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Artificial intelligence-enabled electrocardiography identifies severe dyscalcemias and has prognostic value

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ABSTRACT

Context: Abnormal serum calcium concentrations affect the heart and may alter the electrocardiogram (ECG), but the detection of hypocalcemia and hypercalcemia (collectively dyscalcemia) relies on blood laboratory tests requiring turnaround time.

Objective: The study aimed to develop a bloodless artificial intelligence (AI)-enabled (ECG) method to rapidly detect dyscalcemia and analyze its possible utility for outcome prediction.

Methods: This study collected 86,731 development, 15,611 tuning, 11,105 internal validation, and 8401 external validation ECGs from electronic medical records with at least 1 ECG associated with an albumin-adjusted calcium (aCa) value within 4 h. The main outcomes were to assess the accuracy of AI-ECG to predict aCa and follow up these patients for all-cause mortality, new-onset acute myocardial infraction (AMI), and new-onset heart failure (HF) to validate the ability of AI-ECG-aCa for previvor identification.

Results: ECG-aCa had mean absolute errors (MAE) of 0.78/0.98 mg/dL and achieved an area under receiver operating characteristic curves (AUCs) 0.9219/0.8447 and 0.8948/0.7723 to detect severe hypercalcemia and hypocalcemia in the internal/external validation sets, respectively. Although < 20 % variance of ECG-aCa could be explained by traditional ECG features, the ECG-aCa was found to be associated with more complications. Patients with ECG-hypercalcemia but initially normal aCa were found to have a higher risk of subsequent all-cause mortality [hazard ratio (HR): 2.05, 95 % conference interval (CI): 1.55–2.70], new-onset AMI (HR: 2.88, 95 % CI: 1.72–4.83), and new-onset HF (HR: 2.02, 95 % CI: 1.38–2.97) in the internal validation set, which were also seen in external validation.

Conclusion: The AI-ECG-aCa may help detecting severe dyscalcemia for early diagnosis and ECG-hypercalcemia also has prognostic value for clinical outcomes (all-cause mortality and new-onset AMI and HF).

Abbreviations: ECG, Electrocardiography; AI, Artificial intelligence; DLM, Deep learning models; CVD, cardiovascular diseases; AI-ECG, AI-enabled ECG; AMI, Acute myocardial infraction; HF, Heart failure; aCa, Albumin-adjusted calcium; tCa, Total calcium; Alb, albumin; ICD, International classification of diseases; DM, Diabetes mellitus; HTN, Hypertension; HLP, Hyperlipidemia; CKD, Chronic kidney disease; STK, Stroke; CAD, Coronary artery disease; Afib, Atrial fibrillation; COPD, Chronic obstructive pulmonary disease; HCO_3, Bicarbonate; GLU, Glucose; CK, Creatine kinase; CRP, C-reactive protein; TnI, Troponin I; pBNP, NT-pro-B type natriuretic peptide; ROC, Receiver operating characteristic; AUC, Area under curve; HR, Hazard ratios; 95 % CI, 95 % conference interval; NPV, Negative predictive value; PPV, Positive predictive value; Na, Sodium; BCP, bromocresol purple.

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1. Introduction

Calcium is an important cation involved in several biological activities and neuromuscular functions Its homeostasis is maintained by the gastrointestinal tract (absorption), bone (resorption), and kidneys (reabsorption) and regulated by several factors including parathyroid hormone, vitamin D, and various cytokines etc. Calcium disturbance or dysregulation leads to abnormal serum calcium concentration (hypocalcemia or hypercalcemia, collectively dyscalcemia), commonly encountered electrolyte imbalances in clinical practice. It has been reported that the incidence of hypocalcemia and hypercalcemia in hospitalized patients ranges from 20 to 40 % and 3–7 % [1], respectively. Dyscalcemia may cause diverse clinical symptoms and signs, especially neuromuscular features, and are associated with higher morbidity and mortality [2]. To date, the detection of hypocalcemia and hypercalcemia relies on laboratory measurement and associated turnaround times. Therefore, the early diagnosis of dyscalcemia with timely management is still challenging.

Both hypocalcemia and hypercalcemia significantly affect cardiac physiology and activity. Electrocardiography (ECG) may detect these cardiac electrical changes and is a prompt and non-invasive bedside tool. The reported ECG findings associated with hypocalcemia include ST segment and QT prolongation [3], ST-elevation [4], AV block [5], and intraventricular conduction delay [6]. The ECG findings associated with hypercalcemia include shortened ST segment and QT interval [7], Osborn J-wave [8], widespread T-wave inversion [9], and Torsades de pointes [10]. Although these ECG changes have been well emphasized, even experienced clinicians frequently do not notice all these changes.

Artificial intelligence (AI) techniques based on deep learning models (DLM) have been shown to achieve human-level performance [11] and effectively detect cardiac diseases in large, annotated ECG datasets [12–17]. Using a large data-driven DLM, we have successfully developed the AI-ECG12Net to rapidly detect dyskalemias in the ED [18]. Building on this platform, we sought to expand detection to the early diagnosis of hypocalcemia and hypercalcemia. Moreover, AI-enabled ECG (AI-ECG) systems have been demonstrated to identify previvors of cardiovascular diseases (CVD) [19]. Recently, we have also demonstrated that ECG-dyskalemia (normal potassium by lab but dyskalemia by AI-ECG) may serve as a biomarker for worse physical conditions and an independent predictor for future adverse outcomes [20]. Similarly, we sought to investigate the additional value of AI-identified dyscalcemia for prdicting clinical outcomes (all-cause mortality, new-onset acute myocardial infarction [AMI] and new-onset heart failure [HF]).

The aim of this study was to build a DLM for dyscalcemia detection, validate its performance in two independent hospitals, and to examine the previvors identified by ECG-dyscalcemia. Our AI-ECG dyscalcemia platform demonstrated accurate performance in detecting severe dyscalcemia and was a prognostic indicator of subsequent all-cause mortality, new-onset AMI, and new-onset HF in patients with ECG-hypercalcemia but initial normocalcemia.

2. Material and methods

2.1. Data source and population

The dataset generation is summarized in Fig. 1. We did a retrospective study from two hospitals of the Tri-Service General Hospital system in Taipei, Taiwan between January 1, 2010 and September 30, 2021. The academic medical center in NeiHu District (hospital A) provided the samples for DLM training and internal validation, and the community hospital in Zhongzheng District (hospital B) was used for external validation. We collected patients who had at least one pair of ECG and albumin-adjusted calcium (aCa) measurement within 4 h, and there were 69,627 and 8,401 patients from hospitals A and B, respectively.

The development set included 52,528 patients who first visited hospital A between January 2017 and September 2021 and provided 86,731 ECGs for DLM training. The tuning set included 5,994 patients who first visited hospital A between January 2016 and December 2016 and provided 15,611 ECGs to guide the training process and determine cut-off points. The internal validation set included 11,105 patients who first visited hospital A before December 2015 and it was the primary source of accuracy tests of the DLM. We only used each patient's first record to avoid data dependency and ensure statistical independence. Using the same criteria for hospital B, we identified 8,401 patients as the external validation set.

2.2. Data collection

This study used the standard 12-lead ECG collected from Philips machines (PH080A), which involved 5,000 voltage–time trace signals for each lead (500 Hz sampling frequency for 10 s). Because the sensitivity for the diagnosis of dyscalcemia using serum total calcium (tCa) was low [21] and the number of serum ionized calcium measurement

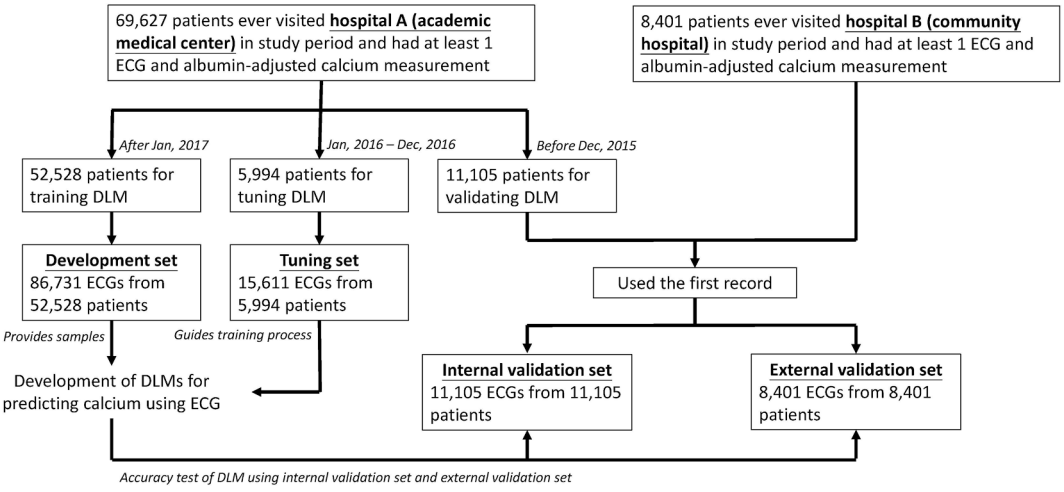

Fig. 1. Development, tuning, internal validation, and external validation set generation and ECG labeling of albumin-adjusted calcium. Schematic of the data set creation and analysis strategy, which was devised to ensure robust and reliable data sets for training, validating, and testing of the network. Once a patient's data were placed in one of the data sets, that individual's data were used only in that set, avoiding 'cross-contamination' among the training, validation, and test data sets. The details of the flow chart and how each of the data sets was used are described in the Methods.

was limited, aCa was used as the target indicator in this study. The aCa was calculated using the formula: aCa = tCa + [4 − Alb] × 0.8, where tCa is the serum concentration of tCa in mg/dL and Alb is the serum concentration of albumin in g/dL. We divided the data into seven categories based on aCa concentrations: severe hypocalcemia (aCa ≤ 6.5), moderate hypocalcemia (6.5 < aCa ≤ 7.5), mild hypocalcemia (7.5 < aCa ≤ 8.5), normal (8.5 < aCa < 10.5), mild hypercalcemia (10.5 ≤ aCa < 11.5), moderate hypercalcemia (11.5 ≤ aCa < 12.5), and severe hypercalcemia (12.5 ≤ aCa).

Patients' characteristics and associated co-morbid conditions were collected using an electronic health record system. We used International Classification of Diseases (ICD), Ninth Revision and Tenth Revision to define diabetes mellitus (DM), hypertension (HTN), hyperlipidemia (HLP), chronic kidney disease (CKD), AMI, stroke (STK), coronary artery disease (CAD), HF, atrial fibrillation (Afib), and chronic obstruction pulmonary disease (COPD) as previously reported [22]. The time nearest laboratory data were assigned to each ECG records, including renal and liver function profiles, complete blood cell count, electrolytes, blood pH, bicarbonate (HCO_3), glucose (GLU), creatine kinase (CK), C-reactive protein (CRP), troponin I (TnI), NT-pro-B type natriuretic peptide (pBNP), and D-dimer. Missing data were imputed using multiple imputations in multivariate analysis [23].

2.3. Investigation of clinical outcomes

Hypercalcemia may cause ST-segment elevation mimicking AMI [24–26] and AI-ECG has already been validated to identify previvors of HF [27]. Considering the association between dyscalcemia and mortality [2], we therefore selected all-cause mortality, new-onset AMI, and new-onset HF as endpoints to explore the ramifications of false positive findings in patients with lab-normal calcium levels [19]. For mortality, the survival time was calculated with reference to the date of the ECG record and we only included patients with followup hospital visits. Patient status (dead/alive) was captured through the electronic medical record. Moreover, data for alive visits were censored at the patient's last known hospital alive encounter to limit bias from incomplete records. For new-onset AMI and HF, patients with prior history of these diseases were excluded. The new-onset events were defined as the ICD records after the reference date and data were similarly censored to the patient's last hospital visit. There were 9,097, 7,300, and 6,781 at-risk cases in the internal validation set for all-cause mortality, new-onset AMI, and new-onset HF, respectively with median followup (in years, interquartile range, IQR) of 2.84 (0.44–5.96), 3.39 (1.10–6.15), and 3.48 (1.18–6.22) years, respectively. The longest follow up for every endpoint was just over of 10 years. The external validation set included 6,839, 6,242, and 5,428 at risk cases with median follow up (IQR) of 1.45 (0.22–3.86), 1.76 (0.39–4.07), and 1.69 (0.35–4.02) years, respectively. The longest follow up for every endpoint, again, was around 10 years.

2.4. Deep learning model

We developed a DLM using raw 12-lead ECG traces signals as input to estimate actual aCa, and the predicted aCa was called ECG-aCa in this study. We used the architecture of the ECG12Net [18] with a value range of ECG-aCa from 5 to 13. This value range was based on the number of samples (<200 out of range) and clinical relevance. Since physicians are most interested in symptomatic hypocalcemia (aCa ≤ 7) or symptomatic hypercalcemia (aCa ≤ 12), a value range of ECG-aCa from 5 to 13 mg/dl may be acceptable in clinical practice. The category-wise encoding technology and training details have been previously reported [22]. During the training process, we randomly cropped a length of 4,096 sequences as input. During the inference stage, two overlapping lengths of 4,096 sequences from the start and the end were used to generate predictions and averaged to give the final prediction. An oversampling process was implemented to ensure that rare cases of extreme aCa values were adequately recognized, which was based on weights computed on the prevalence of 20 equidistant intervals in the development cohort [22]. In summary, the DLM will provide aCa prediction using the raw ECG voltage–time traces of a 5,000 by 12 matrix.

Since the characteristics of "black box" in DLM [28], we tried to used known ECG features to establish the components of DLM. The known ECG features included the 8 quantitative ECG measures and 31 most popular diagnostic pattern classes. The 8 ECG measurements included heart rate, PR interval, QRS duration, QT interval, correct QT interval, P wave axis, RS wave axis, and T wave axis. Data for these variables were 88–100 % complete, and missing values were imputed using multiple imputations [23]. The 31 clinical diagnosis patterns were parsed from the structured findings statements based on the key phrases that are standard within the Philips system, which included abnormal T wave, atrial fibrillation, atrial flutter, atrial premature complex, complete AV block, complete left bundle branch block, complete right bundle branch block, first degree AV block, incomplete left bundle branch block, incomplete right bundle branch block, ischemia/infarction, junctional rhythm, left anterior fascicular block, left atrial enlargement, left axis deviation, left posterior fascicular block, left ventricular hypertrophy, low QRS voltage, pacemaker rhythm, prolonged QT interval, right atrial enlargement, right ventricular hypertrophy, second degree AV block, sinus bradycardia, sinus pause, sinus rhythm, sinus tachycardia, supraventricular tachycardia, ventricular premature complex, ventricular tachycardia, and Wolff-Parkinson-White syndrome. We used above variables to predict DLM-aCa using XGB classifier in tuning set, and the final XGB classifier only included the features could significantly improve the predictability. This analysis may increase the transparency of DLM prediction.

2.5. Statistical analysis and model performance assessment

All statistical analyses were completed in R version 3.4.4 and the significance level was set as $p < 0.05$. All analyses were conducted in both internal and external validation sets. The mean difference, Pearson correlation coefficients, and mean absolute errors were used for comparing the ECG-aCa and actual aCa. Receiver operating characteristic (ROC) curve and its area under curves (AUC) were the primary analyses for evaluating the diagnostic value of ECG-aCa for identifying mild to severe dyscalcemia. For the follow-up analysis, Kaplan-Meier (KM) curves were generated to evaluate the prognostic utility of ECG-aCa in patients with an initially normal measured aCa (8.5 < aCa < 10.5). Cox proportional hazard models were also fitted to calculate the grouping hazard ratios (HRs) and corresponding 95 % conference intervals (95 % CI). The C-index was the global indicator to quantify the contribution of continuous ECG-aCa to each cardiovascular event.

3. Results

3.1. Patients' characteristics

Patients' characteristics are shown in Table 1. In the internal/external validation sets, there were 20/27 (0.2 %/0.3 %), 68/77 (0.6 %/0.9 %), and 1,937/1,344 (17.4 %/16.0 %) patients with severe, moderate, and mild hypocalcemia, respectively. For hypercalcemia, 13/20 (0.1 %/0.2 %) severe, 22/41 (0.2 %/0.5 %) moderate, and 123/143 (1.1 %/1.7 %) mild cases in the internal/external validation sets, respectively. The patients in the internal validation set were 57.7 % male with mean age 55.1 ± 18.3 years old, which was significantly younger than the external validation set (53.9 % male, mean age 69.5 ± 17.2 years old). Corresponding to the older population, a higher prevalence of all disease histories was noted in the external validation set. The population heterogeneity between the two hospitals served to better evaluate the possible real-world performance of the system.

Table 1
Baseline characteristics.

	Development set	Tuning set	Internal validation set	External validation set
aCa group				
aCa ≤ 6.5	114(0.1 %)	47(0.3 %)	20(0.2 %)	27(0.3 %)
6.5 < aCa ≤ 7.5	536(0.6 %)	126(0.8 %)	68(0.6 %)	77(0.9 %)
7.5 < aCa ≤ 8.5	7766(9.0 %)	1664 (10.7 %)	1937(17.4 %)	1344(16.0 %)
8.5 < aCa < 10.5	76969(88.7 %)	13403 (85.9 %)	8922(80.3 %)	6749(80.3 %)
10.5 ≤ aCa < 11.5	955(1.1 %)	275(1.8 %)	123(1.1 %)	143(1.7 %)
11.5 ≤ aCa < 12.5	199(0.2 %)	44(0.3 %)	22(0.2 %)	41(0.5 %)
12.5 ≤ aCa	192(0.2 %)	52(0.3 %)	13(0.1 %)	20(0.2 %)
Demography				
Sex (male)	50676(58.4 %)	8651 (55.4 %)	6410(57.7 %)	4532(53.9 %)
Age (years)	60.8 ± 18.4	68.9 ± 16.4	55.1 ± 18.3	69.5 ± 17.2
BMI (kg/m^2)	24.1 ± 4.2	23.9 ± 4.3	24.3 ± 4.0	24.1 ± 4.2
Disease history				
DM	18569(21.4 %)	6121 (39.2 %)	2202(19.8 %)	3088(36.8 %)
HTN	26101(30.1 %)	8911 (57.1 %)	3505(31.6 %)	4810(57.3 %)
HLP	20676(23.8 %)	7707 (49.4 %)	2133(19.2 %)	3142(37.4 %)
CKD	21607(24.9 %)	6948 (44.5 %)	3318(29.9 %)	3748(44.6 %)
AMI	4193(4.8 %)	1461(9.4 %)	264(2.4 %)	285(3.4 %)
STK	13245(15.3 %)	4138 (26.5 %)	1405(12.7 %)	2236(26.6 %)
CAD	15302(17.6 %)	5520 (35.4 %)	2003(18.0 %)	2545(30.3 %)
HF	8188(9.4 %)	3360 (21.5 %)	950(8.6 %)	1410(16.8 %)
Afib	3958(4.6 %)	1749 (11.2 %)	502(4.5 %)	709(8.4 %)
COPD	9893(11.4 %)	3776 (24.2 %)	1620(14.6 %)	2406(28.6 %)
Laboratory data				
WBC (10^3/ul)	8.9 ± 7.4	10.0 ± 5.4	7.7 ± 4.6	9.8 ± 6.7
PLT (10^3/ul)	231.6 ± 90.8	219.6 ± 93.7	231.1 ± 74.6	213.7 ± 88.9
Hb (gm/dL)	12.7 ± 2.6	11.8 ± 2.6	13.3 ± 2.4	12.3 ± 2.6
Blood pH	7.4 ± 0.1	7.4 ± 0.1	7.4 ± 0.1	7.4 ± 0.1
HCO_3 (mmol/L)	23.2 ± 5.5	23.7 ± 5.0	24.1 ± 4.2	24.0 ± 4.6
Na^+ (mmol/L)	137.5 ± 5.4	136.3 ± 5.9	139.0 ± 5.0	136.1 ± 5.9
K^+ (mmol/L)	4.0 ± 0.7	4.0 ± 0.7	3.9 ± 0.5	4.0 ± 0.6
Cl^- (mmol/L)	103.8 ± 5.6	103.0 ± 6.6	104.1 ± 4.7	103.4 ± 6.1
tCa^{++} (mg/dL)	8.8 ± 0.8	8.6 ± 0.8	8.9 ± 0.7	8.5 ± 0.8
Mg^{++} (mg/dL)	2.1 ± 0.4	2.1 ± 0.4	2.1 ± 0.3	2.0 ± 0.3
IP (mg/dL)	3.6 ± 1.2	3.5 ± 1.3	4.1 ± 1.9	3.4 ± 1.2
iPTH (pg/mL)	261.9 ± 407.7	122.8 ± 235.7	75.5 ± 156.8	96.0 ± 182.8
GLU (gm/dL)	154.6 ± 100.2	165.0 ± 108.1	126.1 ± 83.7	158.9 ± 103.4
AST (U/L)	40.0 ± 141.3	46.1 ± 153.5	29.2 ± 76.8	39.2 ± 126.3
ALT (U/L)	35.8 ± 123.6	36.5 ± 128.6	27.6 ± 58.4	32.5 ± 93.7
BUN (mg/dL)	24.1 ± 24.0	32.4 ± 30.1	19.9 ± 20.2	26.8 ± 25.7
Cr (mg/dL)	1.5 ± 2.0	2.2 ± 2.8	1.3 ± 1.8	1.7 ± 2.1
Alb (g/dL)	3.7 ± 0.7	3.4 ± 0.6	4.0 ± 0.7	3.5 ± 0.6
CRP (mg/L)	6.2 ± 7.9	5.2 ± 7.1	2.8 ± 5.3	5.4 ± 7.2
pBNP (pg/mL)	6046.5 ± 10159.3	6035.7 ± 10515.8	2516.7 ± 6592.4	3891.7 ± 8028.6
D-dimer (ng/mL)	3586.3 ± 6223.9	2966.9 ± 5290.5	1897.8 ± 4309.1	2664.1 ± 5046.1
TnI (ng/mL)	1438.4 ± 7268.6	1128.2 ± 7144.9	285.2 ± 2746.2	393.1 ± 3524.5
CK (U/L)	351.0 ± 1371.8	259.1 ± 988.2	170.8 ± 722.9	202.2 ± 784.8

Abbreviations: aCa, albumin-adjusted calcium; BMI, body mass index; DM, diabetes mellitus; HTN, hypertension; HLP, hyperlipidemia; CKD, chronic kidney disease; AMI, acute myocardial infraction; STK, stroke; CAD, coronary artery disease; HF, heart failure; Afib, atrial fibrillation; COPD, chronic obstructive pulmonary disease; WBC, white blood cell count; PLT, platelet; Hb: hemoglobin; HCO_3, bicarbonate; Na^+, sodium; K^+, potassium; Cl^-, chloride; tCa^{++}, total calcium; Mg^{++}, magnesium; IP, inorganic phosphorus; iPTH, intact parathyroid hormone; GLU, glucose; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BUN, blood urea nitrogen; Cr, Creatinine; Alb, albumin; CRP, C-reactive protein; pBNP, NT-pro-B type natriuretic peptide; TnI, troponin I; CK, creatine kinase.

3.2. The comparison between ECG-aCa and actual aCa

Fig. 2A shows the scatter plot between ECG-aCa and actual aCa in the internal and external validation sets. The mean differences with standard deviations were −0.12(1.01) and −0.27(1.22) in the internal and external validation sets, respectively, which corresponded to mean absolute errors of 0.78 and 0.98 mg/dL. The results demonstrated a slight overestimation of ECG-aCa by the DLM, which might be due to the lower prevalence of hypocalcemia in the development set (9.7 %) compared to the internal/external validation sets (18.2 %/17.2 %). A modest correlation was seen in the Pearson correlation coefficients of 0.23/0.18 in the internal/external validation sets.

Although the absolute value of ECG-aCa might not be accurate enough to be a surrogate indicator of actual aCa, we still explored the diagnostic value of ECG-aCa in severe-to-mild dyscalcemia (Fig. 2B). Satisfactory AUCs of 0.9219 and 0.8948 were found to detect severe hypercalcemia and hypocalcemia in the internal validation set and external validation still found reliability (AUC = 0.8447/0.7723 for severe hyper/hypocalcemia) in a heterogeneous population. These high AUCs corresponded to sensitivities of 84.6 %/60.0 % for severe hypercalcemia and 75.0 %/63.0 % for severe hypocalcemia in the internal/external validation sets, respectively, and specificities of 95.2 %/90.5 % for severe hypercalcemia and 79.7 %/81.5 % for severe hypocalcemia. However, the values of AUCs were significantly diminished for detecting moderate (0.8031/0.7687) to mild (0.7285/0.6860) hypercalcemia and moderate (0.7837/0.7723) to mild (0.5949/0.5672) hypocalcemia. Although the ECG-aCa had very high negative predictive values (NPVs) of ≥ 99.9 % for severe hypercalcemia and hypocalcemia, the relatively low positive predictive values (PPVs) of 0.7–2.0 % were due to low prevalence, which might require further prognostic analysis in these false positive cases.

3.3. The components of ECG-aCa

Fig. 3A shows the relationship between known ECG changes and ECG-aCa. DLM identified ECG-hypercalcemia was associated with shorter QT interval, prolonged PR interval, higher T wave axis, lower RS wave axis, prolonged QRS duration, increased heart rate, and higher prevalence of left ventricular hypertrophy compared with ECG-normal cases. Conversely, DLM identified ECG-hypocalcemia was associated with prolonged QT interval, shorter PR interval, smaller T wave axis,

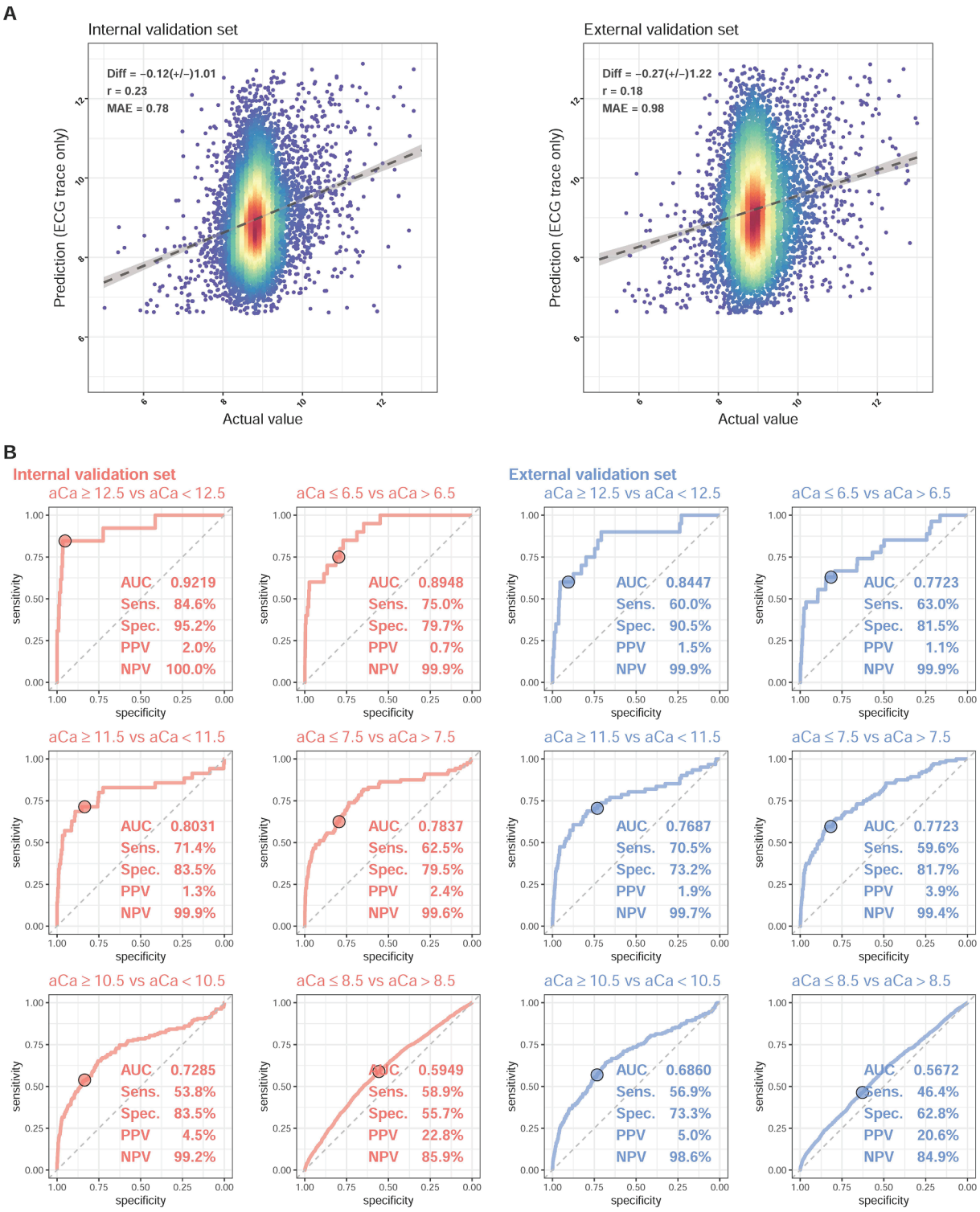

Fig. 2. Accuracy of albumin-adjusted calcium (ECG-aCa). A. Scatter plots of predicted ECG-aCa compared to the actual aCa (Lab-aCa). The x-axis indicates the actual aCa and the y-axis presents the ECG-aCa. Red points represent the highest density, followed by yellow, green light blue, and dark blue. We presented the mean difference (Diff, Lab-aCa minus ECG-aCa), Pearson correlation coefficients (r), and mean absolute errors (MAE) to demonstrate the accuracy of DLM. The black lines with 95 % conference intervals are fitted via simple linear regression. B. The ROC curve of DLM predictions based on ECG to detect mild to severe dyscalcemia. Mild, moderate, and severe dyscalcemia were defined as an actual aCa (Lab-aCa) of ≥ 10.5, ≥11.5, and ≥ 12.5 for hypercalcemia and ≤ 8.5, ≤7.5, and ≤ 6.5 for hypocalcemia, respectively. The operating point was selected based on the maximum of Yunden's index in the tuning set and presented as a circle and the area under ROC curve (AUC), sensitivity (Sens.), specificity (Spec.), positive predictive value (PPV), and negative predictive value (NPV) were calculated based on it.

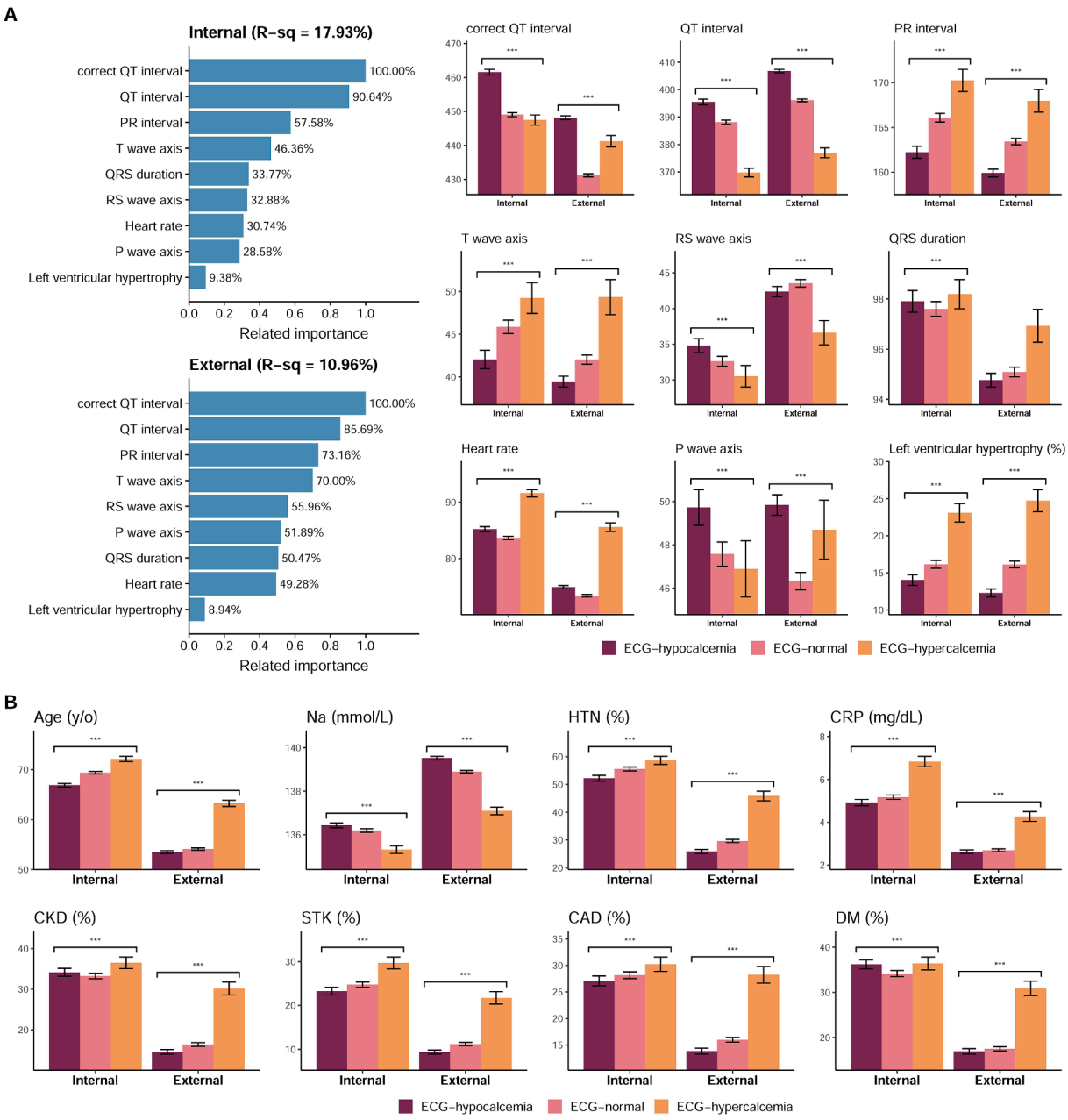

Fig. 3. The components of albumin-adjusted calcium (ECG-aCa). A. Corrected QT Interval and Relative Importance. The relative importance is based on the information gain of the XGB model and the R-square (R-sq) is the coefficient of determination to use selected ECG features for predicting ECG-aCa. B. Selected patients' characteristics in ECG-hypocalcemia, ECG-normal, and ECG-hypercalcemia. The AI-ECG predictions were classified as ECG-hypocalcemia (ECG-aCa $\leq$ 8.5), ECG-normal (8.5 < ECG-aCa < 10.5), and ECG-hypercalcemia (ECG-aCa $\geq$ 10.5). The analyses are conducted both in internal and external validation sets. (*: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$).

higher RS wave axis, prolonged QRS duration, and slight increased heart rate compared with ECG-normal cases. However, the explainable variation by these known ECG features for DLM-based ECG-aCa were only 17.93 % and 10.96 % in internal and external validation sets, respectively, which implies the presence of other features in the ECG extracted by the DLM. Patients with ECG-hypercalcemia (ECG-aCa $\geq$ 10.5) exhibited significantly greater age, predilection for HTN, CKD, STK, CAD, DM, higher CRP, and lower serum sodium (Na) than patients with normal ECG-aCa and ECG-hypocalcemia, which were consistent in both internal and external validation sets (Fig. 3B). The patient characteristics of ECG-hypocalcemia patients were closer to those in the normal ECG-aCa group. These results showed that patients with ECG-hypercalcemia were more likely to have complex medical illness than those with ECG-hypocalcemia and normocalcemia.

3.4. *All-cause mortality and the risk of developing new-onset AMI and HF*

All-cause mortality and the development of two major cardiovascular events in patients with normal serum aCa but abnormal ECG-aCa (false positive identifications by DLM) are shown in Fig. 4. The cumulative incidence rates at 2/4/6 years for all-cause mortality, new-onset AMI, and new-onset HF were 10.5 %/11.9 %/14.1 %, 2.9 %/4.6 %/5.4 %, and 5.7 %/7.1 %/9.8 % in the ECG-hypercalcemia (false positive) group with corresponding significant HRs (95 % CI) of 2.05 (1.55–2.70), 2.88 (1.72–4.83), and 2.02 (1.38–2.97) compared to the ECG-normal (true negative) group in the internal validation set, respectively. The C-index analyses also show the significant prognostic value on all-cause mortality (0.582, 95 % CI: 0.544–0.610), new-onset AMI (0.595, 95 % CI: 0.534–0.656), and new-onset HF (0.591, 95 %

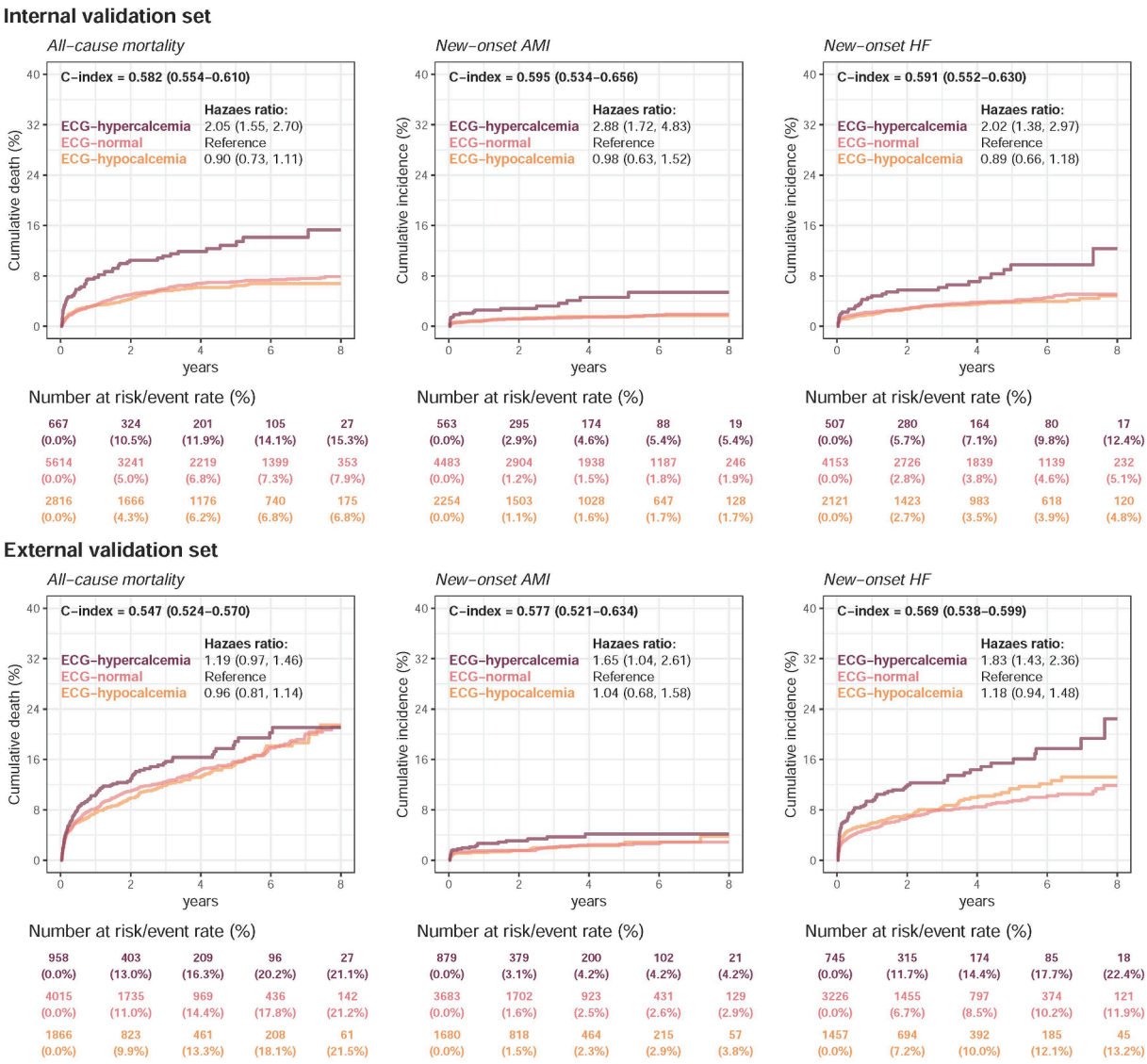

Fig. 4. Long-term incidence of developing cardiovascular outcomes in patients with an initially normal albumin-adjusted calcium (8.5 < aCa < 10.5) stratified by ECG-aCa. The AI-ECG predictions were classified as ECG-hypocalcemia (ECG-aCa $\leq$ 8.5), ECG-normal (8.5 < ECG-aCa < 10.5), and ECG-hypercalcemia (ECG-aCa $\geq$ 10.5). The C-index is calculated based on the continuous value of ECG-aCa with smoothing splines using the pspline basis function. The analyses are conducted both in internal and external validation sets. The table shows the at-risk population and cumulative risk for the given time intervals in each risk stratification.

CI: 0.552–0.630). In the external analysis, significantly higher risk of ECG-hypercalcemia on new-onset AMI (HR: 1.65, 95 % CI: 1.04–2.61), and new-onset HF (HR: 1.83, 95 % CI: 1.43–2.36) were still observed. Despite less significance of ECG-hypercalcemia on all-cause mortality, the C-index for continuous ECG-aCa was still significant for all-cause mortality (0.547, 95 % CI: 0.524–0.570). Similar analyses were also significant on new-onset AMI (C-index: 0.577, 95 % CI: 0.521–0.634) and new-onset HF (C-index: 0.569, 95 % CI: 0.538–0.599) in the external validation set. These results emphasize the relevance of ECG-aCa on prognosis.

4. Discussion

In this retrospective cohort study, we first built a DLM with segregated development, training, and tuning data of annotated aCa and ECG for dyscalcemia detection, then validated its performance in two independent hospitals, and further evaluated the prognostic value of ECG-dyscalcemia. AI-enabled ECG analysis achieved satisfactory diagnostic accuracy to detect severe hypercalcemia and hypocalcemia in both internal/external validation sets. For previvor prediction, patients with ECG-hypercalcemia but initially normal serum aCa had a higher risk of developing all-cause mortality, new-onset AMI, and new-onset HF in both internal and external validation sets.

Since the symptoms and signs of dyscalcemia may be subtle and vague, the awareness and recognition of dyscalcemia is still low [29]. It has been reported that many patients with final dyscalcemia had already received inappropriate treatment due to delayed diagnosis [30,31]. Furthermore, serum Ca concentration is not routinely measured in clinical practice worldwide; thus, the early detection of dyscalcemia remains challenging. A simple, convenient method of detecting dyscalcemia would be clinically useful. ECG is a noninvasive bedside tool which can detect the electrical signature of the heart's activity associated with dyscalcemia. Using a large aCa-annotated ECG driven DLM, we have successfully developed an AI-enabled ECG platform to identify dyscalcemia. The diagnostic accuracy with AUCs of 0.9219/0.8447 and 0.8948/0.7723 to detect severe hypercalcemia and hypocalcemia in internal and external validation were convincing.

Patients with symptomatic hypocalcemia such as carpopedal spasm,

tetany, seizures, heart failure, and abnormal ECG signs including QT interval prolongation need emergent intravenous calcium supplementation to prevent the devastating complications. Similarly, there is an urgent need to rapidly lower serum Ca concentration in patients with symptomatic hypercalcemia, including encephalopathy and abnormal hypercalcemia-related ECG findings (shortened QT interval, Osborn J-wave, widespread T-wave inversion, and Torsades de pointes). Of note, both severe hypocalcemia and hypercalcemia may decompensate from a chronic to acute state with critical dyscalcemia-induced cardiac events. Our AI-ECG aCa analysis also demonstrated a strong correlation between prolonged QT interval and ECG-hypocalcemia as well as shortened QT interval and ECG-hypercalcemia, which partially explains how DLM recognizes severe hypocalcemia and hypercalcemia with high accuracy. However, both mild hypocalcemia and hypercalcemia were difficult to diagnose by AI-ECG due to less changes to the ECG. This shortcoming of AI-ECG detection for mild dyscalcemia should be acknowledged, highlighting the need for more advanced AI-ECG training and development for early detection of mild dyscalcemia.

We also investigated the prognostic value of ECG-dyscalcemia, called previvors [19], since the ECG reflects the heart and systemic physiologic condition. We found that patients with ECG-hypercalcemia were more likely to have complex medical illnesses than those with ECG-hypocalcemia and normocalcemia. Patients with ECG-hypercalcemia also had higher risk of all-cause mortality and cardiovascular events. The prognostic information encapsulated by ECG-aCa was independent of the actual aCa, thus AI-enabled ECG identifies previvors of complications based on Ca, similar to predictions based on left ventricular dysfunction [27], age [32], and potassium [20]. Importantly, we also demonstrated that ECG-aCa was extensively associated with known ECG changes, as well as many unknown and higher order ECG abnormalities identified by the DLM. Unlike our group's recent findings that patients with ECG-hypokalemia carried a higher risk of mortality [20], we did not find a similar mortality risk with ECG-hypocalcemia. The reason may be related to lower accuracy of detecting mild hypocalcemia (AUC = 0.567–0.595).

Comparing our work with a previous study using DLM-enabled ECG with demographic information to detect dyscalcemia [33], there are some crucial differences to note. First, we used ECGs annotated with aCa, which is a better indicator of physiologic Ca since total calcium is affected by serum protein and albumin binding to free calcium. Second, the definition and gradation of dyscalcemia were different. In contrast to the previous study which only defined hypocalcemia as <8.5 mg/dl and hypercalcemia as greater than 10.5 mg/dl (three categories), our study further graded dyscalcemia into mild, moderate, and severe hypocalcemia and hypercalcemia (seven categories). Third, our AI-ECG Ca offered continuous quantitative output like laboratory Ca data despite similar AUCs (0.905 and 0.901) in both studies [33]. Fourth, our study demonstrated similar AUCs of 0.9219/0.8447 and 0.8948/0.7723 for detecting severe hypercalcemia and hypocalcemia without demographic information, respectively. Finally, the most distinguishing aspect of our study was the clinical outcomes follow up.

Some limitations of this study should be mentioned. First, we used albumin adjustment [34] to standardize biologically active Ca. This correction may be inappropriate in patients with CKD or end-stage renal disease and hyperbilirubinemia may present challenges to the bromocresol purple (BCP) method for measuring serum albumin [35], leading to mismatch between serum and biologically-active ECG data. Future studies directly annotating ECGs with ionized Ca are warranted. Second, the retrospective design only annotated the ECGs by the laboratory results closest in time. A prospective study should be conducted to validate the DLM's performance in a target population. Third, we acknowledged that low prevalence of hypercalcemia (~2 %) and low positive predictive value (4.5 %) of ECG-aCa for hypercalcemia prediction may limit clinical application of this algorithm. However, we still found that ECG-aCa hypercalcemia with normal serum aCa (false positive) had a higher risk of poor outcome. Fourth, the DLM design currently precludes full interpretability. Our study showed<20 % of the predictions could be explained by known ECG features and full interpretability will be a focus of future work. Finally, POC-Ca^{+} has been used to detect dyscalcemia; we did not compare the accuracy of these two methods to detect severe dyscalcemia.

5. Conclusion

In conclusion, severe dyscalcemia are potentially life-threatening emergencies requiring prompt recognition and management. Our AI-enabled ECG analysis provides a quantitative indicator, ECG-aCa, for severe dyscalcemia and prognostic prediction for decision support. Like the guideline recommending prompt ECG in the management of hyperkalemia [36], we also recommend prompt ECG in the management of hypercalcemia. Since ECG is also extensively used when considering many CV diagnoses, our AI-enabled ECG platform may actively detect potential patients with severe dyscalcemia in unexpected situations. A larger prospective cohort study should be conducted to further validate our findings.

Ethics approval and consent to participate

This study was approved by the institutional review board (IRB) of Tri-Service General Hospital, Taipei, Taiwan (IRB NO. C202105049). Patients' consent was waived because data were collected retrospectively in anonymized files and encrypted from the hospital to the data controller.

Availability of data and materials

The datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Author contributions

Shih-Hua Lin provided contributions to the study conception and design, acquisition of data or analysis and interpretation of data, or revising it critically for important intellectual content and final approval of the version to be published. Chin Lin and Chien-Chou Chen drafted the initial manuscript and analyzed the data. Chia-Cheng Lee and Hung-Sheng Shang provided the retrospective data for model training. Tom Chau, Chin-Sheng Lin, Ding-Jie Lee, and Shi-Hung Tsai revised the manuscript for important intellectual content. Shih-Hua Lin takes final responsibility for this article.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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