

# Sex Differences in Acute Kidney Injury Risk and Outcomes - Insights from MIMIC-III and MIMIC-IV

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## Abstract

**Purpose:** Acute kidney injury (AKI) affects 13–18% of U.S. hospitalizations, with men showing higher incidence than women and worse Chronic Kidney Disease (CKD) and mortality. The biologic and clinical drivers of these sex differences remain unclear. We developed machine-learning models to predict AKI, and post-AKI CKD and death, and assessed common and sex-specific risk factors. **Methods:** We conducted a secondary analysis of MIMIC-III (2001–2012) and MIMIC-IV (2008–2019) adult ICU databases. Predictors included demographics, comorbidities, pre-event vital signs, laboratory values, medications, procedures, and clinical notes. We trained Elastic Net logistic, random forest, XGBoost, DNN, DCN, Transformer models in MIMIC-IV, and validated them in MIMIC-III. Performance was evaluated using AUC-ROC, accuracy, precision, recall, and F1. Sex–predictor interactions for AKI were interpreted using regression coefficients and H-statistics. Time from AKI to CKD and to death was analyzed using competing-risk models and DeepSurv. **Results:** In regression, higher creatinine, lower bicarbonate, and lower hemoglobin were more strongly associated with AKI in men; liver disease and widowed status increased risk in both sexes with modest attenuation in men. From H-statistics, sex modified the effects of age, insurance/marital status, Black race, vascular comorbidities, and creatinine. After AKI, CKD hazards increased with Black, unmarried status, cardiovascular comorbidities, and higher potassium in both sexes; effects were stronger in men for lower pH and higher creatinine, and in women for lower sodium. **Conclusion:** Our findings support sex-specific risk stratification and targeted prevention to reduce AKI-related CKD burden.

**Keywords:** Acute Kidney Injury, Sex Differences, Interaction Effect, Deep Learning

## 1 Introduction

Acute kidney injury (AKI), a critical and often overlooked condition, affects 13–18% of hospitalized patients and 1.5–2 million people annually in the United States [1, 2]. In-hospital men have higher incidence (15–20% vs 10–15% in women) [3] and are more likely to experience severe AKI, complications, and death. Within five years, approximately 50% of men with AKI develop chronic kidney disease (CKD) compared with 40% of women; post-AKI mortality is around 30% in men and 20% in women [2, 4]. These differences may reflect a greater burden of comorbidities such as hypertension and diabetes in men [4, 5].

Despite these disparities, mechanisms driving sex differences in AKI incidence and outcomes remain poorly characterized [6]. The Medical Information Mart for Intensive Care (MIMIC) databases provide ICU data to build and validate predictive models and to characterize overall AKI risk [7]. Leveraging these resources, we investigated sex differences in AKI and developed models to identify common and sex-specific risk factors for AKI and CKD.

Machine-learning (ML) models for AKI prediction have been emerged rapidly. A systematic review of 46 studies, many based on MIMIC, reported models ranging from random forests and gradient-boosting trees to deep neural networks, with AUC-ROC values from 0.49 to 0.99 [8]. However, common limitations included high risk of bias, poor calibration, suboptimal handling of missingness, scarce external validation, and limited emphasis on interpretability and translational clinical use.

In addition, existing ML work rarely treats sex as a biological and clinical modifier. Our study explicitly models sex-specific main effects and interactions to deliver interpretable, clinically applicable prediction of AKI, CKD, and mortality.

## 2 Method

### 2.1 Data Description

We used MIMIC-III (2001–2012) and MIMIC-IV (2008–2019), de-identified ICU EHRs from Beth Israel Deaconess Medical Center. MIMIC-III includes >50,000 adult ICU admissions for >38,000 patients; MIMIC-IV expands to >546,000 admissions for >364,000 patients with an updated schema and richer documentation. We also used MIMIC-IV-ED (2011–2019; >400,000 ED encounters) aligned to MIMIC-IV. Access was obtained via PhysioNet after required training and a data-use agreement. These databases provide extensive structured (demographics, vitals, labs, medications, procedures) and unstructured (clinical notes) data for AKI prediction and outcomes research [9, 10].

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## 2.2 Primary Outcomes and Subject Selection

We included patients aged 18 years or older. Incident AKI during hospitalization was defined by AKI diagnosis codes (ICD-9 584.\*, ICD-10 N17.\*) or KDIGO criteria (serum creatinine increase (i)  $\geq 0.3$  mg/dL within 48 h or (ii) to  $\geq 1.5\times$  baseline within 7 days). We excluded prior kidney transplant (ICD-9 V42.0; ICD-10 Z94.0), ESRD/dialysis dependence (ICD-9 585.6, V45.11, V56.\*; ICD-10 N18.6, Z99.2), and pre-existing CKD (ICD-9 585.1–585.5, 585.9; ICD-10 N18.1–N18.5, N18.9). For patients with multiple admissions, we retained the first admission with AKI for cases and the last admission without AKI for controls.

CKD was identified using ICD codes (ICD-9 585.1–585.5, 585.9; ICD-10 N18.1–N18.5, N18.9). Among patients with incident AKI, CKD required a diagnosis  $\geq 90$  days after the AKI admission. For those without CKD, we flagged post-CKD events (ESRD/dialysis/transplant)  $\geq 90$  days. Times to CKD/post-CKD were calculated from the AKI admission. Death and time to death were identified from discharge, ED records, and death dates. Patients without CKD/post-CKD/death required evidence of follow-up and were censored at last observed discharge day; individuals with no post-AKI encounters were excluded.

## 2.3 Candidate Predictor Variables

For AKI modeling, predictors included demographics, vital signs, laboratory results, medications, procedures, and pre-admission clinical notes (Table A1). To minimize post-outcome leakage, we excluded variables observable only after AKI onset (e.g., AKI stage, in-hospital treatments, length of stay) and omitted composite scores (Charlson, GCS, SAPS II, SOFA) because they are derived from included measurements and introduce collinearity.

To balance recency and availability, we applied clinically meaningful look-back windows pre-event: (i) laboratory tests within **7 days** before the AKI admission for cases or the most recent admission for non-AKI; (ii) vital signs within **48 hours** before admission; and (iii) medications and procedures within **6 months** before admission. Text features, when used, were limited to notes authored before the admission timestamp.

For CKD modeling, we defined three pre-event windows: 0–90, 91–180, and 181–365 days before CKD admission (or censoring) to separate short-, intermediate-, and long-term effects of laboratory and medication exposures; text inputs were excluded due to extreme imbalance.

Compared with prior work [8, 11], we incorporated broader data modalities (including nominal variables, longitudinal records, and unstructured texts), and restricted

all predictors to pre-event windows for AKI and CKD, to ensure temporal alignment between exposures and outcomes. This design reflects real-world decision-making and reduces the risk of incorporating post-diagnosis information and enabled a more accurate and interpretable modeling for predicting AKI and its downstream outcomes.

## 2.4 Data Pre-processing

Clinical notes were normalized (lowercasing, stopword removal, lemmatization) and embedded with SentenceTransformer (SBERT) to map semantically similar text to nearby vectors [12, 13]. Categorical predictors with very low prevalence ( $< 1\%$ ) were collapsed into clinically similar groups. Repeated labs and vitals within look-back windows were summarized by minimum, maximum, mean, standard deviation, most recent value, and count to mitigate noise and irregular sampling. Medication and procedure exposures were encoded in two windows (0–30 and 31–180 days pre-admission) to distinguish acute from chronic use. For CKD prediction, window-specific lab means (0–90, 91–180, 181–365 days) and any exposure indicator were created. Candidate predictors included demographics, insurance, comorbidities, labs, medications, procedures, and sex–predictor interactions.

## 2.5 AKI Risk Prediction Model

We developed AKI prediction models using Random Forests [14], XGBoost [15], a deep neural network (DNN) [16], Deep & Cross Network (DCN) [17, 18], and a Transformer [19]. These methods capture nonlinearities and interactions, handle collinearity and missingness, and scale to high-dimensional EHR data. For comparison, we fit an Elastic Net–regularized logistic regression [20]. To limit multicollinearity from summary statistics, we retained only pre-event means for labs and vitals in the regression model.

Models were trained on MIMIC-IV with a 60/20/20% train/validation/test split and externally validated on MIMIC-III. Performance was evaluated on test sets using AUC-ROC, accuracy, precision, recall, and F1-score.

## 2.6 Post-AKI Outcome Prediction Model

In a competing-risks framework, we fit a Fine–Gray subdistribution hazard model for CKD after AKI, treating death as the competing event. Because post-CKD events were rare, we merged them with CKD as late surrogates. Candidate predictors included demographics, medical history, pre-AKI 7-day mean biomarkers, and pre-AKI medications and procedures, plus sex $\times$ predictor interactions. We use Elastic Net combined with a stepwise selection (entry/stay  $p < 0.05$ ) for variable selection.

We also fit a deep learning Cox model (DeepSurv) for time-to-event outcomes [21], using baseline demographics/comorbidities and short-, intermediate-, and long-term biomarker exposures before AKI. Models were trained on MIMIC-IV and tested on MIMIC-III. Survival performance was evaluated with time-dependent AUC [22].

## 2.7 Predictor Explainability and Sex–Predictor Interaction

We quantified feature contributions using three complementary approaches: feature importance (FI), SHAP values, and Integrated Gradients (IG). For tree ensembles (Random Forests, XGBoost), FI was computed from gain/split improvements [14, 23]. For neural models (DNN, DCN, Transformer), we computed SHAP and IG attributions with  $m=50$  path steps from cohort-specific baselines (sex- and age-stratified medians;  $\pm 2$  years) [24–26]. Importances were aggregated across models for ranking.

Sex–predictor interactions were assessed directly in regression through interaction terms. To capture nonlinear interactions, we used the Friedman–Popescu  $H$ -statistic [27], which measures the fraction of prediction variance explained by the interaction beyond additive main effects (0 = none; larger values = stronger interaction). We applied  $H$  to sex–predictor pairs and used stratified sampling to scale partial-dependence evaluations on large EHR data.

## 2.8 Sensitivity Analyses

We performed sensitivity analyses to address missingness, feature availability, and case mix.

For AKI models, variables with  $> 70\%$  missingness were excluded. Remaining missing values were imputed using sex- and age-stratified ( $\pm 2$  years) medians. As a check, we applied multiple imputation (10 datasets) via sequential regression (SRMI/mice), assuming missing at random [28, 29].

Because transport-related injuries may represent a distinct clinical profile, we repeated AKI analyses after excluding automobile/transport accident encounters (ICD-9 E810–E829; ICD-10 V00–V89).

For CKD and mortality, we also evaluated 60-day event windows to account for potential delays in AKI time stamping.

# 3 Results

## 3.1 Study Cohort Characteristics

Table 1 summarizes cohort characteristics. In MIMIC-III, AKI occurred in 20.0% of eligible admissions (6,828/34,181); in MIMIC-IV, 13.1% (26,184/199,822). AKI patients were older (MIMIC-III:  $66.7 \pm 16.3$  vs  $62.1 \pm 17.8$  years; MIMIC-IV:  $64.1 \pm 16.7$  vs  $52.2 \pm 20.0$ ), male-dominant (56.6% and 56.4% in MIMIC-III and MIMIC-IV), and more often Black (MIMIC-III: 9.9% vs 6.1%; MIMIC-IV: 13.2% vs 12.4%). Marital status skewed toward widowed/divorced in AKI, and insurance toward Medicare (MIMIC-III: 61.4% vs 48.3%; MIMIC-IV: 54.5% vs 32.2%) with lower private coverage. Figure 1 shows higher AKI incidence in males across ages in both MIMIC; absolute rates were higher in ICU-only MIMIC-III, but male:female relative risk was similar across cohorts.

### 3.2 AKI Prediction Model

Figure 2 shows ROC curves of all models. XGBoost achieved the highest AUC-ROC in MIMIC-IV test data (0.927) and in external validation on MIMIC-III (0.829), which outperformed logistic regression by +0.076 and +0.055, respectively. In MIMIC-IV testing set, subsequent AUCs were Transformer (0.916), Random Forest (0.909), DNN (0.908), and DCN (0.904); in MIMIC-III, Random Forest (0.777), Logistic (0.774), DNN (0.764), Transformer (0.739), and DCN (0.723). All models degraded on external validation (AUC drop 0.077–0.181); logistic showed the smallest decline (−0.077), followed by XGBoost (−0.098). A demographics-only logistic reference yielded AUCs of 0.696 (MIMIC-IV) and 0.581 (MIMIC-III). Accuracy, precision/F1, and sensitivity/specificity tracked the AUC ranking (Table B); precision was modest across models given class imbalance.

### 3.3 Sex-Interaction Effects for AKI

Table 2 shows the odds ratio estimates of the main and interaction effects from the final logistic model. Serum creatinine was more strongly associated with AKI in men (OR=1.014 per mg/dL increase) than women (OR=1.003), consistent with biological differences in muscle mass and KDIGO thresholding. Liver disease history was strong risk in women (OR = 3.71) and in men (OR=3.04) with modest attenuation in men (interaction ROR = 0.82). Other sex modifications were modest: higher bicarbonate remained protective with slightly stronger effects in men (OR=0.91 vs. 0.93 per mmol/L); higher hemoglobin showed greater protection in women (OR=0.86 vs. 0.93 per g/dL); recent mechanical ventilation carried higher risk in men (OR=3.25 vs. 2.92); infection was strongly associated with AKI in both sexes (OR=3.48 and 3.26). Unadjusted distributions by sex/AKI status (Figure F3) were directionally consistent; infection history was sparsely captured in MIMIC-III.

Random-forest  $H$ -statistics (Figure D2) identified a dditional s ex interactions including age, race, insurance, and marital status, suggesting intersections of sex with aging, access to care, social context, and race. Cardiovascular comorbidities (hypertension, coronary artery disease, cerebrovascular disease) also ranked highly. Among biomarkers, 7-day mean creatinine showed the strongest interaction with sex. Because  $H$  captures nonlinear, non-additive structure that logistic regression may miss, these results complement our regression findings and motivate threshold-focused validation for sex-specific stratification.

Other main effects were clinically coherent: higher WBC and potassium increased AKI odds; higher sodium, platelets, and hemoglobin were protective. Hypertension, diabetes, coronary artery disease, COPD, cancer, heart failure, and obesity were independently associated with higher AKI risk; cerebrovascular disease was not. Associations with age, marital status, and Medicare coverage were expected. The positive association with male was not significant, probably because observed sex differences in AKI risk were captured by other predictors and their sex–interactions rather than by sex alone.

Sensitivity analyses (Table E) excluding transport-related admissions yielded slightly lower AUC in MIMIC-IV but higher in MIMIC-III. The widowed $\times$ male interaction dropped out, while a BUN $\times$ male interaction was selected with a stronger BUN effect in women. Multiple imputation (MICE) produced similar results; one difference was a protective association of married status in men not observed in women (Table E).

### 3.4 Risk Factors for CKD

Among AKI patients in MIMIC-IV, men had a slightly higher cumulative incidence of CKD (12.3% vs 12.0%) and developed CKD slightly earlier than women (median 1.84 vs 1.89 years). In MIMIC-III, fewer than 2% developed CKD during follow-up, precluding reliable sex comparisons.

CKD-free survival curves separated by sex in MIMIC-IV (Figure 1c). By 5 years after AKI, 3–4% more men had developed CKD than women; by 10 years, the gap widened to ~5%.

In Fine-Gray models of CKD after AKI (Table 3), risk increased with Black race (HR=1.15), divorced/widowed status (HR=1.18), hypertension (HR=1.27), diabetes (HR=1.59), coronary artery disease (HR=1.11), and heart failure (HR=1.41). Cancer, infection, and liver disease were associated with lower CKD hazards (HRs 0.63, 0.51, 0.73), likely reflecting competing mortality rather than renoprotection. Among 90-day labs, higher potassium increased CKD hazard (HR=1.04 per mmol/L).

Sex modified several effects on CKD: the cancer association was attenuated in men vs women (interaction HR=1.26,  $p = 0.024$ ); higher pH was protective in men (HR=0.66 per unit) but not women; higher sodium increased risk in men (HR=1.01 per mmol/L) but decreased risk in women (HR=0.99 per mmol/L); creatinine showed slightly stronger association in men (interaction HR=1.01 per mg/dL).

For death (Table 3), hazards increased with age (HR=1.02 per year), heart failure (HR=1.29), COPD (HR=1.19), cancer (HR=1.71), infection (HR=2.59), liver disease (HR=2.61), and cerebrovascular disease (HR=1.62). Higher WBC (HR=1.01 per unit), potassium (HR=1.03 per mmol/L), and creatinine (HR=1.004 per mg/dL) were also associated with increased mortality. Unmarried status showed HRs  $< 1$  vs married, likely due to competing CKD rather than true protection. Heart failure exhibited sex modification: no excess risk in men (HR=1.00) but higher risk in women (HR=1.29; interaction HR=0.78).

Because deaths were less completely captured in MIMIC-IV than in MIMIC-III, survival models trained in MIMIC-IV generalized poorly to MIMIC-III (AUC ~80% in MIMIC-IV vs 65–75% in MIMIC-III). Conversely, earlier deaths in MIMIC-III yielded fewer CKD events and less stable CKD prediction (AUC 55–65%; Figure G4).

DeepSurv resulted in higher time-dependent AUC than Fine-Gray but does not account for competing risks (Figure G5). In DeepSurv, the most recent biomarker values dominated CKD risk; sex modified effects of hypertension, cardiovascular disease, and potassium—patterns not detected by the competing-risk model (Figure H6). For death, DeepSurv identified similar major risk factors but did not detect sex modifiers.

## 4 Conclusion and Discussion

Our findings advance sex-aware views of AKI and post-AKI CKD: risk differences were driven largely by other predictors and their sex-interactions rather than sex alone. Key laboratory markers improved AKI and CKD discrimination and may support earlier identification of high-risk patients. The effects of several predictors, including creatinine, bicarbonate, and hemoglobin, were modified by sex, which can help inform targeted surveillance, medication stewardship, and identify more precise pathways.

This study has limitations. First, AKI timing was imprecise; exact diagnosis timestamps were unavailable, so AKI was anchored to admission, and incident CKD required a diagnosis  $\geq 90$  days later. This may underestimate time-to-event and attenuate associations. Second, phenotyping relied on ICU/ED encounters; outpatient CKD or events at other institutions may be missed, biasing estimates toward the null. Third, missingness, especially for labs and meds, was substantial. Primary imputation used sex- and age-specific medians, with similar results under multiple imputation; however, missingness may be informative and violate MAR assumption. Fourth, several predictors are correlated and susceptible to confounding by indication (e.g., WBC with infection; trauma with multiple risks). Sensitivity analyses excluding transport-related admissions showed similar performance and associations, but residual confounding may persist. Finally, MIMIC reflects critically ill populations; generalizability to non-ICU settings requires external validation.

Longitudinal data before the AKI index were sparse, so we did not encode full temporal trajectories; within-subject dynamics may be lost. Future work should incorporate richer pre-admission time series and prospectively evaluate sex-specific thresholds and alerts.

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## Statements and Declarations

- Competing interests: Authors declared no conflict of interest.
- Code availability: <https://github.com/noboundarystat/AKI-prediction-MIMIC>
- Author contribution: Both authors contributed to data acquisition and analysis, result interpretation, and manuscript writing.

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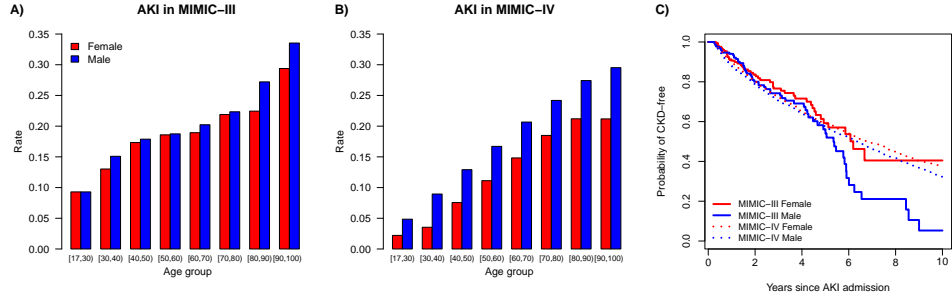
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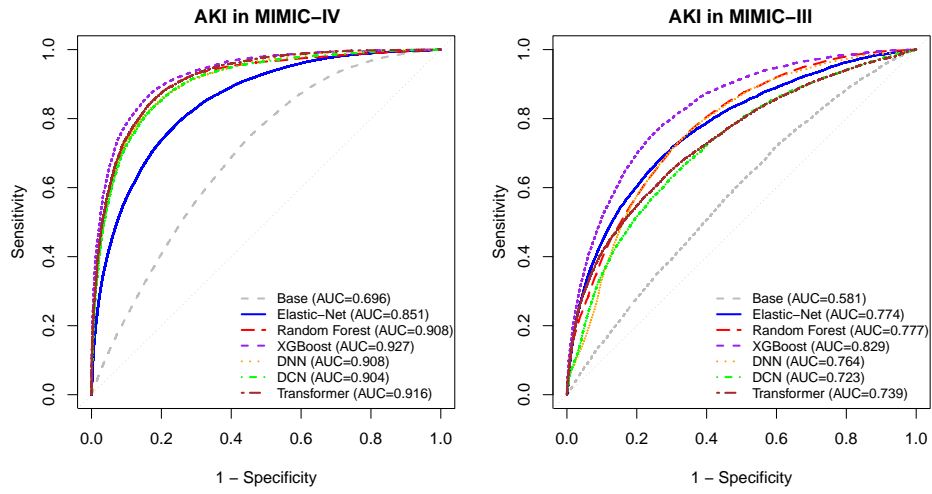
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**Fig. 1** AKI rates in age groups and CKD-free curves of males and females in MIMIC-III and MIMIC-IV



**Fig. 2** ROC of Prediction models for AKI in MIMIC-III and MIMIC-IV

**Table 1** Characteristics of Study Cohorts

Variable	MIMIC-III		MIMIC-IV	
	No AKI (N=27,353)	AKI (N=6,828)	No AKI (N=173,638)	AKI (N=26,184)
<b>Age</b> Mean $\pm$ SD	62.1 $\pm$ 17.8	66.7 $\pm$ 16.3	52.2 $\pm$ 20.0	64.1 $\pm$ 16.7
<b>Gender</b>				
Female	12,049 (44.1%)	2,965 (43.4%)	96,865 (55.8%)	11,408 (43.6%)
Male	15,304 (56.0%)	3,863 (56.6%)	76,773 (44.2%)	14,776 (56.4%)
<b>Race and Ethnicity</b>				
White	19,471 (71.2%)	4,889 (71.6%)	114,777 (66.1%)	17,451 (66.6%)
Black	1,682 (6.1%)	679 (9.9%)	21,613 (12.4%)	3,455 (13.2%)
Hispanic	930 (3.4%)	185 (2.7%)	10,102 (5.8%)	1,067 (4.1%)
Asian	635 (2.3%)	171 (2.5%)	8,195 (4.7%)	816 (3.1%)
Others	3,652 (13.4%)	716 (10.5%)	10,258 (5.9%)	2,391 (9.1%)
Unknown	983 (3.6%)	188 (2.8%)	8,693 (5.0%)	1,004 (3.8%)
<b>Marital Status</b>				
Married	13,357 (48.8%)	3,072 (45.0%)	74,208 (42.7%)	11,019 (42.1%)
Single	6,707 (24.5%)	1,684 (24.7%)	68,665 (39.5%)	8,010 (30.6%)
Widowed	3,444 (12.6%)	1,144 (16.8%)	12,836 (7.4%)	3,420 (13.1%)
Divorced/Separated	1,847 (6.7%)	548 (8.1%)	10,648 (6.1%)	1,938 (7.4%)
Others/Unknown	1,998 (7.3%)	380 (5.6%)	7,281 (4.2%)	1,797 (6.9%)
<b>Insurance</b>				
Private	10,479 (38.3%)	1,767 (25.9%)	74,288 (42.8%)	6,763 (25.8%)
Medicare	13,222 (48.3%)	4,193 (61.4%)	55,831 (32.2%)	14,279 (54.5%)
Assistant	3,652 (13.4%)	868 (12.7%)	32,005 (18.4%)	4,174 (15.9%)
Unknown	0 (0.0%)	0 (0.0%)	11,514 (6.6%)	968 (3.7%)
<b>Comorbidity</b>				
Hypertension	13,652 (49.9%)	3,537 (51.8%)	63,895 (36.8%)	16,038 (61.3%)
Diabetes	5,562 (20.3%)	1,973 (28.9%)	22,849 (13.2%)	7,446 (28.4%)
Coronary artery disease	7,903 (28.9%)	1,918 (28.1%)	19,818 (11.4%)	6,818 (26.0%)
Heart failure	4,477 (16.4%)	2,372 (34.7%)	9,487 (5.5%)	5,836 (22.3%)
COPD	4,492 (16.4%)	1,340 (19.6%)	14,700 (8.5%)	4,143 (15.8%)
Cancer	3,219 (11.8%)	1,223 (17.9%)	14,509 (8.4%)	5,182 (19.8%)
Infection	1,945 (7.1%)	2,340 (34.3%)	15,600 (9.0%)	9,224 (35.2%)
Liver disease	1,307 (4.8%)	1,324 (19.4%)	6,646 (3.8%)	4,822 (18.4%)
Cerebrovascular disease	1,994 (7.3%)	482 (7.1%)	5,469 (3.1%)	1,539 (5.9%)
Obesity	1,213 (4.4%)	405 (5.9%)	13,085 (7.5%)	3,094 (11.8%)
<b>AKI Outcomes</b>				
All-cause death	-	4,104 (60.1%)	-	4,265 (16.3%)
CKD after 90 days	-	113 (1.7%)	-	2,990 (11.4%)
ESRD/TX/Dialysis	-	23 (0.3%)	-	188 (0.7%)

**Table 2** Adjusted Effects for AKI in Study Cohort (sex-age-specific mean imputation)

Variable (units)	Odds Ratio (95% CI)	p-value
<b>Demographic</b>		
Age (per year)	1.012 (1.011, 1.013)	$< 2.2 \times 10^{-16}$
Male (vs. female)	1.125 (0.776, 1.629)	0.535
Other Race (vs. White)	0.954 (0.890, 1.023)	0.186
Single (vs. Married)	1.185 (1.142, 1.230)	$< 2.2 \times 10^{-16}$
Widowed (vs. Married)	1.210 (1.140, 1.285)	$3.9 \times 10^{-10}$
Unknown (vs. Married)	1.040 (0.959, 1.127)	0.344
Private Insurance (vs. Medicare)	0.905 (0.871, 0.940)	$3.3 \times 10^{-7}$
Unknown Insurance (vs. Medicare)	0.784 (0.724, 0.848)	$1.6 \times 10^{-9}$
<b>Medical History</b>		
Obesity	1.342 (1.277, 1.411)	$< 2.2 \times 10^{-16}$
Hypertension	1.432 (1.384, 1.483)	$< 2.2 \times 10^{-16}$
Diabetes	1.433 (1.382, 1.487)	$< 2.2 \times 10^{-16}$
Coronary artery disease	1.185 (1.138, 1.233)	$1.0 \times 10^{-16}$
COPD	1.237 (1.183, 1.294)	$< 2.2 \times 10^{-16}$
Cancer	1.688 (1.619, 1.760)	$< 2.2 \times 10^{-16}$
Heart failure	2.396 (2.291, 2.505)	$< 2.2 \times 10^{-16}$
Infection	3.478 (3.307, 3.658)	$< 2.2 \times 10^{-16}$
Liver disease	3.709 (3.438, 4.000)	$< 2.2 \times 10^{-16}$
Cerebrovascular disease	0.958 (0.894, 1.026)	0.222
<b>Biomarker</b>		
WBC, 7-d mean (scaled $\times 100$ )	1.794 (1.488, 2.163)	$8.7 \times 10^{-10}$
Platelet, 7-d mean (scaled $\times 1000$ )	0.700 (0.580, 0.845)	$2.0 \times 10^{-4}$
Hemoglobin, 7-d mean (g/dL)	0.862 (0.849, 0.875)	$< 2.2 \times 10^{-16}$
Sodium, 7-d mean (mmol/L)	0.971 (0.968, 0.974)	$< 2.2 \times 10^{-16}$
Potassium, 7-d mean (mmol/L)	1.018 (1.006, 1.030)	0.002
Creatinine, 7-d mean (mg/dL)	1.003 (1.002, 1.004)	$7.9 \times 10^{-11}$
BUN, 7-d mean (mg/dL)	1.024 (1.023, 1.025)	$< 2.2 \times 10^{-16}$
Bicarbonate, 7-d mean (mmol/L)	0.931 (0.923, 0.940)	$< 2.2 \times 10^{-16}$
Mechanical ventilation in prior 30 d	2.923 (2.675, 3.194)	$< 2.2 \times 10^{-16}$
<b>Sex-Interaction</b>		
Infection History $\times$ Male	0.967 (0.901, 1.037)	0.347
Liver disease $\times$ Male	0.820 (0.745, 0.903)	$5.1 \times 10^{-5}$
Widowed $\times$ Male	0.838 (0.752, 0.933)	0.001
Bicarbonate $\times$ Male	0.982 (0.970, 0.995)	0.006
Hemoglobin $\times$ Male	1.079 (1.058, 1.100)	$2.6 \times 10^{-14}$
Mechanical ventilation $\times$ Male	1.113 (0.993, 1.247)	0.065
Creatinine $\times$ Male	1.011 (1.008, 1.014)	$1.2 \times 10^{-16}$

**Table 3** Adjusted Hazard Ratios for CKD and Death after AKI in Competing Risk Models

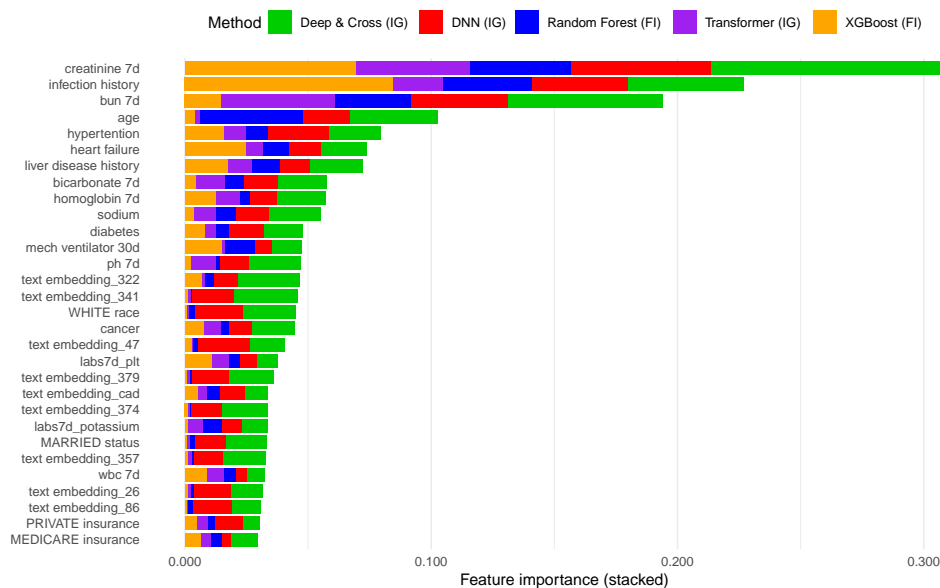
Outcome	Variable (units)	Hazard Ratio (95% CI)	p-value
CKD	<b>Demographic</b>		
	Age (per year)	1.003 (1.000, 1.006)	0.032
	Black race	1.154 (1.055, 1.261)	0.0016
	Divorced (vs. Married)	1.179 (1.039, 1.337)	0.011
	Widowed (vs. Married)	1.176 (1.058, 1.308)	0.0027
	<b>Medical history</b>		
	Hypertension	1.271 (1.174, 1.376)	$3.6 \times 10^{-9}$
	Diabetes	1.594 (1.487, 1.710)	$< 2.2 \times 10^{-16}$
	Coronary artery disease	1.114 (1.031, 1.204)	0.0062
	Heart failure	1.412 (1.305, 1.527)	$< 2.2 \times 10^{-16}$
	Cancer	0.631 (0.537, 0.742)	$2.5 \times 10^{-8}$
	Infection	0.505 (0.463, 0.550)	$< 2.2 \times 10^{-16}$
	Liver disease	0.726 (0.655, 0.805)	$1.3 \times 10^{-9}$
	<b>Biomarkers (90-day mean)</b>		
	Sodium (mmol/L)	0.986 (0.974, 0.998)	0.022
	Potassium (mmol/L)	1.036 (1.008, 1.065)	0.012
	<b>Sex interactions</b>		
	Cancer $\times$ Male	1.260 (1.031, 1.542)	0.024
Death	pH (unitless) $\times$ Male	0.658 (0.560, 0.773)	$3.3 \times 10^{-7}$
	Sodium (mmol/L) $\times$ Male	1.021 (1.013, 1.029)	$1.0 \times 10^{-7}$
	Creatinine (mg/dL) $\times$ Male	1.011 (1.006, 1.016)	$2.6 \times 10^{-5}$
	<b>Demographic</b>		
	Age (per year)	1.018 (1.015, 1.020)	$< 2.2 \times 10^{-16}$
	Single (vs. Married)	0.747 (0.693, 0.805)	$1.9 \times 10^{-14}$
	Divorced (vs. Married)	0.726 (0.645, 0.817)	$1.2 \times 10^{-7}$
	Widowed (vs. Married)	0.816 (0.738, 0.902)	$7.0 \times 10^{-5}$
	<b>Medical history</b>		
	Heart failure	1.286 (1.172, 1.411)	$1.1 \times 10^{-7}$
	COPD	1.186 (1.098, 1.281)	$1.3 \times 10^{-5}$
	Cancer	1.711 (1.600, 1.830)	$< 2.2 \times 10^{-16}$
	Infection	2.592 (2.432, 2.762)	$< 2.2 \times 10^{-16}$
	Liver disease	2.614 (2.445, 2.796)	$< 2.2 \times 10^{-16}$
	Cerebrovascular disease	1.624 (1.463, 1.803)	$< 2.2 \times 10^{-16}$
	<b>Biomarkers (90-day mean)</b>		
	WBC ( $\times 10^9/L$ )	1.013 (1.010, 1.017)	$5.0 \times 10^{-12}$
	Potassium (mmol/L)	1.029 (1.009, 1.050)	0.0053
	Creatinine (mg/dL)	1.004 (1.001, 1.008)	0.021
	<b>Sex interactions</b>		
	Heart failure $\times$ Male	0.777 (0.689, 0.878)	$4.8 \times 10^{-5}$

# Supplemental Materials

## Appendix A Predictors for AKI from MIMIC-III and MIMIC-IV Databases

## Appendix B Model Performance Metrics from all AKI prediction Models

## Appendix C Feature Importance results from the top 30 features



**Fig. C1** Feature Importance of predictors in AKI prediction machine learning models. The top features are consistent with the predictors selected in logistic regression. in general, tree-based method and transformers are likely to prioritize explainable features, while DNN and DCN can pick many text embedding components.



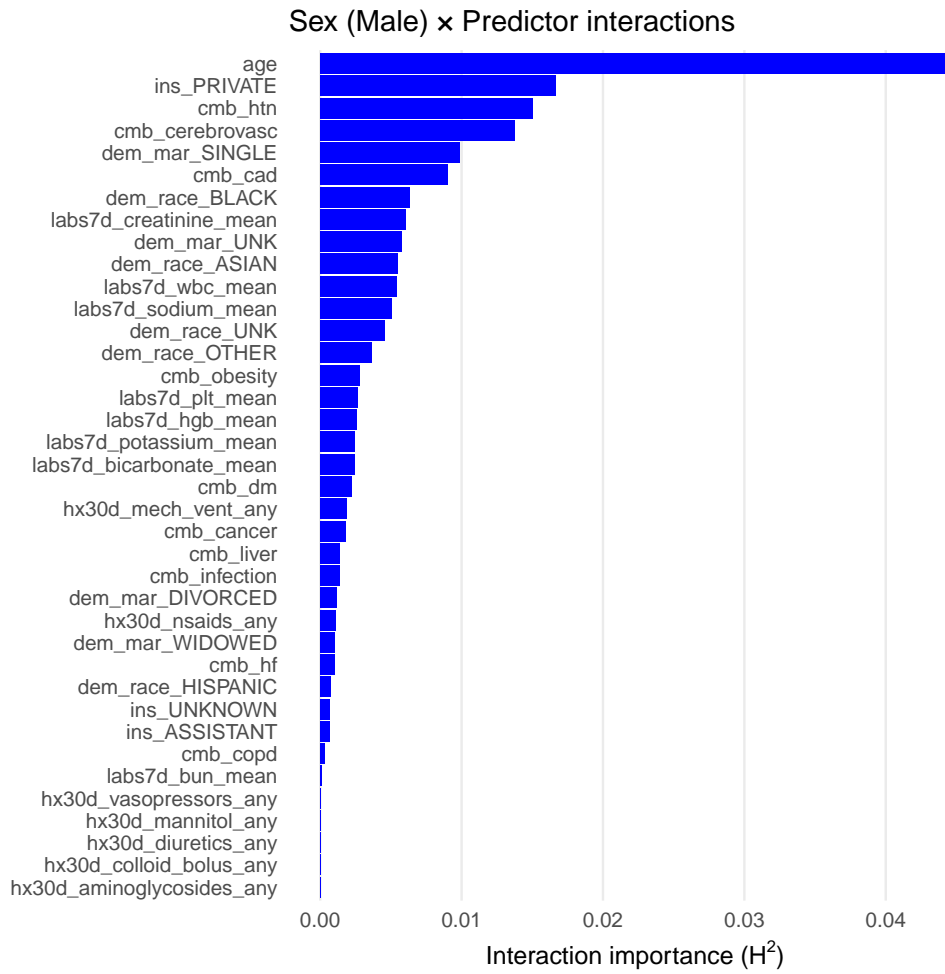
**Table A1** Candidate Predictors for AKI Prediction Models

Category (Modifiable)	Variables	Time Window	MIMIC III/IV tables
Demographics (No)	sex, age, race, ethnicity, marital status	adm'n	patients, admissions
Insurance (No)	Private; Medicare; Assistant (Medicaid, government, self-pay)	adm'n	admissions
Comorbidities (Indirect)	Hypertension, diabetes, cancer, heart failure, coronary artery disease, infection history, COPD, liver disease, cerebrovas- cular disease, obesity, CKD	adm'n	diagnoses_icd
Laboratory Tests (Partial)	white blood counts (WBC), hemoglobin, platelets, creatinine, blood urea nitrogen (BUN), albumin, sodium, potassium, bicarbonate, lactate, anion gap, base excess, INR, PTT, prothrombin time, glucose, ABGs (pH, PaO <sub>2</sub> , PaCO <sub>2</sub> )	7 days pre-ICU	labevents chartevents
Physiologic signs (Partial)	heart rate, SBP/DBP, MAP, respiratory rate, FiO <sub>2</sub> , SpO <sub>2</sub> , temperature, cardiac output, central venous pressure (CVP), pulmonary artery pressures, tidal vol- ume, minute ventilation; fluid input/out- put	48 hours pre-ICU	chartevents, inputevents_mv, inputevents_cv, outputevents, icustays
Medications (Partial)	Diuretics, non-steroidal anti- inflammatory drugs (NSAIDs), vasopressors, aminoglycosides, manni- tol, colloid bolus	30-day & 6-month pre-ICU	prescriptions
Procedures (Partial)	mechanical ventilation, vasopressors, central line	30-day & 6-month pre-ICU	inputevents_mv, inputevents_cv, procedureevents_mv, chartevents
Text (No)	notes Nursing/physician notes, progress/dis- charge summaries, radiology, procedure, medication, admission notes	During hospital- ization	noteevents

"Assistant" aggregates Medicaid, government, and self-pay. Time windows are relative to the index AKI admission or ICU admission as indicated. "Modifiable" denotes potential clinical intervenability of the exposure (not causality).

**Table B2** AKI Prediction Model Evaluation Metrics

Method	AUC-ROC	Sensitivity/Recall	Specificity	Accuracy	Precision	F <sub>1</sub>
<b>MIMIC-IV testing set</b>						
Logistic	0.851	0.790	0.751	0.756	0.324	0.459
Random Forest	0.909	0.864	0.814	0.821	0.414	0.560
XGboost	0.927	0.877	0.827	0.833	0.435	0.582
DNN	0.908	0.841	0.819	0.822	0.412	0.553
DCN	0.904	0.831	0.825	0.826	0.418	0.556
Transformer	0.916	0.845	0.832	0.834	0.431	0.571
<b>MIMIC-III</b>						
Logistic	0.774	0.681	0.735	0.724	0.390	0.496
Random Forest	0.777	0.767	0.646	0.670	0.351	0.481
XGboost	0.829	0.752	0.757	0.756	0.436	0.552
DNN	0.764	0.761	0.652	0.674	0.353	0.482
DCN	0.723	0.628	0.703	0.688	0.345	0.446
Transformer	0.739	0.651	0.702	0.692	0.353	0.457

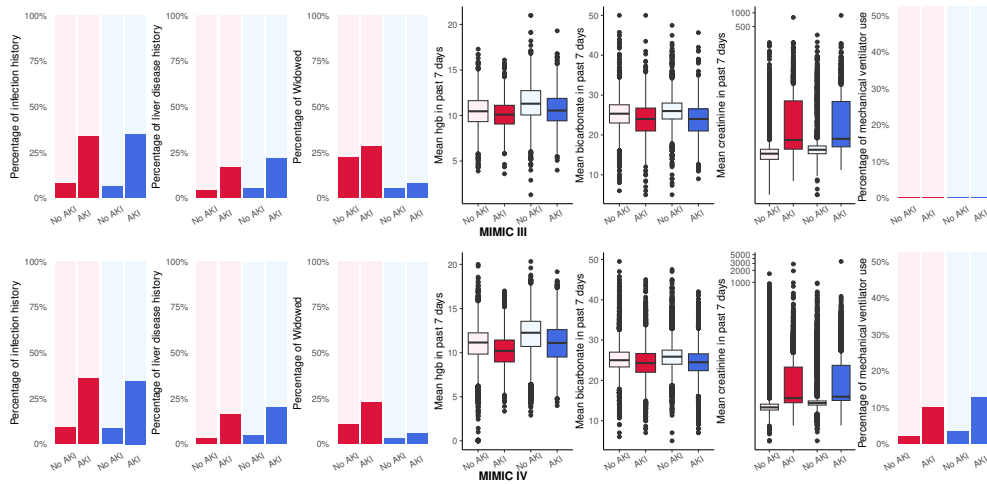


**Fig. D2** Distribution of  $H$ -statistics for sex–biomarker interactions in the random forest model (MIMIC-IV)

## Appendix D $H^2$ Statistic for Sex-Predictor Interactions in Random Forest Model

## Appendix E Sensitivity Analysis in Subgroup and with alternative missing value imputation approach

## Appendix F Sex-specific distributions of biomarkers in AKI and no AKI groups



**Fig. F3** Sex-specific distributions of biomarkers in AKI and no AKI groups. Red and blue are for females and males, respectively.

## Appendix G Evaluation of Competing Risk and DeepSurv Models for CKD and Death

## Appendix H DeepSurv model fitting and feature importance

## Appendix I Sensitivity Analysis for 60-day CKD

**Table E3** Adjusted Effects for AKI in Non-auto-accident Admissions with Sex-Age-Specific Mean Imputation for Missing Values

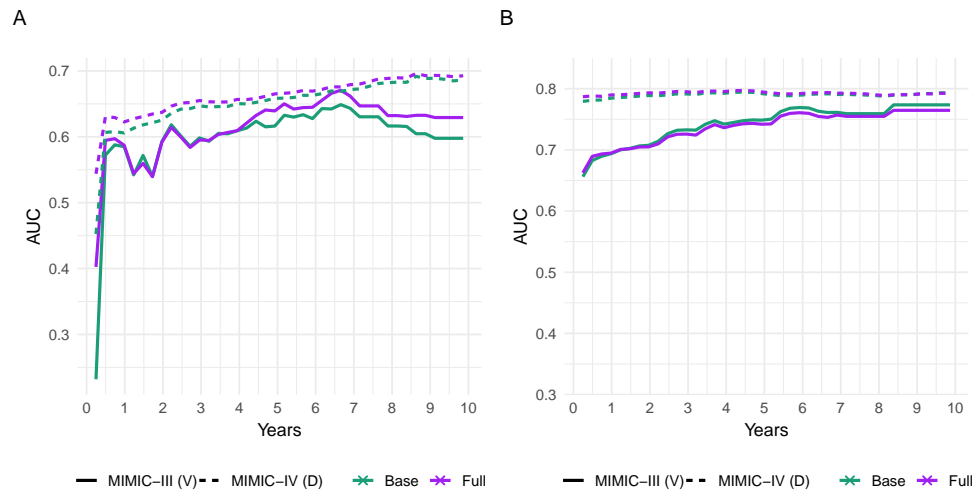
Variable (units)	Odds Ratio (95% CI)	p-value
<b>Demographic</b>		
Age (per year)	1.009 (1.008, 1.011)	$< 2.2 \times 10^{-16}$
Sex: Male (vs. female)	1.030 (0.651, 1.629)	0.900
Race: Other (vs. White)	1.051 (0.979, 1.129)	0.172
Marital status: Single (vs. married)	1.159 (1.109, 1.211)	$5.3 \times 10^{-11}$
Marital status: Widowed (vs. married)	1.132 (1.061, 1.207)	$1.7 \times 10^{-4}$
Insurance: Private (vs. Medicare)	0.870 (0.831, 0.911)	$3.321 \times 10^{-9}$
Insurance: Unknown (vs. Medicare)	0.794 (0.723, 0.872)	$1.364 \times 10^{-6}$
<b>Medical History</b>		
Obesity	1.375 (1.295, 1.458)	$< 2.2 \times 10^{-16}$
Hypertension	1.479 (1.418, 1.542)	$< 2.2 \times 10^{-16}$
Diabetes	1.463 (1.399, 1.529)	$< 2.2 \times 10^{-16}$
Coronary artery disease	1.203 (1.145, 1.264)	$2.0 \times 10^{-13}$
Heart failure	2.600 (2.463, 2.744)	$< 2.2 \times 10^{-16}$
COPD	1.219 (1.150, 1.292)	$2.9 \times 10^{-11}$
Cancer	1.537 (1.458, 1.619)	$< 2.2 \times 10^{-16}$
Infection	3.568 (3.363, 3.785)	$< 2.2 \times 10^{-16}$
Liver disease	3.584 (3.280, 3.915)	$< 2.2 \times 10^{-16}$
Cerebrovascular disease	0.939 (0.857, 1.029)	0.178
<b>Biomarker</b>		
WBC, 7-d mean (scaled $\times 100$ ) <sup>a</sup>	1.442 (1.134, 1.833)	0.003
Platelet, 7-d mean ( $1000 \times 10^9/L$ ) <sup>a</sup>	0.709 (0.562, 0.894)	0.004
Hemoglobin, 7-d mean (g/dL)	0.857 (0.841, 0.873)	$< 2.2 \times 10^{-16}$
Sodium, 7-d mean (mmol/L)	0.977 (0.973, 0.982)	$< 2.2 \times 10^{-16}$
Creatinine, 7-d mean (scaled $\times 100$ ) <sup>a</sup>	1.303 (1.179, 1.440)	$2.235 \times 10^{-7}$
BUN, 7-d mean (per 10 mg/dL) <sup>a</sup>	1.363 (1.336, 1.390)	$< 2.2 \times 10^{-16}$
Potassium, 7-d mean (per 100 mmol/L) <sup>a</sup>	1.056 (0.202, 5.514)	0.949
Bicarbonate, 7-d mean (per 10 mmol/L) <sup>a</sup>	0.389 (0.348, 0.435)	$< 2.2 \times 10^{-16}$
Mechanical ventilation in prior 30 d	3.376 (3.002, 3.797)	$< 2.2 \times 10^{-16}$
<b>Sex-Interaction</b>		
Infection History $\times$ Male	0.926 (0.854, 1.005)	0.065
Liver disease $\times$ Male	0.742 (0.661, 0.832)	$3.3 \times 10^{-7}$
Hemoglobin $\times$ Male	1.068 (1.043, 1.093)	$4.1 \times 10^{-8}$
BUN (per 10) $\times$ Male	0.929 (0.906, 0.953)	$1.2 \times 10^{-8}$
Bicarbonate (per 10) $\times$ Male	0.975 (0.833, 1.140)	0.749
Mechanical ventilation $\times$ Male	1.067 (0.919, 1.239)	0.393
Creatinine (per 100) $\times$ Male	3.589 (2.611, 4.933)	$3.5 \times 10^{-15}$

<sup>a</sup> Variables labeled “scaled” are reported per the analysis coding (e.g., WBC  $\times 100$ , platelets  $\times 1000$ , creatinine  $\times 100$ , BUN/bicarbonate per 10 units).

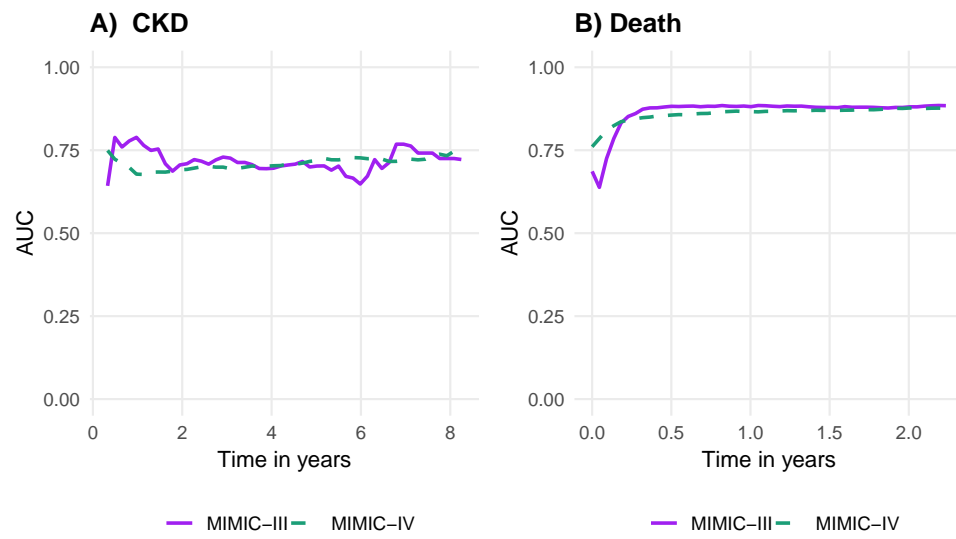
**Table E4** Adjusted Effects for AKI in Non-auto-accident Admissions with Multiple Imputation for Missing Values

Variable (units)	Odds Ratio (95% CI)	p-value
<b>Demographic</b>		
Age (per year)	1.016 (1.015, 1.017)	$< 2.2 \times 10^{-16}$
Sex: Male (vs. female)	1.164 (0.826, 1.640)	0.384
Race: Black (vs. White)	1.552 (1.473, 1.636)	$< 2.2 \times 10^{-16}$
Race: Other (vs. White)	0.995 (0.926, 1.068)	0.883
Insurance: Assistant (vs. Medicare)	0.979 (0.923, 1.038)	0.476
Insurance: Private (vs. Medicare)	0.883 (0.838, 0.930)	$2.6 \times 10^{-6}$
Insurance: Unknown (vs. Medicare)	0.784 (0.712, 0.863)	$7.4 \times 10^{-7}$
<b>Medical History</b>		
Obesity	1.387 (1.308, 1.470)	$< 2.2 \times 10^{-16}$
Hypertension	1.454 (1.395, 1.515)	$< 2.2 \times 10^{-16}$
Diabetes	1.438 (1.377, 1.502)	$< 2.2 \times 10^{-16}$
Coronary artery disease	1.214 (1.156, 1.274)	$5.3 \times 10^{-15}$
Heart failure	2.654 (2.517, 2.799)	$< 2.2 \times 10^{-16}$
COPD	1.244 (1.175, 1.318)	$8.1 \times 10^{-14}$
Cancer	1.587 (1.508, 1.670)	$< 2.2 \times 10^{-16}$
Infection	3.575 (3.374, 3.788)	$< 2.2 \times 10^{-16}$
Liver disease	3.035 (2.866, 3.215)	$< 2.2 \times 10^{-16}$
Cerebrovascular disease	0.921 (0.841, 1.008)	0.074
<b>Biomarker</b>		
Platelet, 7-d mean (per $100 \times 10^9/L$ ) <sup>a</sup>	0.948 (0.931, 0.966)	$2.2 \times 10^{-8}$
Hemoglobin, 7-d mean (g/dL)	0.905 (0.892, 0.918)	$< 2.2 \times 10^{-16}$
Sodium, 7-d mean (mmol/L)	0.822 (0.796, 0.848)	$< 2.2 \times 10^{-16}$
Creatinine, 7-d mean (scaled $\times 100$ ) <sup>a</sup>	0.853 (0.779, 0.933)	$5.5 \times 10^{-4}$
BUN, 7-d mean (per 10 mg/dL) <sup>a</sup>	1.123 (1.113, 1.134)	$< 2.2 \times 10^{-16}$
Potassium, 7-d mean (per 100mmol/L)	0.868 (0.261, 2.886)	0.817
Bicarbonate, 7-d mean (per 10 mmol/L) <sup>a</sup>	0.514 (0.472, 0.559)	$< 2.2 \times 10^{-16}$
Mechanical ventilation in prior 30 day	2.377 (2.107, 2.682)	$< 2.2 \times 10^{-16}$
<b>Sex-Interaction</b>		
Married $\times$ Male	0.868 (0.825, 0.913)	$4.8 \times 10^{-8}$
Infection History $\times$ Male	0.904 (0.835, 0.979)	0.013
BUN (per 10) $\times$ Male	0.996 (0.984, 1.008)	0.484
Hemoglobin $\times$ Male	1.032 (1.013, 1.052)	0.0007
Creatinine (per 100) $\times$ Male	1.472 (1.268, 1.710)	$4.0 \times 10^{-7}$
Bicarbonate (per 10) $\times$ Male	1.054 (0.938, 1.183)	0.377
Mechanical ventilation $\times$ Male	1.094 (0.938, 1.275)	0.254

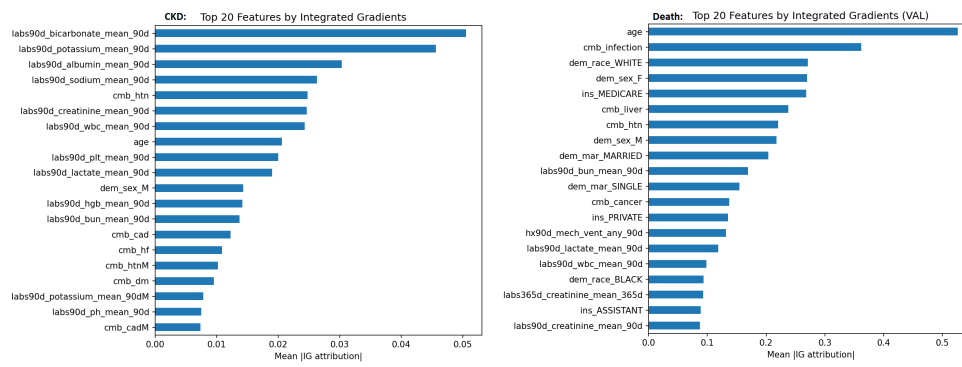
Platelets per  $100 \times 10^9/L$ ; BUN and bicarbonate per 10 units; creatinine scaled by 100 (presented per scaled unit).



**Fig. G4** Time-dependent AUC from competing risk survival models in MIMIC-IV (derivation) and MIMIC-III (validation)



**Fig. G5** Time-dependent AUC from DeepSurv in MIMIC-IV (derivation) and MIMIC-III (validation)



**Fig. H6** The most important features for time to CKD prediction using Integrated Gradient in DeepSurv



**Table I5** Adjusted Hazard Ratios for 60d-CKD and Death after AKI in Competing Risk Models

Outcome	Variable (units)	Hazard Ratio (95% CI)	p-value
CKD	<b>Demographic</b>		
	Black race	1.120 (1.028, 1.221)	0.0093
	Divorced (vs. Married)	1.169 (1.036, 1.320)	0.012
	Widowed (vs. Married)	1.189 (1.078, 1.312)	$5.5 \times 10^{-4}$
	<b>Medical history</b>		
	Hypertension	1.266 (1.175, 1.363)	$5.6 \times 10^{-10}$
	Diabetes	1.607 (1.502, 1.719)	$< 2.2 \times 10^{-16}$
	Coronary artery disease	1.102 (1.023, 1.187)	0.011
	Heart failure	1.432 (1.328, 1.544)	$< 2.2 \times 10^{-16}$
	Cancer	0.669 (0.573, 0.780)	$3.2 \times 10^{-7}$
	Infection	0.532 (0.490, 0.577)	$< 2.2 \times 10^{-16}$
	Liver disease	0.762 (0.691, 0.840)	$5.1 \times 10^{-8}$
	<b>Biomarkers (90-day mean)</b>		
	Hemoglobin (g/dL)	1.058 (1.022, 1.095)	$1.2 \times 10^{-3}$
	Sodium (mmol/L)	0.987 (0.977, 0.998)	0.018
	BUN (mg/dL)	1.003 (1.001, 1.005)	$3.3 \times 10^{-3}$
	Potassium (mmol/L)	1.035 (1.007, 1.065)	0.015
	<b>Sex interactions</b>		
	Cancer $\times$ Male	1.224 (1.010, 1.483)	0.039
	pH (unitless) $\times$ Male	0.720 (0.611, 0.848)	$8.9 \times 10^{-5}$
	Sodium (mmol/L) $\times$ Male	1.017 (1.009, 1.025)	$3.6 \times 10^{-5}$
Death	<b>Demographic</b>		
	Age (per year)	1.017 (1.015, 1.020)	$< 2.2 \times 10^{-16}$
	Single (vs. Married)	0.754 (0.700, 0.813)	$1.4 \times 10^{-13}$
	Divorced (vs. Married)	0.733 (0.651, 0.825)	$2.7 \times 10^{-7}$
	Widowed (vs. Married)	0.814 (0.736, 0.900)	$5.5 \times 10^{-5}$
	<b>Medical history</b>		
	Heart failure	1.283 (1.170, 1.408)	$1.3 \times 10^{-7}$
	COPD	1.195 (1.107, 1.291)	$5.3 \times 10^{-6}$
	Cancer	1.690 (1.580, 1.807)	$< 2.2 \times 10^{-16}$
	Infection	2.551 (2.393, 2.718)	$< 2.2 \times 10^{-16}$
	Liver disease	2.590 (2.423, 2.770)	$< 2.2 \times 10^{-16}$
	Cerebrovascular disease	1.606 (1.447, 1.783)	$< 2.2 \times 10^{-16}$
	<b>Biomarkers (90-day mean)</b>		
	WBC ( $\times 10^9/L$ )	1.014 (1.010, 1.018)	$1.8 \times 10^{-12}$
	Potassium (mmol/L)	1.033 (1.012, 1.055)	0.0018
	<b>Sex interactions</b>		
	Heart failure $\times$ Male	0.769 (0.681, 0.868)	$2.1 \times 10^{-5}$