eligible potassium measurements. Potassium values underwent prespecified plausibility screening and were harmonized to mmol/L before exposure construction.

Exposure

The primary exposure was K-TIR during the first 24 hours of ICU care. The target interval was prespecified as 4.0–5.0 mmol/L (1, 3). Potassium concentration between consecutive measurements was estimated by linear interpolation (12). K-TIR was calculated as the proportion of the observed interval between the first and last eligible potassium measurements during which the interpolated concentration was within the target range. The denominator was therefore the actual monitoring interval, not an assumed complete 24-hour period. The primary effect estimate was expressed per 10-percentage-point increase in K-TIR.

Outcomes

The primary outcome was ICU length of stay of at least 72 hours. Secondary outcomes were invasive mechanical ventilation and in-hospital mortality. Mortality models were not forced when event counts or authoritative outcome availability were insufficient for reliable adjusted estimation.

Covariates

The harmonized primary adjustment set included age, sex, initial serum potassium, initial glucose, initial creatinine, initial sodium, initial anion gap, and initial acid-base severity. The prespecified hierarchy preferred pH, with bicarbonate used as a cross-database fallback when pH could not be harmonized. Bicarbonate was therefore used in all final primary models. Covariates were selected a priori rather than through stepwise or significance-based selection.

Statistical analysis

Each database was analyzed independently. Multivariable logistic regression estimated the adjusted association between K-TIR and the primary outcome, with results reported as ORs and 95% CIs per 10-percentage-point increase in K-TIR. The primary models used complete cases for the prespecified exposure, outcome, and covariates.

Database-specific log-ORs were summarized with a DerSimonian-Laird random-effects model. Between-database heterogeneity was assessed with Cochran Q and I2. Potential nonlinear associations were examined separately within each database using restricted cubic splines with four prespecified knots at the 0.05, 0.35, 0.65, and 0.95 quantiles of K-TIR; the database-specific median K-TIR served as the reference. Overall and nonlinearity likelihood-ratio tests were calculated.

The same harmonized adjustment set was used for invasive mechanical ventilation. Mortality models were classified as not estimable when sparse events or unavailable authoritative outcome data precluded reliable adjusted estimation. All effect estimates were interpreted as associations rather than causal effects.

Ethics and data governance

Use of MIMIC-IV and eICU followed the access and data-use requirements of their respective repositories (13, 14).

This study was a secondary analysis of existing deidentified critical-care databases and involved no direct participant contact or intervention. The collection of patient information and creation of MIMIC-IV were reviewed by the Institutional Review Board of Beth Israel Deaconess Medical Center, which approved the data-sharing initiative and granted a waiver of informed consent. The eICU-CRD is deidentified in accordance with the HIPAA Safe Harbor standard; access requires human-research training and a data use agreement. The Northwestern ICU (NWICU) project was approved by the Northwestern University Institutional Review Board, which granted a waiver of informed consent, and release of data was authorized by the Northwestern Medicine Data Steward. The authors used the databases in accordance with the applicable PhysioNet credentialing and data-use requirements. No direct identifiers were available to the authors.

Results

Study population

Across the three databases, 1,672 ICU stays met the final analytic cohort definition: 968 in MIMIC-IV, 174 in eICU, and 530 in NWICU. Despite use of a common exposure definition, the distribution of K-TIR differed across data environments: median K-TIR was 46.14% [IQR, 14.69–77.66] in MIMIC-IV, 25.57% [IQR, 0-56.63] in eICU, and 24.96% [IQR, 0-51.10] in NWICU. The median number of potassium measurements during the first 24 hours was 5 in each database, with median observed potassium spans of approximately 18 hours (Table 1). The harmonized primary complete-case analysis included 1,639 stays and 381 events of ICU length of stay of at least 72 hours. Bicarbonate served as the common acid-base severity covariate in all three primary models.

Table 1
Baseline characteristics of the database-specific analytic cohorts

Characteristic	MIMIC-IV	eICU	NWICU
Cohort size, N	968	174	530
Age, years	52.23 ± 18.47; 53 [37, 67]	46.62 ± 16.90; 49 [31.25, 58]	46.52 ± 18.04; 45 [31, 60]
Initial potassium, mmol/L	4.29 ± 0.85; 4.20 [3.78, 4.70]	4.08 ± 0.76; 4.00 [3.60, 4.40]	4.06 ± 0.74; 4.00 [3.60, 4.50]
Initial glucose	306.19 ± 201.94; 258.5 [189, 364]	362.92 ± 238.89; 284.5 [202.75, 465.75]	373.14 ± 240.04; 300.5 [209.25, 464.75]
Initial creatinine	1.76 ± 1.80; 1.20 [0.80, 1.90]	1.65 ± 1.30; 1.20 [0.88, 2.00]	1.75 ± 1.92; 1.20 [0.90, 1.80]
Initial sodium	138.04 ± 6.82; 137 [134, 141]	136.87 ± 6.93; 137 [133, 141]	136.25 ± 6.76; 136 [132, 140]
Initial anion gap	19.87 ± 6.34; 19 [16, 23]	18.89 ± 7.56; 18 [13, 23.25]	18.99 ± 7.05; 18 [14, 24]
Initial bicarbonate	16.15 ± 5.94; 17 [12, 20]	13.78 ± 5.94; 13.5 [9, 18]	14.05 ± 6.29; 14 [9, 19]
K-TIR, %	46.93 ± 34.90; 46.14 [14.69, 77.66]	33.51 ± 33.53; 25.57 [0, 56.63]	31.51 ± 30.66; 24.96 [0, 51.10]
Potassium measurements in first 24 h	4.86 ± 1.49; 5 [4, 6]	4.87 ± 1.66; 5 [4, 6]	5.70 ± 2.13; 5 [4, 7]
Observed potassium span, h	18.32 ± 2.85; 18.70 [16.33, 20.55]	17.88 ± 2.76; 17.94 [16.05, 19.83]	18.19 ± 2.84; 18.46 [15.99, 20.33]
ICU LOS ≥ 72 h, n/N (%)	230/968 (23.8%)	41/174 (23.6%)	115/530 (21.7%)
Invasive mechanical ventilation, n/N (%)	180/968 (18.6%)	18/174 (10.3%)	39/530 (7.4%)

Continuous variables are presented as mean ± SD; median [Q1, Q3]. K-TIR denotes potassium time in target range. Sex was included as a prespecified binary adjustment variable in the fitted models. Sex-specific counts are not reported because the retained harmonized analysis file did not preserve the source label mapping for the binary sex variable; no male/female category interpretation was inferred.

Primary outcome

The database-specific adjusted estimates were directionally concordant despite differences in cohort size and K-TIR distribution. The adjusted OR per 10-percentage-point increase in early K-TIR was 0.977 (95% CI, 0.932–1.025; P = 0.338) in MIMIC-IV, 0.935 (95% CI, 0.811–1.079; P = 0.357) in eICU, and 0.929 (95% CI, 0.853–1.010; P = 0.086) in NWICU (Table 2; Fig. 1). The random-effects pooled OR was 0.963 (95% CI, 0.925–1.002; P = 0.062). No statistical heterogeneity was detected (I2 = 0.0%; Q = 1.219; P =

0.544). Thus, all three point estimates lay below 1.0, but every database-specific confidence interval and the pooled confidence interval included the null; the observed pattern was reproducible in direction but not statistically definitive in magnitude.

Table 2
Cross-database association between early potassium time in target range and ICU length of stay of at least 72 hours

Database	N	Events	Adjusted OR	95% CI	P value
MIMIC-IV	968	230	0.977	0.932–1.025	0.338
eICU	146	37	0.935	0.811–1.079	0.357
NWICU	525	114	0.929	0.853–1.010	0.086
Random-effects pooled	1639	381	0.963	0.925–1.002	0.062
Odds ratios are reported per 10-percentage-point increase in K-TIR.					

Abbreviations: CI, confidence interval; ICU, intensive care unit; K-TIR, potassium time in target range; OR, odds ratio. Random-effects heterogeneity: I2=0.0%; Q=1.219; P=0.544.

Restricted cubic spline analysis

Restricted cubic spline analyses did not identify evidence of a nonlinear association between K-TIR and prolonged ICU stay. Overall and nonlinearity P values were 0.613 and 0.642 in MIMIC-IV, 0.275 and 0.222 in eICU, and 0.082 and 0.161 in NWICU, respectively (Supplementary Table S1). Within the available data, these analyses provided no basis for replacing the prespecified guideline-anchored range with an outcome-derived threshold.

Secondary outcomes

The secondary analysis of invasive mechanical ventilation showed a pattern similar to the primary outcome. Adjusted ORs per 10-percentage-point increase in K-TIR were 0.963 (95% CI, 0.915–1.015) in MIMIC-IV, 0.953 (95% CI, 0.774–1.173) in eICU, and 0.903 (95% CI, 0.784–1.041) in NWICU. The pooled OR was 0.956 (95% CI, 0.912–1.002; P = 0.062; I2 = 0.0%) (Fig. 2; Supplementary Table S2). As with the primary outcome, the point estimates were directionally aligned while the pooled confidence interval included the null.

Mortality could not provide a comparable cross-database replication test. The MIMIC-IV analysis dataset did not contain an authoritative hospital mortality outcome for this analysis, and the eICU complete-case sample contained only two deaths. In NWICU, 10 deaths were available; the exploratory adjusted OR was 0.601 (95% CI, 0.384–0.939; P = 0.025). Because this estimate arose from a single database with sparse events and could not be synthesized across cohorts, it was treated as exploratory and was not used to define the study conclusion (Supplementary Table S3).

Discussion

Principal findings

Across three independent critical-care databases, higher guideline-defined K-TIR during early DKA treatment yielded lower adjusted point estimates for prolonged ICU stay in every cohort, although the pooled confidence interval included the null. The principal finding is therefore not evidence that increasing K-TIR improves outcome. Rather, a longitudinal, guideline-anchored potassium phenotype could be operationalized across distinct ICU data environments and produced directionally reproducible clinical information. The absence of detected nonlinearity and the similarly directed mechanical-ventilation estimates further support the coherence of the observed pattern, while the statistical uncertainty of the pooled estimates defines its evidentiary boundary.

Relation to previous evidence

The rationale for K-TIR begins with a mismatch between DKA physiology and conventional measurement. Potassium during DKA treatment is a trajectory, not a fixed state: insulin-mediated intracellular shifts, correction of acidosis, osmotic diuresis, renal function, fluid therapy, and potassium replacement can change serum concentrations over hours (1–3, 18). Previous DKA studies have appropriately identified clinically important associations involving severe hypokalemia, replacement practices, admission potassium, and the depth of subsequent hypokalemia (4–7). However, two patients with the same admission potassium can experience very different subsequent potassium courses. A longitudinal measure therefore asks a different question from a baseline value or extreme: how consistently was potassium within the clinically intended range during the observed treatment interval?

Time-in-range methodology provides a natural way to represent that question. Potassium variability and time outside reference ranges have been associated with outcomes in broader ICU populations (8–10), and potassium time in target range has been studied in heart failure (11). The conceptual contribution here is not the invention of time in range itself, but its use to translate a guideline-defined DKA treatment target into a time-integrated exposure. The 4.0–5.0 mmol/L range was specified from clinical guidance rather than selected from the observed outcome distribution (1, 3), preserving a direct link between the measurement framework and the clinical process it is intended to describe.

Clinical interpretation

K-TIR should therefore be interpreted first as a longitudinal phenotype, not as a validated prognostic tool. It captures information that an admission value or simple mean may miss: a patient can begin within range yet spend much of the subsequent interval outside it, whereas a brief excursion can be followed by sustained control. The present study did not test discrimination, calibration, or incremental prognostic value over conventional potassium summaries, and it cannot establish that K-TIR should be used for bedside risk stratification.

The distinction between phenotype, marker, and treatment target is especially important. Higher K-TIR may reflect more stable physiology, more effective potassium management, less severe illness, differences in renal function or treatment intensity, or some combination of these factors. It may therefore summarize the course of recovery rather than determine it. Only a design capable of separating treatment-induced changes in K-TIR from the underlying trajectory of illness could establish whether actively increasing K-TIR improves outcomes.

The pooled primary OR of 0.963 per 10-percentage-point increase in K-TIR corresponds to an approximately 3.7% lower odds estimate on the multiplicative odds scale, not a 3.7-percentage-point reduction in absolute risk. More importantly, the 95% CI included 1.0. The data therefore support neither a protective-effect claim nor a therapeutic threshold; they define a directionally reproducible signal whose magnitude remains uncertain.

Cross-database reproducibility

The multicohort architecture was intended to challenge, rather than merely enlarge, the association. MIMIC-IV, eICU, and NWICU differ in cohort composition, monitoring practice, and data-generating structure, yet all three database-specific point estimates for the primary outcome lay on the same side of the null. This directional concordance reduces the likelihood that the observed pattern is unique to one data source. It does not, however, establish transportability or eliminate biases shared by retrospective ICU data. Likewise, I2 = 0% with only three databases indicates no detected statistical heterogeneity, not proof of identical underlying effects.

Strengths and limitations

The study has several design strengths for evaluating a longitudinal phenotype: a clinically interpretable target specified before outcome analysis, serial measurements incorporated through a time-integrated exposure, a common covariate set selected a priori, independent database-specific estimation before meta-analytic synthesis, and restraint in treating the sparse single-database mortality finding as exploratory rather than confirmatory. Together, these features prioritize reproducibility of the measurement framework over outcome-driven optimization.

The limitations define what can and cannot be inferred. First, residual confounding by DKA severity (16, 20), insulin and fluid treatment, potassium replacement, renal function, precipitating illness, and local practice prevents causal interpretation; higher K-TIR may mark recovery rather than cause it. Second, potassium sampling was clinically driven, so informative monitoring can shape the estimated exposure and prevents equating K-TIR with continuously observed potassium control. Third, linear interpolation assumes a smooth trajectory between measurements and may miss rapid unobserved excursions. Fourth, ICU length of stay reflects discharge practice, bed availability, institutional workflow, and nonphysiologic factors in addition to clinical recovery (15, 19), limiting its interpretation as a purely biological endpoint. Fifth, sample size and outcome availability differed substantially across databases, particularly for mortality, and only three cohorts were available for heterogeneity assessment. Finally, K-TIR was not compared head-to-head with time below range, time above range, within-patient variability,

or other conventional potassium summaries. The present study therefore establishes neither incremental prognostic value nor superiority of K-TIR over simpler metrics.

Conclusions

In critically ill adults with DKA, guideline-defined potassium time in range during early treatment showed directionally consistent associations with prolonged ICU stay across three independent critical-care databases, although the pooled estimate remained statistically uncertain. These findings support K-TIR as a reproducible longitudinal phenotype for studying potassium management in DKA, not as an established prognostic tool or therapeutic target. Prospective work should determine whether K-TIR merely tracks recovery or represents a modifiable feature of care.

Declarations

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

During manuscript preparation, the authors used ChatGPT, GPT-5.6 Sol (OpenAI), for assistance with manuscript organization, language editing, and drafting support. The authors reviewed and verified the scientific content, numerical results, interpretations, citations, and final wording and take full responsibility for the submitted manuscript. Generative AI was not used to generate, alter, or analyze the study data or statistical results.

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Author Contribution

Zheng Yao: Conceptualization, Data curation, Formal analysis, Methodology, Software, Validation, Visualization, Writing – original draft, Writing – review & editing.Zhaotao Fang: Methodology, Validation, Clinical interpretation, Writing – review & editing.Shijia Zhu: Validation, Clinical interpretation, Literature review, Writing – review & editing.All authors read and approved the final manuscript.

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Not applicable.

Data availability statement

The existing datasets analyzed in this study are available through PhysioNet under the applicable credentialing, training, and data-use requirements: MIMIC-IV version 3.1, eICU Collaborative Research Database version 2.0, and NWICU version 0.1.0. Participant-level data are not redistributed by the authors because access is governed by the repositories' credentialing and data-use requirements. No new participant-level dataset was generated. Aggregate study results are reported in the article and Supplementary Material.

Ethics statement

This study was a secondary analysis of existing deidentified critical-care databases and involved no direct participant contact or intervention. The collection of patient information and creation of MIMIC-IV were reviewed by the Institutional Review Board of Beth Israel Deaconess Medical Center, which approved the data-sharing initiative and granted a waiver of informed consent. The eICU Collaborative Research Database is deidentified in accordance with the HIPAA Safe Harbor standard; access requires human-research training and a data use agreement. The Northwestern ICU project was approved by the Northwestern University Institutional Review Board, which granted a waiver of informed consent, and release of data was authorized by the Northwestern Medicine Data Steward. Zheng Yao obtained PhysioNet credentialing and accessed all databases in compliance with the corresponding data-use requirements. No direct identifiers were available to the authors.

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Figures

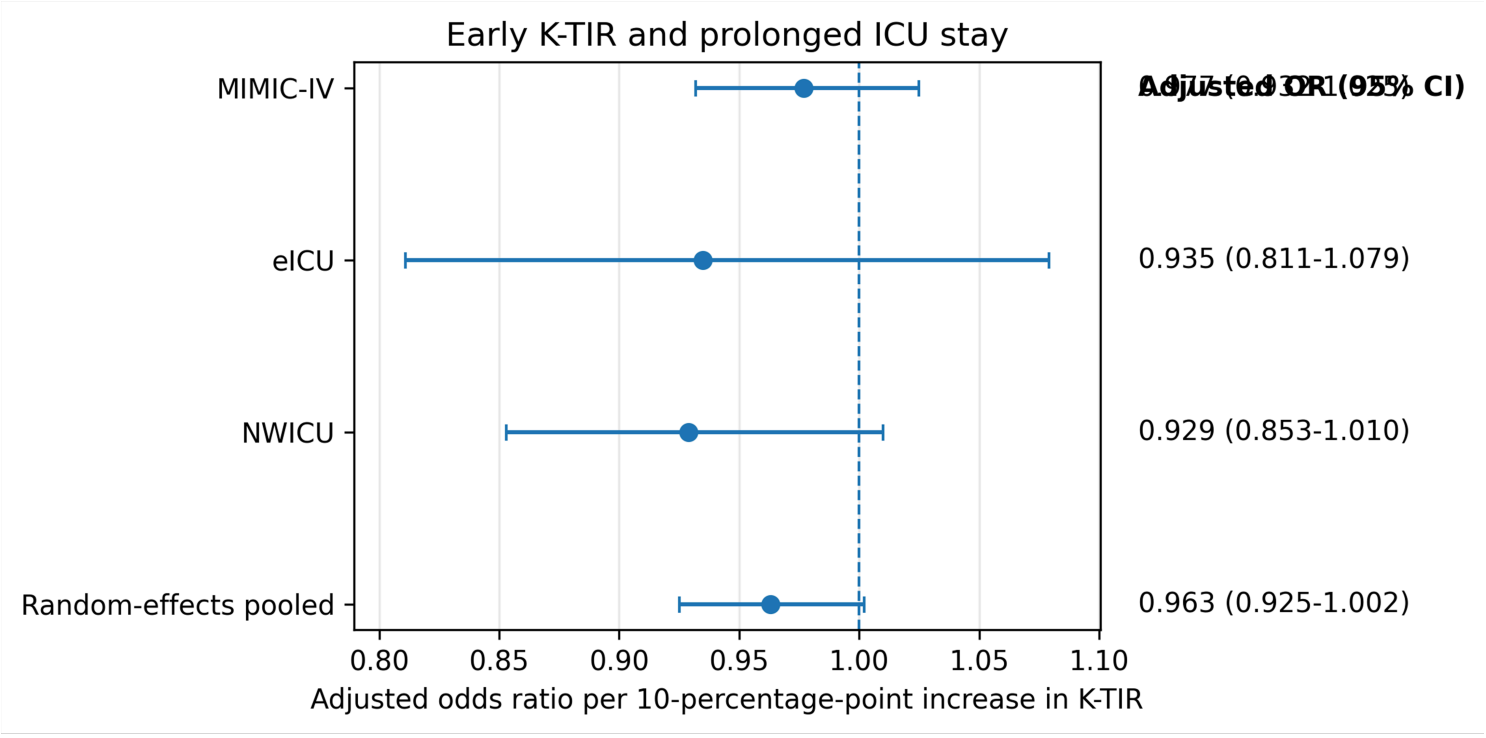


Figure 1

Cross-database reproducibility of the association between early potassium time in target range and ICU length of stay of at least 72 hours. Database-specific adjusted odds ratios and the random-effects pooled estimate are shown per 10-percentage-point increase in K-TIR. Point estimates were below 1.0 in all three databases; confidence intervals, including the pooled interval, crossed the null.

Alt text: Forest plot of adjusted odds ratios for ICU stay of at least 72 hours per 10-percentage-point increase in potassium time in target range across MIMIC-IV, eICU, and NWICU, with a random-effects pooled estimate. All database-specific point estimates are below 1.0, while confidence intervals cross 1.0.

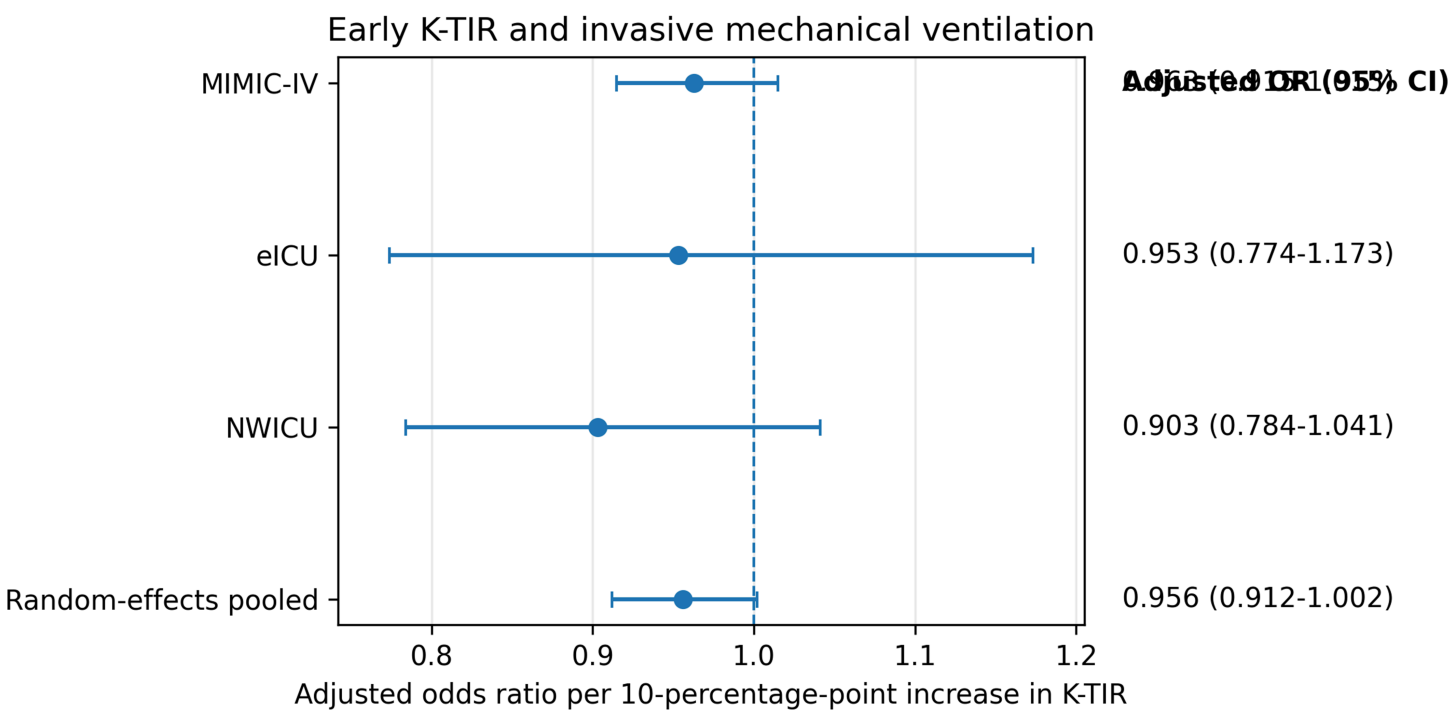


Figure 2

Early potassium time in target range and invasive mechanical ventilation across three ICU databases. Database-specific adjusted odds ratios and the random-effects pooled estimate are shown per 10-percentage-point increase in K-TIR.

Alt text: Forest plot of adjusted odds ratios for invasive mechanical ventilation per 10-percentage-point increase in potassium time in target range across MIMIC-IV, eICU, and NWICU, with a random-effects pooled estimate.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryMaterial.docx