JACC: ADVANCES VOL. 3, NO. 9, 2024

ORIGINAL RESEARCH

CRITICAL CARE AND RESUSCITATION

Mortality Risk Stratification Utilizing Artificial Intelligence Electrocardiogram for Hyperkalemia in Cardiac Intensive Care Unit Patients

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ABSTRACT

BACKGROUND Hyperkalemia has been associated with increased mortality in cardiac intensive care unit (CICU) patients. An artificial intelligence (AI) enhanced electrocardiogram (ECG) can predict hyperkalemia, and other AI-ECG algorithms have demonstrated mortality risk-stratification in CICU patients.

OBJECTIVES The authors hypothesized that the AI-ECG hyperkalemia algorithm could stratify mortality risk beyond laboratory serum potassium measurement alone.

METHODS We included 11,234 unique Mayo Clinic CICU patients admitted from 2007 to 2018 with a 12-lead ECG and blood potassium (K) level obtained at admission with K ≥5 mEq/L defining hyperkalemia. ECGs underwent AI evaluation for the probability of hyperkalemia (probability >0.5 defined as positive). Hospital mortality was analyzed using logistic regression, and survival to 1 year was estimated using Kaplan-Meier and Cox analysis.

RESULTS In the final cohort (n = 11,234), the mean age was 69.6 ± 10.5 years, 37.8% were females, and 92.4% were White. Chronic kidney disease was present in 20.2%. The mean laboratory potassium value for the cohort was 4.2 ± 0.3 mEq/L. The AI-ECG predicted hyperkalemia in 33.9% (n = 3,810) of CICU patients and 12.9% (n = 1,451) of patients had laboratory-confirmed hyperkalemia (K ≥5 mEq/L). In-hospital mortality increased in false-positive, false-negative, and true-positive patients, respectively ($P < 0.001$), and each of these patient groups had successively lower survival out to 1 year.

CONCLUSIONS AI-ECG-based prediction of hyperkalemia, even with a normal laboratory potassium value, was associated with higher in-hospital mortality and lower 1-year survival in CICU patients. This study demonstrated that AI-ECG probability of hyperkalemia may enable rapid individualized risk stratification in critically ill patients beyond laboratory value alone. (JACC Adv. 2024;3:101169) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received November 7, 2023; revised manuscript received May 24, 2024, accepted June 7, 2024.

ISSN 2772-963X https://doi.org/10.1016/j.jacadv.2024.101169

ABBREVIATIONS AND ACRONYMS

AI = artificial intelligence

APACHE = Acute Physiology and Chronic Health Evaluation

AUC = area under the curve

CCI = Charlson Comorbidity Index

CICU = cardiac intensive care unit

ECG = electrocardiogram

FN = false negative

FP = false positive

LVSD = left ventricular systolic dysfunction

M-CARS = Mayo Cardiac Intensive Care Unit Admission Risk Score

SOFA = Sequential Organ Failure Assessment

TN = true negative

TP = true POSITIVE

Blood electrolyte disturbances are common in critically ill patients and have been associated with adverse outcomes.[1-3] Within the cardiac intensive care unit (CICU) population, hyperkalemia, hyponatremia, and hypochloremia have all been associated with increased short- and long-term mortality.[2,4,5] Abnormalities in serum potassium can affect cardiac myocytes, and underlying acute cardiac disease could magnify the association between dyskalemia and adverse outcomes in CICU patients.[2,6]

Hyperkalemia specifically has been associated with mortality and fatal arrhythmias in the critically ill, including CICU patients.[2] Abnormalities on a standard 12-lead electrocardiogram (ECG) tracing remain a rapid and simple way to detect hyperkalemia. However, hyperkalemia must be severe to produce ECG abnormalities, and the sensitivity of physician ECG interpretation to diagnose hyperkalemia remains relatively low.[6,7] Accordingly, we created and validated an artificial intelligence (AI) enhanced ECG algorithm to predict hyperkalemia from 2 leads of a standard 12-lead ECG in a large, heterogeneous patient cohort with chronic kidney disease.[8] As the relationship between laboratory measured potassium and mortality in the critically ill is well defined, a knowledge gap remains if a similar mortality association exists for patients with AI-ECG predicted hyperkalemia in a CICU setting.

There is precedent for using AI-ECG to perform risk stratification in CICU patients, as we have shown using an AI-ECG algorithm designed to detect left ventricular systolic dysfunction (LVSD).[9] In this separate investigation, we found patients with LVSD based on AI-ECG or transthoracic echocardiogram had an increased risk of mortality, particularly those patients with an abnormality on both tests.[9] Interestingly, patients with normal left ventricular function on transthoracic echocardiogram, but AI-ECG predicted LVSD (ie, a false-positive [FP] test), were also at increased risk of in-hospital and 1-year mortality, demonstrating the independent and complementary prognostic value of the AI-ECG algorithm beyond what was visible by diagnostic imaging for LVSD alone.[9]

In this present study, we aim to better understand the contribution of the AI-ECG algorithm for the prediction hyperkalemia as a novel prognostic biomarker in the CICU setting, similar to our prior AI-ECG LVSD study. Specifically, we hope to elucidate the mortality risk association from the AI-ECG results in patients with correlative laboratory potassium values (ie, true positives [TPs]) and in patients with discordant AI-ECG/lab results (ie, FPs and FNs). This type of analysis will highlight the potential added value of this and similar AI-ECG algorithms in CICU patient care.

MATERIALS AND METHODS

This study was approved by the Institutional Review Board at the Mayo Clinic (Rochester, Minnesota, USA) as a minimal-risk investigation. All clinical data, including patient information, digitally stored ECGs, and values from laboratory testing, were obtained from the Mayo Clinic electronic health records. The Mayo Clinic Institutional Review Board waived the need for informed consent because of the study's retrospective nature. We excluded patients who had previously declined to have their health records utilized for research. Race/ethnicity and sex data were self-reported by individual patients.

STUDY POPULATION. We included unique Mayo Clinic patients admitted to the CICU, located at Saint Mary's campus of Mayo Clinic Hospital, Rochester, Minnesota, between 2007 and 2018 with a standard 10-second, 12 lead ECG and laboratory potassium (serum or plasma) level obtained during admission.[10] While small differences may exist between types of laboratory potassium measured, these variations are typically modest and of unlikely statistical significance.[2] Patients without either an admission ECG or laboratory potassium were excluded. The current database only included admission data (ie, ECG, lab potassium value) without specific time-stamp of collection. Each patient collected 12 lead ECG was processed by the AI-ECG algorithm for hyperkalemia, as described below.

DATA SOURCES. Demographic, clinical, vital signs, laboratory, outcome, and diagnosis data were extracted from the electronic medical record using the Mayo Clinic Multidisciplinary Epidemiology and Translational Research in Intensive Care Data Mart and data on critical care procedures and therapies.[11] Admission diagnoses were identified by the International Statistical Classification of Diseases-9/10 codes recorded within 1 day before or after CICU admission.[12] The Charlson Comorbidity Index (CCI), individual comorbidities, and severity of illness scores, including the SOFA (Sequential Organ Failure Assessment), M-CARS (Mayo Cardiac Intensive Care Unit Admission Risk Score), and APACHE (Acute Physiology and Chronic Health Evaluation) III and IV

scores were extracted from the electronic medical record using previously validated algorithms.[1,3,13,14] The M-CARS is a novel risk score which utilizes multiple variables at the time of CICU admission (ie, cardiac arrest, shock, respiratory failure, Braden skin score, blood urea nitrogen, anion gap, and red blood cell distribution width) to predict in-hospital and 1-year mortality amongst critically ill patients. This risk score was derived and validated in this CICU cohort, which has been demonstrated to outperform SOFA or APACHE in this population.[3]

DEEP LEARNING MODEL. The AI-ECG algorithm in this study has been previously described in detail.[8] Briefly, the AI algorithm used in this study was developed as a convolutional neural network with 11 layers. Using a standard 10-second, 12-lead ECG recording, the network processes the data from simultaneously acquired ECG lead data and produces a parameter output between 0 and 1 that represents the probability of hyperkalemia (defined as serum potassium >5.5 mEq/L in the original derivation). In its original derivation, 2 independent models were developed based on 2- and 4-lead ECGs.[8] The 2-lead AI-ECG demonstrated an area under the receiver operating characteristic curve (AUC) of 0.85 to 0.88 at a threshold where sensitivity was equal to specificity.[8] In this current study, we used the previously developed 2-lead model (leads I and II of a standard 12-lead ECG) and selected an operating threshold similar to the derivation study, ie, where sensitivity is equal to specificity.

This algorithm was originally developed to estimate the risk of hyperkalemia from a 12-lead ECG. In this current analysis, we used this same algorithm to understand if the AI-ECG predicted risk of hyperkalemia could determine mortality risk in a similar way that we have observed other AI-ECG algorithms to be predictive of mortality in the CICU population.[9]

GROUP DEFINITIONS. Based on our prior outcomes work, hyperkalemia was defined as serum potassium >5.0 mEq/L.[2] In this study, we determined patients with an AI-ECG probability of hyperkalemia >0.5 to be considered "high probability" for suspected hyperkalemia. We defined 4 subgroups after AI-ECG processing: 1) normal AI-ECG without laboratory hyperkalemia (true negative [TN]); 2) isolated AI-ECG hyperkalemia without laboratory hyperkalemia (FP); 3) isolated laboratory hyperkalemia with normal AI-ECG (FN); and 4) both laboratory and AI-ECG-predicted hyperkalemia (TP).

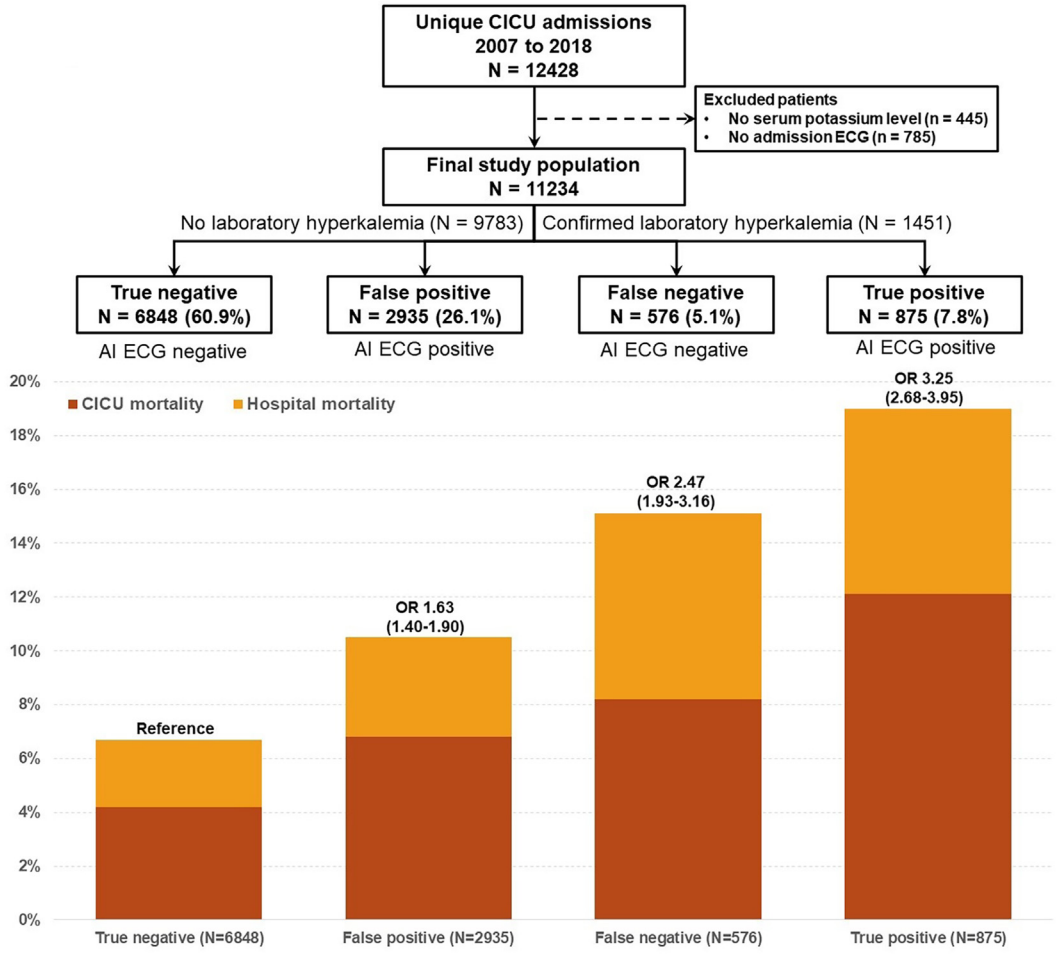
STATISTICAL ANALYSIS. The primary outcome of interest was all-cause in-hospital mortality, which included all CICU deaths, and the key secondary outcomes were all-cause 30-day and 1-year mortality. ORs and 95% CI values for the primary outcome of all-cause-in-hospital mortality were calculated using logistic regression. Survival to 1 year was estimated using Kaplan-Meier curves, with groups compared using the log-rank test. HR and 95% CI values for the secondary outcomes of all-cause 30-day and 1-year mortality were calculated using Cox proportional-hazards analysis. Multivariable logistic regression and Cox models were adjusted for age, CCI, and M-CARS for both the primary (in-hospital mortality) and secondary (1-year mortality) outcomes.[3] Discrimination was evaluated using the AUC (C-statistic) values. To determine the relative importance of laboratory potassium valve and AI-ECG probability of hyperkalemia for prediction of in-hospital mortality, the mean decrease in accuracy and Gini Index (higher reflecting greater variable importance) were derived from a random forest including these variables along with age, CCI, and M-CARS; number of trees was 300 with 2 variables per split based on tuning to minimize the out-of-bag error rate. Analysis was performed using BlueSky version 10.3.1 Pro (BlueSky LLC).

RESULTS

PARTICIPANT CHARACTERISTICS. We screened a pre-existing CICU database of 12,428 unique patients and excluded 1,194 patients who did not have an ECG (n = 785) or laboratory potassium level (n = 445) on CICU admission (**Figure 1**). In the final cohort (n = 11,234), the mean age was 69.6 ± 10.5 years, 37.8% were females, and 92.4% were White. Chronic kidney disease was present in 20.2%, and 5.1% were dialysis dependent. Admission diagnoses included cardiac arrest (12.6%), cardiogenic shock (12.6%), acute coronary syndrome (44.4%), and congestive heart failure (48.4%) (**Table 1**).

AI-ECG HYPERKALEMIA AND LABORATORY POTASSIUM VALUES. The mean laboratory potassium value for the cohort was 4.2 ± 0.3 mmol/L, and the mean probability of hyperkalemia by AI-ECG was 0.39 ± 0.16. Overall discrimination of hyperkalemia by AI-ECG was lower than observed in the derivation study (AUC 0.71) using a more lenient definition of laboratory hyperkalemia than in the derivation study.[8] The AUC improved to 0.76 with use of a K cutoff of 5.5 mEq/L and further to 0.79 with a cutoff of 6 mEq/L. The AI-ECG predicted hyperkalemia in 33.9% (n = 3,810) of CICU patients and 12.9% (n = 1,451) of patients had laboratory-confirmed hyperkalemia (potassium ≥5 mEq/L). In this CICU cohort, more than half (60.9%; n = 6,848) were TN, 26.1% (n = 2,935) were FP, 5.1% (n = 576) were FN,

FIGURE 1 Prevalence and Short-term Outcomes of Hyperkalemia as Predicted by AIECG and Measured by Laboratory Analysis



Patient flow diagram (Top). Unadjusted cardiac intensive care unit and hospital mortality as it relates to lab hyperkalemia (K >5.0 mEq/L) and artificial intelligence electrocardiogram predicted hyperkalemia (bottom). $P < 0.05$ across categories. AI-ECG = artificial intelligence electrocardiogram; CICU = cardiac intensive care unit.

and 7.8% (n = 875) were TP. (Table 1). There were substantial differences in baseline characteristics between predicted vs observed groups, and patients with either laboratory or AI-ECG-predicted hyperkalemia were older and had more comorbidities with greater severity of illness (Table 1).

IN-HOSPITAL AND 30-DAY MORTALITY. A total of 1,022 (9.1%) patients died in the hospital, including 641 (5.7%) that died during the CICU stay. A total of 1,299 (11.6%) patients died within 30 days of CICU admission, including 985 in-hospital deaths; 37 in-hospital deaths occurred after 30 days. Inpatient deaths had a higher mean AI-ECG probability for hyperkalemia (0.471 ± 0.175 vs 0.382 ± 0.16) and higher mean laboratory potassium values (4.4 ± 0.5 mEq/L vs 4.2 ± 0.4 mEq/L; $P < 0.001$). Accordingly, the distribution of AI-ECG and laboratory hyperkalemia groups differed between hospital survivors and nonsurvivors, with more AI-ECG predicted and laboratory hyperkalemia in patients who died during hospitalization (Supplemental Figure 1).

UNADJUSTED IN-HOSPITAL AND 30-DAY MORTALITY. Evaluating AI-ECG as a continuous variable, the AI-ECG probability of hyperkalemia was directly associated with in-hospital mortality (unadjusted OR: 1.16 per 0.1 unit increase in AI-ECG predicted hyperkalemia; 95% CI: 1.13-0.1.19; $P < 0.0001$; AUC: 0.59) (Supplemental Figure 2) and 30-day mortality (unadjusted HR: 1.14 per 0.1 higher; 95% CI: 1.11-1.16; $P < 0.001$). Compared to the TN group, patients with

TABLE 1 Baseline Characteristics

	True Negative (n = 6,848)	False Positive (n = 2,935)	False Negative (n = 576)	True Positive (n = 875)	Total (N = 11,234)	*P* Value
Age, y	68.5 (57.4-78.4)	70.8 (59.5-80.6)	70.4 (59.4-80.6)	72.1 (61.5-82.1)	69.6 (58.3-79.4)	<0.001
Female	2,690 (39.3%)	1,051 (35.8%)	182 (31.6%)	320 (36.6%)	4,243 (37.8%)	<0.001
White	6,321 (92.3%)	2,724 (92.8%)	531 (92.2%)	809 (92.5%)	10,385 (92.4%)	0.847
AI-ECG probability for hyperkalemia	0.291 (0.201-0.384)	0.635 (0.562-0.739)	0.344 (0.250-0.423)	0.727 (0.611-0.841)	0.392 (0.249-0.573)	<0.001
CICU mortality	287 (4.2%)	201 (6.8%)	47 (8.2%)	106 (12.1%)	641 (5.7%)	<0.001
Hospital mortality	460 (6.7%)	309 (10.5%)	87 (15.1%)	166 (19.0%)	1,022 (9.1%)	<0.001
Comorbidities						
Chronic kidney disease	1,100 (16.1%)	645 (22.0%)	171 (29.8%)	352 (40.3%)	2,268 (20.2%)	<0.001
Dialysis before admission	226 (3.3%)	148 (5.0%)	62 (10.8%)	139 (15.9%)	575 (5.1%)	<0.001
Myocardial infarction	1,126 (16.5%)	639 (21.8%)	106 (18.5%)	213 (24.4%)	2,084 (18.6%)	<0.001
Congestive heart failure	1,114 (16.3%)	652 (22.2%)	131 (22.8%)	263 (30.1%)	2,160 (19.3%)	<0.001
Diabetes mellitus	1,672 (24.5%)	919 (31.4%)	206 (35.9%)	419 (47.9%)	3,216 (28.7%)	<0.001
Comorbidity score	1 (0, 3)	2 (0, 4)	2 (1, 4)	3 (1, 6)	2 (0, 4)	<0.001
Electrolytes at ICU admission						
Potassium mEq/L	4.1 (3.8-4.4)	4.3 (4.0-4.6)	5.2 (5.1-5.5)	5.4 (5.2-5.8)	4.2 (3.9-4.6)	<0.001
Sodium mEq/L	139 (136-141)	138 (136-141)	138 (135-141)	136 (133-139)	138 (136-141)	<0.001
Bicarbonate	24 (22-26)	24 (21-26)	23 (21-26)	22 (19-25)	24 (21-26)	<0.001
Creatinine mg/dL	1.0 (0.8-1.3)	1.1 (0.8-1.5)	1.3 (1.0-2.1)	1.8 (1.3-2.8)	1.0 (0.8-1.4)	<0.001
Blood urea nitrogen, mg/dL	18 (14-27)	22 (16-33)	27 (19-43)	42 (27-59)	20 (15-31)	<0.001
Chloride, mEq/L	103 (100-106)	103 (99-106)	102 (98-105)	101 (97-105)	103 (100-106)	<0.001
Anion gap	12 (10-14)	12 (10-15)	13 (10-16)	13 (11-16)	12 (10-15)	<0.001
Admission diagnosis						
Cardiac arrest	796 (11.7%)	403 (13.8%)	83 (14.5%)	126 (14.4%)	1,408 (12.6%)	0.004
Shock	879 (12.9%)	515 (17.6%)	122 (21.3%)	220 (25.2%)	1,736 (15.6%)	<0.001
Cariogenic shock	710 (10.5%)	414 (14.2%)	106 (18.5%)	173 (19.8%)	1,403 (12.6%)	<0.001
Septic shock	386 (5.7%)	224 (7.7%)	46 (8.0%)	87 (10.0%)	743 (6.7%)	<0.001
Congestive heart failure	2,947 (43.4%)	1,549 (53.1%)	339 (59.2%)	564 (64.6%)	5,399 (48.4%)	<0.001
Respiratory failure	1,469 (21.6%)	811 (27.8%)	197 (34.4%)	347 (39.7%)	2,824 (25.3%)	<0.001
Acute coronary syndrome	3,263 (48.0%)	1,148 (39.3%)	241 (42.1%)	307 (35.2%)	4,959 (44.4%)	<0.001
Illness severity scores						
APACHE score	55 (42-69)	61 (47-75)	65 (51-83)	74 (61-91)	58 (45-74)	<0.001
SOFA score on admission	2 (1-4)	3 (1-6)	4 (2-6)	5 (3-8)	2 (1-5)	<0.001
Braden score	18 (16-20)	18 (15-20)	18 (15-20)	17 (14-19)	18 (15-20)	<0.001
M-CARS	1 (0-3)	2 (1-4)	2 (1-4)	3 (2-5)	2 (0-3)	<0.001
Ventilatory status						
Any ventilation	1,737 (25.4%)	957 (32.6%)	204 (35.4%)	372 (42.5%)	3,270 (29.1%)	<0.001
Invasive ventilation	1,037 (15.1%)	556 (18.9%)	118 (20.5%)	215 (24.6%)	1,926 (17.1%)	<0.001
Noninvasive ventilation	930 (13.6%)	531 (18.1%)	123 (21.4%)	220 (25.1%)	1,804 (16.1%)	<0.001
Length of stay (d)						
ICU length of stay	1.8 (1.0-2.9)	1.8 (1.0-3.0)	1.9 (1.0-3.1)	1.9 (1.0-3.4)	1.8 (1.0-2.9)	0.001
Hospital length of stay	4.3 (2.7-8.1)	4.8 (2.7-9.1)	5.1 (2.8-9.0)	5.5 (3.0-9.9)	4.6 (2.8-8.7)	<0.001
Misc ICU therapies						
CVVH during ICU stay	82 (1.2%)	61 (2.1%)	18 (3.1%)	51 (5.8%)	212 (1.9%)	<0.001
Dialysis during ICU stay	219 (3.2%)	149 (5.1%)	44 (7.6%)	99 (11.3%)	511 (4.5%)	<0.001
Vasopressors combined	1,300 (19.0%)	671 (22.9%)	147 (25.5%)	303 (34.6%)	2,421 (21.6%)	<0.001
Inotropes combined	488 (7.1%)	264 (9.0%)	48 (8.3%)	97 (11.1%)	897 (8.0%)	<0.001
Intra-aortic balloon pump	541 (7.9%)	281 (9.6%)	58 (10.1%)	61 (7.0%)	941 (8.4%)	0.008
Coronary angiography	4,357 (63.6%)	1,554 (52.9%)	304 (52.8%)	374 (42.7%)	6,589 (58.7%)	<0.001
Percutaneous coronary intervention	2,745 (40.1%)	919 (31.3%)	195 (33.9%)	210 (24.0%)	4,069 (36.2%)	<0.001
In-hospital arrest	157 (2.3%)	90 (3.1%)	17 (3.0%)	29 (3.3%)	293 (2.6%)	0.069
LVEF from TTE in iospital	52 (37-61)	49 (32-60)	49 (32-60)	45 (30-60)	50 (35-60)	<0.001
Other mechanical circulatory support	40 (0.6%)	25 (0.9%)	8 (1.4%)	3 (0.3%)	76 (0.7%)	0.046
Pulmonary artery catheter	552 (8.1%)	298 (10.2%)	68 (11.8%)	66 (7.5%)	984 (8.8%)	<0.001
Red blood cell transfusion in ICU	682 (10.0%)	396 (13.5%)	77 (13.4%)	147 (16.8%)	1,302 (11.6%)	<0.001

Values are median (IQR) or n (%).

AI-ECG = artificial intelligence enhanced electrocardiogram; APACHE = Acute Physiology and Chronic Health Evaluation; CICU = cardiac intensive care unit; CVVH = continuous veno-venous hemofiltration; ICU = intensive care unit; LVEF = left ventricular ejection fraction; M-CARS = Mayo Cardiac Intensive Care Unit Admission Risk Score; Misc = miscellaneous; SOFA = sequential organ failure assessment; TTE = transthoracic echocardiography.

FP AI-ECG results were at increased risk of in-hospital mortality (unadjusted OR: 1.63; 95% CI: 1.40-1.90; $P < 0.0001$). This mortality risk was incrementally higher for FN patients (unadjusted OR: 2.47; 95% CI: 1.93-3.16; $P = 0.001$) and TP patients, respectively (unadjusted OR: 3.25; 95% CI: 2.68-3.95; $P < 0.0001$; **Figure 1**). The prognostic performance of ICU clinical risk scores (APACHE, M-CARS, SOFA) was less prognostic in comparison to FN and TP patients (OR: 1.05-1.88) (Supplemental Table 1). The mean decrease in accuracy was greatest for M-CARS followed by the AI-ECG probability of hyperkalemia; the mean decrease in Gini Index was greatest for M-CARS, followed by age and the AI-ECG probability of hyperkalemia; the admission laboratory potassium value had lower variable importance by both metrics, suggesting a lesser contribution to prediction of in-hospital mortality.

MULTIVARIABLE ADJUSTMENT; IN-HOSPITAL AND 30-DAY MORTALITY. After multivariable adjustment for age, CCI, and M-CARS, the probability of AI-ECG predicted hyperkalemia on CICU admission remained directly associated with in-hospital mortality (adjusted OR: 1.06 per 0.1 unit increase in AI-ECG predicted hyperkalemia; 95% CI: 1.025-1.097; $P = 0.001$) and 30-day mortality (adjusted HR: 1.03 per 0.1 higher; 95% CI: 1.01-1.06; $P = 0.009$). The association with in-hospital mortality persisted after adjustment for admission potassium value (adjusted OR: 1.041 per 0.1; 95% CI: 1.004-1.080; $P = 0.029$), although the association with 30-day mortality was mitigated (adjusted HR: 1.02 per 0.1 higher; 95% CI: 0.99-1.05; $P = 0.23$). After multivariable adjustment, patients categorized with a TP AI-ECG had higher hospital mortality (adjusted OR: 1.660; 95% CI: 1.323-2.083; $P < 0.0001$) than patients with either FN AI-ECG (adjusted OR: 1.630; 95% CI: 1.221-2.176; $P = 0.001$) or FP AI-ECG (adjusted OR: 1.211; 95% CI: 1.015-1.444; $P = 0.03$).

UNADJUSTED 1-YEAR SURVIVAL. A total of 2,549 patients died within 1 year after CICU admission (including hospital deaths), and 1,200 patients had follow-up of <1 year but were alive at the last follow-up. Evaluating AI-ECG as a continuous variable, the AI-ECG probability of hyperkalemia remained associated with decreased 1-year survival (unadjusted HR: 1.12 per 0.1 U increase in AI-ECG predicted hyperkalemia; 95% CI: 1.10-1.14; $P < 0.0001$). One-year survival incrementally decreased for FP, FN, and TP patients (**Figure 2**). Survival characteristics for patients at 1-year posthospital discharge were similar (Supplemental Figure 3).

MULTIVARIABLE ADJUSTED 1-YEAR SURVIVAL. After multivariable adjustment for age, CCI, and M-CARS, AI-ECG probability of hyperkalemia remained associated with decreased 1-year survival (adjusted HR: 1.031 per 0.1 unit increase in AI-ECG predicted hyperkalemia; 95% CI: 1.013-1.050; $P = 0.001$). This probability association lost statistical significance after further adjustment for potassium value nearest CICU admission (adjusted HR: 1.016 per 0.1 unit increase; 95% CI: 0.997-1.036; $P = 0.1$). After multivariable adjustment, patients categorized as FN by AI-ECG had the lowest 1-year survival (HR: 1.454; 95% CI: 1.25-1.691; $P < 0.0001$) compared to patients with TP AI-ECG (HR: 1.366; 95% CI: 1.211-1.54; $P < 0.0001$) or with FP AI-ECG (HR: 1.123; 95% CI: 1.025-1.230; $P = 0.013$).

We have included full unadjusted and adjusted multivariable analysis tables in our supplement (Supplemental Analyses).

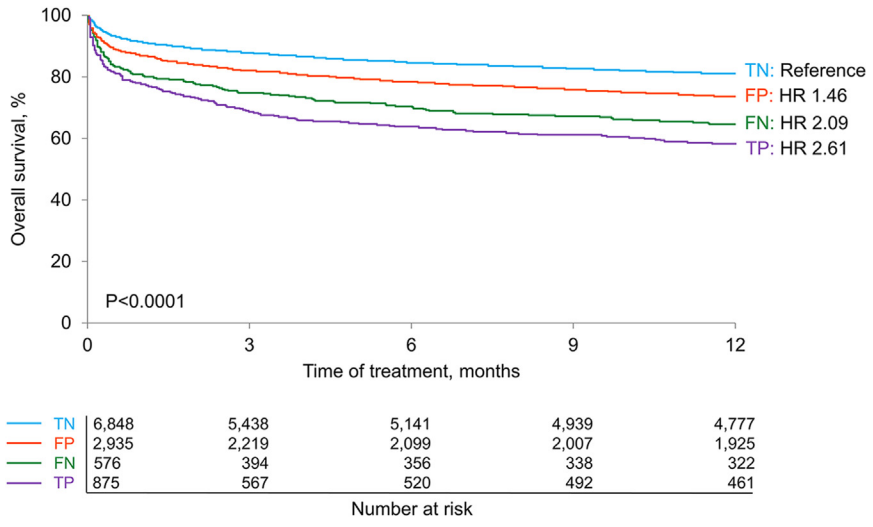
EXCLUSION OF HYPOKALEMIC PATIENTS

As a similar mortality association exists with hypokalemia, a secondary analysis was performed where hypokalemic (K <3.5 mEq/L) were excluded. Results from this analysis were minimally different with similar in-hospital mortality and 1-year survival (Supplemental Figures 4 and 5).

DISCUSSION

In this analysis of more than 11,000 CICU patients, we demonstrated that an AI-ECG algorithm developed to detect hyperkalemia could identify patients with an increased risk of dying during and after hospitalization, acting as a novel ECG-based prognostic biomarker. While the AI-ECG algorithm has been shown to have a valuable ability to predict hyperkalemia, this analysis highlights the associated risk-stratification ability of the AI-ECG, which extends beyond what could be explained by laboratory potassium value alone. We observed that AI-ECG had a strong in-hospital mortality association independently (FP) and in conjunction with laboratory hyperkalemia (TP) with a similar risk association for 1-year survival. The AI-ECG association with in-hospital mortality, and to a lesser extent, 30-day and 1-year mortality, persisted following adjustment for covariates and admission potassium value. This analysis provides evidence that the AI-ECG is a useful diagnostic and prognostic tool in CICU patients, and that the abnormalities identified by AI-ECG can refine risk stratification beyond the underlying conditions they predict (**Central Illustration**).

FIGURE 2 **Long-term Outcomes of Hyperkalemia as Predicted by AIECG and Measured by Laboratory Analysis**

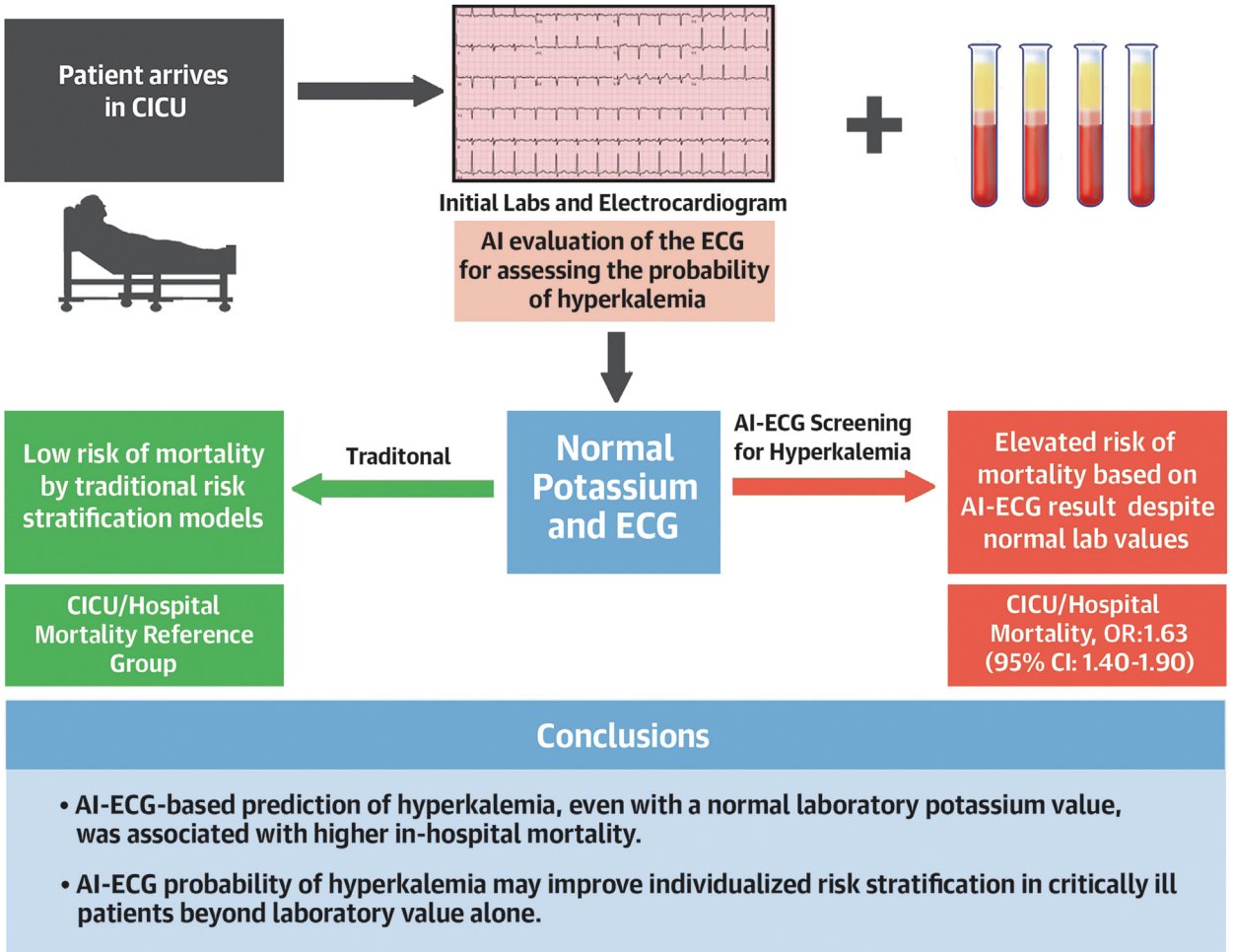


Kaplan-Meier 1-year survival curves based on predicted (by artificial intelligence electrocardiogram) and observed (by laboratory confirmation) hyperkalemia. $P < 0.0001$ between all groups. FN = false negative; FP = false positive; TP = true positive; TN = true negative.

Our work parallels Lin et al, who describe a similar AI-ECG to predict potassium value with outcomes implications.[15] In their study, an AI algorithm applied to a 12-lead ECG yielded blood potassium value predictions (1.5-7.5 mmol/L) rather than a probability of hyperkalemia or hypokalemia. They demonstrated a mortality association with significantly abnormal laboratory potassium values and AI-ECG-predicted dyskalemia.[15] Interestingly, this group identified a similar pattern of AI-ECG risk-modification with a respectively increasing HR for FP, FN, and TP AI-ECG to lab hyperkalemia/mortality relationship, implying that the serum potassium level was more strongly associated with outcomes than the AI-ECG despite their complementary prognostic information.[15] While using an entirely separate AI-ECG model, patient population, and hyperkalemia definition, we identified a strikingly similar pattern of risk stratification. This AI-ECG to laboratory discordance, with independent prognostic value, is an interesting attribute of these algorithms, indicating their potential scalability. The finding that the AI-ECG could provide added risk stratification in patients with either high or normal laboratory potassium levels could suggest that perhaps it is the effect of abnormal potassium levels on the myocardium which is most crucial. We acknowledge that a more transparent AI system to understand better these discrepant results would be beneficial and is an area of ongoing research.

This analysis mirrors our previous work utilizing the AI-ECG algorithm to detect LVSD.[9,16] Similarly, AI-ECG prediction of LVSD was associated with in-hospital mortality and 1-year survival in CICU patients providing an additive risk-modifier alongside LVSD identified by transthoracic echocardiogram.[9] In each of our studies, we observe increasing in-hospital mortality between TN, FP, FN, and TP groups, respectively, based on AI-ECG prediction of underlying pathology (ie, LVSD or hyperkalemia). Interestingly, FP and FN AI-ECG results for LVSD demonstrated similar 1-year survival on Kaplan-Meyer analysis, while we observed higher 1-year mortality with FN vs FP in our present AI-ECG hyperkalemia analysis. The explanation for this 1-year mortality difference is hypothetical. However, early ECG-based identification of imminent structural cardiac pathophysiology (LVSD) may carry a similar risk as the later manifestation of structural heart disease, which does not always trigger a positive AI-ECG result (ie, FN). As hyperkalemia is not a progressive, structural cardiac pathology, nor is it a consistent electrolyte abnormality in critically ill patients, the long-term AI-ECG prediction for hyperkalemia alone (FP result) may not carry the same survival characteristics as the AI-ECG for LVSD. However, it is worth considering that these FP and TP AI-ECG results reflect underlying myocardial disease, which may experience additional impact from

CENTRAL ILLUSTRATION **Mortality Risk-Stratification in the Cardiac Intensive Care Unit Utilizing an Artificial Intelligence Enhanced Electrocardiogram to Predict Hyperkalemia**



Harmon DM, et al. JACC Adv. 2024;3(9):101169.

CICU = cardiac intensive care unit; ECG = electrocardiogram.

fluctuations in blood potassium levels, even within the 'normal' range with prognostic implications. Indeed, those with AI-ECG suggestive of LVSD are substantially more likely to develop LVSD by transthoracic echocardiogram during follow-up.[16] Perhaps a similar phenomenon occurred with the AI-ECG prediction of hyperkalemia.

In this study, we were able to demonstrate that the AI-ECG has similar risk-stratification ability consistent with our prior work, which used a more lenient definition of hyperkalemia (>5.0 mEq/L).[2] Notably, the use of a lower threshold for hyperkalemia has degraded the AUC of the AI-ECG algorithm in prior analyses. Interestingly, from this CICU risk-based analysis, we have identified an at-risk FP group that carries an independently increased risk for overall mortality (both in-hospital and at 1-year), albeit to a lesser extent than laboratory hyperkalemia. The defining characteristic of this FP group is not entirely clear, and further investigation is warranted to understand better what may place this population at elevated mortality risk, even with normokalemia without unprecedented demographic, comorbidity, or illness severity characteristics. We hypothesize that the AI-ECG can detect subtle myocardial electrical signs that correlate predominantly with the myocardial effects of hyperkalemia but may, in some patients, reflect underlying subclinical myocardial

disease with an adverse prognosis. Such abnormalities were surprisingly common in our cohort, particularly in comparison to hyperkalemia which was less prevalent and carried a stronger unfavorable prognosis. However, based on the findings of our machine learning analysis designed to determine the relative importance for mortality prediction, the AI ECG was more important for mortality prediction than the laboratory potassium. Notably, it remains unclear whether hyperkalemia (predominantly mild in our study) directly contributed to mortality or was instead a marker for underlying disease not captured by our covariate adjustment.

Initially, the AI-ECG algorithm for hyperkalemia was intended to identify patients with a high probability of serum potassium >5.5 mEq/L.[8] Unsurprisingly, the use of a lower threshold for hyperkalemia (K >5.0 mEq/L) degraded the AUC of the AI-ECG algorithm compared to the derivation study. We note the AUC of the AI-ECG in this present study, using a K cutoff of 5.0 mEq/L was 0.71, compared to the AUC of 0.85 to 0.88 reported in the original model validation.[8] However, this original validation process excluded patients with lab potassium values between 5.3 and 5.7 mEq/L, and when these patients with mid-range K were included, the performance dropped to 0.82 to 0.84 in supplemental analysis.[8] In our present study, when the K cutoff was increased to 5.5 mEq/L, our AUC improved to 0.76 (and further to 0.79 with a K cutoff of 6 mEq/L). Given the specific use of the algorithm in critically ill CICU patients, a performance drop from 0.83 to 0.76 is unsurprising given the multiple potential confounders present in the CICU setting (ie, mechanical ventilation and vasoactive medications among others). These findings mirror similar validation studies observing the performance drop of the AI-ECG algorithm for LVSD in hospitalized patients.[9,17]

On a similar note, there was a fair amount (5.1%) of patients with FN AI-ECG results. This result is noteworthy as the OR for the FN patient population was 2.47 emphasizing the predictive value of laboratory hyperkalemia in the CICU setting. Given the above discussion, with a more liberal potassium cutoff of 5.0 mEq/L and operating point of sensitivity = specificity compared to a high-sensitivity cutoff, it is unsurprising to see this amount of FN patients. In the CICU, where laboratory draws are frequent, and patients are typically on continuous ECG monitoring, the AI-ECG for hyperkalemia can be used an additive prognostication tool rather than substitute for potassium monitoring. However, when considering use outside the CICU or hospital setting, more stringent potassium cutoffs (5.5 mEq/L or greater) and high-sensitivity thresholds should be applied to help lower the amount of FN test results. Interestingly, in the derivation study, when more stringent thresholds were applied, FN patients underwent repeat laboratory testing within 8 hours.[8] Greater than 50% of these patients had a repeat potassium <5.5 mEq/L and only 14% of FN patients (<1% of all test results) were actually treated for hyperkalemia.[8]

While we acknowledge the differences in AUC and other performance metrics between the derivation study and current study, we similarly emphasize that the present study was *not* a validation study, and these analyses are only exploratory. The study population contained patients included in the original AI-ECG derivation study, which introduces significant bias. Our primary intent from this study was to better understand the relationship between AI-ECG algorithm results and associated mortality-risk, which had not previously been described for this AI-ECG algorithm.

STUDY LIMITATIONS. Our work is best understood in the context of its limitations. Results from this retrospective cohort analysis should be considered hypothesis-generating rather than definitive, as there could be potential underlying biases from missing data or unmeasured confounding variables. We acknowledge the potential overlap in patients included both in this present study and the original derivation study, as this may confound some AI-ECG results. However, this CICU population differs from the mixed inpatient/output populations used to derive and validate the AI-ECG for identification of hyperkalemia, and the focus of this study was patient outcomes rather an algorithm performance. There are also notable limitations of the AI algorithm itself, as the AI-ECG does not currently provide details on how the algorithm's prediction of hyperkalemia was made, as is the case with many similar AI-ECG-based algorithms that lack transparency. A supplemental ECG signal analysis was performed in the algorithm derivation study to better understand what may trigger a positive result. Both markedly abnormal and minimally abnormal ECGs could trigger a positive result, and thus no specific identifiable ECG features were consistently associated with a positive AI-hyperkalemia score.[8] Creating a more transparent model with interpretable results is at the forefront of our team's priorities. We also acknowledge our ECG and potassium data lacked a time-stamp and were

labeled only as 'admission' within the database (ie, ECG on admission and potassium on admission). While it can be assumed the vast majority of these ECG and potassium pairs would both occur within 1 to 2 hours of admission and of each other, as is generally the case for patients admitted to the CICU, this cannot be confirmed. As such, treatment for significant hyperkalemia, acute changes in patient status, and other variables may have impacted the serum potassium between ECG collection and laboratory draw resulting in variations of data/algorithm accuracy.

This cohort was obtained from a single large academic medical center, and our CICU patient population may be different from other centers, particularly in terms of ethnic and racial diversity that could influence generalizability; as such, external validation utilizing our AI algorithm in other CICU settings would be significantly helpful. Our time-to-event analyses including postdischarge survival should be considered exploratory, as we could not ensure that all deaths occurring outside of our health system were captured. We acknowledge the similar findings from Lin et al with their own AI-ECG algorithm demonstrating similar mortality characteristics in a predominantly Asian population as opposed to our mostly White cohort.[15]

CONCLUSIONS

AI-ECG-based prediction of hyperkalemia, even with a normal laboratory potassium value, was associated with higher in-hospital mortality and 1-year survival in CICU patients. This study demonstrated that laboratory potassium value and AI-ECG probability of hyperkalemia are complementary risk factors. The AI algorithm can detect prognostically important ECG abnormalities affecting patients' short- and long-term survival. Integrating this technology into the electronic health record may enable rapid individualized risk stratification in critically ill patients.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Mayo Clinic has licensed the underlying technology to Anumana, a portable, handheld ECG device maker. Mayo Clinic may receive financial benefits from the use of this technology, but at no point will Mayo Clinic benefit financially from its use for the care of patients at Mayo Clinic. Drs Dillon, Attia, and Friedman may also receive financial benefits from this agreement. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Data collection and statistical analysis were performed independently by JCJ, who was not involved in developing or validating the proprietary technology and had no financial stake in the technology.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: This study demonstrates the relationship between AI-ECG prediction of hyperkalemia and associated mortality, similar to the described relationship between laboratory hyperkalemia and mortality in the critically ill. The AI-ECG for hyperkalemia appeared to be an independent risk factor as patients with FP AI-ECG (high AI-ECG probability of hyperkalemia with normal serum potassium) had higher mortality than their TN counterparts (negative AI-ECG and normal serum potassium), possibly reflective of subclinical myocardial disease.

TRANSLATIONAL OUTLOOK: This AI-ECG algorithm, as well as others, may allow for improved, rapid risk-stratification of critically ill patients. Further study should focus on the prospective application of these algorithms in intensive care units and evaluate the clinical impact of AI-ECG enhanced illness triage.

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KEY WORDS artificial intelligence, critical care, electrocardiogram, hyperkalemia, outcomes

APPENDIX For supplemental analysis, tables, and figures, please see the online version of this paper.