116115_Auto_Edited.docx

WORD COUNT	5929	TIME SUBMITTED	16-DEC-2025 04:37PM
		PAPER ID	119501626

Name of Journal: *World Journal of Cardiology*
Manuscript NO: 116115
Manuscript Type: ORIGINAL ARTICLE

Prospective Study

Discriminating Diabetes Mellitus from Single-Lead ECG Using Machine Learning and Multinomial Regression

Current advances in DM diagnostic

Anna Dmitrievna Karbovskaya, Basheer Abdullah Marzoog, Anastasia Stroeva, Peter Chomakhidze, Daria Gognieva, Natalia Kuznetsova, Abromavich Syrkin, Valentin V Fadeev, Irina V Poluboyarinova, Sevindzh M Ismailova, Alexander Suvorov, Philipp Kopylov

Abstract

BACKGROUND

Background: Current advances in diagnostic and therapeutic strategies remain insufficient for reducing the prevalence and incidence rate of diabetes mellitus (DM).

AIM

Aims: To investigate for any association between single-lead ECG parameters and the diagnosis of diabetes mellitus.

METHODS

Material and methods: A single center study involved participants of Caucasian origin for the period 02/05/2022-23/08/2025 with or without DM and aged ≥ 18 years. All participants at the time of participation in the study passed the cardiologist's, random glucose measurement using a glucometer, single lead-electrocardiography registration (using Cardio-Qvark®) and transthoracic echocardiography. Statistical analysis conducted using the R programming language (version 4.5).

RESULTS

Results: The built logistic regression machine learning model demonstrated diagnostic performance in discriminating (AUC) type 1 DM 0,84 (95%CI; 0,76;0,91), type 2 DM 0,69 (95%CI; 0,61;0,76), and healthy control 0,82 (95%CI; 0,76; 0,87).

CONCLUSION

Conclusion: The developed model demonstrates a stronger association between single-lead ECG parameters and the diagnosis of diabetes mellitus. This is probably attributable to relatively stable and long-term physiological alterations associated with the state of the disease.

Key Words: Machine learning, Diabetes mellitus, Diagnosis, Hyperglycemia, HbA1c, Glucose

Core Tip: This study pioneers a novel, non-invasive screening strategy for diabetes mellitus by leveraging the ubiquity of single-lead electrocardiography (ECG). Using a machine learning model, we demonstrate that the diabetic state leaves a distinct electrophysiological signature on the heart, detectable from a simple, consumer-grade ECG. The model excels at ruling out diabetes with high accuracy and can differentiate between Type 1 and Type 2 diabetes based on divergent cardiac electrical patterns, such as opposing QTc interval behaviors. This approach transforms a common cardiac tool into a potential frontline, accessible screening method for one of the world's most prevalent metabolic disorders.

INTRODUCTION

Introduction

Diabetes mellitus (DM) constitutes a pervasive global health crisis, affecting over 500 million individuals worldwide and serving as a primary driver of significant morbidity and mortality, predominantly through its devastating cardiovascular complications [1–3]. The escalating prevalence of this metabolic disorder underscores an urgent and unmet need for innovative diagnostic strategies that are both accessible and capable of facilitating early intervention [4–6]. Early detection is paramount for effective management and the prevention of long-term sequelae, including neuropathy, retinopathy, nephropathy, and atherosclerotic cardiovascular disease [7–16]. However, the current diagnostic paradigm, reliant on biomarkers such as fasting plasma glucose, oral glucose tolerance tests, and glycated hemoglobin (HbA1c), presents significant limitations[17,18]. These methods are inherently invasive, require laboratory infrastructure and trained personnel, and may fail to identify individuals with subclinical disease or early autonomic neuropathy, a common and serious complication of diabetes. Consequently, a substantial number of at-risk individuals remain

undiagnosed until complications arise, highlighting a critical gap in our preventive healthcare arsenal.

The electrocardiogram (ECG), a cornerstone of cardiovascular assessment, offers a non-invasive window into cardiac electrophysiology and autonomic nervous system function[19]. In recent years, the proliferation of wearable technology and consumer-grade devices capable of recording medical-grade single-lead ECGs has created an unprecedented opportunity for decentralized, continuous health monitoring. These devices provide a low-cost, scalable, and readily accessible platform for population-level screening[20,21]. The ECG signal contains a wealth of data beyond standard intervals; subtle alterations in repolarization, depolarization, heart rate variability, and signal morphology can reflect underlying metabolic and neuroautonomic disturbances, such as those induced by chronic hyperglycemia and insulin resistance [22–25].

The extraction and interpretation of these subtle, complex patterns from the ECG waveform transcend the capabilities of traditional analysis. This is where the transformative potential of artificial intelligence, specifically machine learning (ML) and deep learning (DL), comes to the fore [26–29]. ML algorithms excel at identifying intricate, multidimensional patterns within large datasets that are often imperceptible to the human eye. Several pioneering studies have demonstrated the feasibility of using ML-based analysis of multi-lead ECGs to detect conditions like atrial fibrillation, left ventricular dysfunction, and even hyperkalemia[30,31]. The logical extension of this research is the application of these powerful analytical tools to the challenge of diabetes diagnosis, leveraging the ubiquitous single-lead ECG as a novel data source.

While the concept is promising, the specific application of machine learning to single-lead ECG for differentiating not only diabetes from health but also between its principal types (Type 1 and Type 2) remains a developing field. The pathophysiological pathways leading to T1DM (autoimmune beta-cell destruction) and T2DM (insulin resistance and progressive secretory defect) impart distinct, yet poorly characterized, impressions on cardiac electrophysiology. A model that can decipher these unique

signatures could revolutionize screening protocols and provide profound insights into the cardiac manifestations of different diabetic states[32,33].

Therefore, this study aims to investigate the association between a comprehensive set of parameters derived from a single-lead ECG and the diagnosis of diabetes mellitus. We hypothesize that machine learning analysis of single-lead ECG features can identify a unique electrophysiological signature associated with DM and develop a validated model capable of distinguishing between healthy individuals, patients with T1DM, and patients with T2DM. By harnessing the synergy of consumer-grade technology and advanced analytics, this research seeks to contribute to the development of a novel, non-invasive, and accessible tool for the early detection and differentiation of diabetes mellitus.

MATERIALS AND METHODS

Material and methods

A single center prospective study conducted at University clinical hospital number 2 for the period 02/05/2022-23/08/2025. The study included participants with *vs* without diabetes mellitus (both first and second type). The study was carried out according to the principles of Good Clinical Practice and Helinski declaration. All participants gave an informed written consent to participate in the study and publish any associated results anonymously. The study protocol was approved by the Local Ethical Committee of Sechenov University (Excerpt from Protocol No. 14-19 dated 13.11.2019). The study was also registered on the ClinicalTrials.gov website (ID: NCT04788342, https://clinicaltrials.gov/study/NCT04788342).

Patient Inclusion and Exclusion Criteria

Patients from University Clinical Hospital Number 2 undergoing outpatient or inpatient examination and treatment, including in the endocrinology department with a diagnosis of diabetes mellitus, were included in the study. The inclusion and exclusion criteria are presented in the below.

Inclusion:

- Patient age over 18 years;

- Agreement to participate in the study.

Exclusion:

- Significant changes in the morphology of the QRS complex (such as bundle branch block and ventricular extrasystole);

- Poor quality ECG recorded from the fingers (Parkinson's disease, tremor of any origin, mental disorders).

- Unsatisfactory quality of ECG and/or PPG;

- Withdrawal of consent for further participation in the study.

Clinical data collection

The patients underwent a comprehensive examination, including:

-Clinical Examination: Collection of complaints, auscultation, palpation, percussion, assessment of edema syndrome, measurement of heart rate (HR) and blood pressure (BP) level.

-Medical History Analysis: Collection of cardiological history and diabetes mellitus history.

-Transthoracic Echocardiography (TTE): Performed using a GE Vivid 5 device. Assessment of cardiac chamber volumes, wall thickness, diastolic and systolic function status, and detection of valvular apparatus and major cardiac vessel dysfunction according to current guidelines[34].

-Standard 12-Lead ECG Recording: Performed using a SCHILLER AT-5 device. Determination of temporal and amplitude ECG parameters, cardiac electrical axis direction, and assessment of cardiac cycle morphology.

-Capillary Blood Glucose Analysis: Fasting blood glucose level measured twice within 1-3 days, in a seated position, adhering to the following requirements: Analysis performed after a 12-hour fast; abstinence from alcohol 2-3 days prior; avoidance of stress or heavy physical exertion; refraining from tooth brushing, smoking, or consumption of fatty foods, sugary drinks, or confectionery products the day before. The type of the diabetes mellitus is classified based on the history of the patients, and

the drug they take to manage it. The diagnostic thresholds for diabetes mellitus (DM) are a fasting plasma glucose of 126 mg/dL (7 mmol/L) or higher and the presence of diabetes mellitus history.

-Single-Channel ECG and PPG Recording: Recorded using the QardioQVARK device (LLC "L Card", Moscow, Russia; registered with the Federal Service for Surveillance in Healthcare No. RZN 2019/8124 dated 15.02.2019) immediately after each blood glucose analysis. Recordings lasted 1 minute, performed at rest in a seated position. The recorder has a smartphone case form factor and features 2 sensors for recording ECG and PPG. Recordings were transmitted to a cloud-based platform for analysis using proprietary machine learning algorithms.

Statistical Data Analysis

Statistical analysis was performed using the R programming language (version 4.5). For quantitative variables, the distribution normality was assessed using the Shapiro-Wilk test. Descriptive statistics were calculated, including the mean, standard deviation, median, interquartile range (IQR), and minimum and maximum values.

For categorical and qualitative variables, proportions (percentages) and absolute frequencies were calculated.

Comparative analysis for independent, normally distributed quantitative variables was performed using Welch's *t*-test (for two groups) or one-way ANOVA (for more than two groups), followed by post-hoc pairwise comparisons. For independent, non-normally distributed quantitative variables, the Mann-Whitney *U* test (for two groups) or the Kruskal-Wallis test (for more than two groups) was employed.

For related (paired) samples, comparative analysis of normally distributed quantitative variables was conducted using a paired Welch's *t*-test (for two groups) or repeated-measures ANOVA (for more than two groups), again followed by post-hoc pairwise comparisons. For related, non-normally distributed quantitative variables, the Wilcoxon signed-rank test (for two groups) or Fisher's test (for more than two groups) was used.

To analyze dynamic changes across visits, Cochran's Q test was applied. Where necessary, pairwise comparisons for these dynamic changes were performed using McNemar's test.

The Holm-Bonferroni method was used to correct for multiple comparisons. A significance level (α) of 0.05 was adopted for all analyses, corresponding to a 5% probability of committing a Type I error.

Mathematical modelling pipeline

The sample size was sufficient to allocate the majority of the data for building associative models (70% of the data), with a separate hold-out set reserved for subsequent validation (20% of the data).

To assess associations with a quantitative outcome (glycemia), a linear regression model with combined L1 and L2 (Elastic Net) regularization was employed. This approach significantly mitigated the risk of multicollinearity and facilitated the selection of factors contributing most substantially to the outcome's variance. Quantitative data were normalized prior to analysis. The model's performance was evaluated on the validation set using the coefficient of determination (R^2), mean absolute error (MAE), maximum error, and the correlation coefficient between predicted and true values.

To evaluate the diagnostic properties of single-lead ECG in determining the presence of diabetes mellitus (DM) and its types (resulting in three classes: No diabetes, type 1 DM, and type 2 DM), a multinomial logistic regression model with L1 (Lasso) regularization was utilized. This algorithm enabled the selection of the strongest predictors, after which associations were assessed through the conventional calculation of odds ratios (OR), using the non-diabetic class as the reference. The model's performance was evaluated on the validation set using the area under the curve (AUC), sensitivity, specificity, and positive and negative predictive values.

RESULTS

Results

A total of 743 patients with data on the presence or absence of type 1 or type 2 diabetes mellitus (DM) were included in the study. The control group included 537 (72,3 %), T1DM group included 61 (8,2 %), and T2DM included 145 (19,5 %) participants.

Information on random glucose level at the time of single-lead ECG recording was available for 696 participants; control 145 (19,5 %), T1DM 535 (99,6 %) , and T2DM 100 (69 %).

The general characteristics of the study group are presented in the Supplementary 1.

No significant differences were observed in key cardiovascular risk factors, namely sex and age, among the included participants.

Body mass index (BMI) demonstrated overall statistical significance (P = 0.032), which was primarily driven by a marked difference between non-diabetic patients and those with type 2 diabetes mellitus (P = 0.024), with the latter group exhibiting higher values. No significant differences were observed between type 1 and type 2 diabetes groups (Supplementary 2).

Statistical analysis of smoking prevalence revealed a significant overall difference (P < 0.001). Both insulin-dependent and non-insulin-dependent diabetic patients were significantly more likely to smoke compared to healthy controls (P = 0.002 and P = 0.001, respectively). However, no substantial differences were found between the two diabetic groups.

Blood group distribution showed significant variations across all compared subgroups (P < 0.001). The most pronounced deviation was observed in the type 2 diabetes subgroup, which demonstrated a predominance of blood group AB (44.8% vs. 15.7% and 8.2% in other groups, respectively).

Systolic blood pressure showed a significant difference in the overall sample (P = 0.005), attributable to lower blood pressure levels in type 2 diabetic patients compared to the control group (P = 0.012) (Supplementary 2).

The prevalence of coronary artery disease (CAD) reached statistical significance (P = 0.005), primarily due to lower disease frequency among type 2 diabetic patients compared to non-diabetic subjects (P = 0.009).

The distribution of peak location values showed significant variation (P = 0.004), particularly evidenced by the complete absence of anterior peak cases in the insulin-dependent diabetes group.

Finally, glucose levels demonstrated highly significant overall differences (P < 0.001), resulting from substantially elevated values in both diabetic groups compared to healthy controls, while no significant differences were observed between the two diabetic subgroups for this parameter (Supplementary 2).

Table of Pairwise Comparisons for Categorical Variables (Holm Correction) represented in Supplementary 3.

Features associated with the pulse wave

The greatest number of significant differences was identified in the analysis of pulse wave parameters. Statistically significant differences were observed for the majority of the measured indices.

Due to distributions that deviated from normality, central tendency and variability are presented as medians with 25th and 75th percentiles (interquartile range). Group comparisons for these parameters are presented in the supplementary 4.

Pairwise comparisons (adjusted for multiple comparisons using the Holm method) revealed statistically significant differences not only relative to the non-diabetic control group but also between the two types of diabetes mellitus (Table 1).

Table 1: Adjusted pairwise comparisons for multiple comparisons using the Holm method.

Factor	No DM – T1DM	No DM – T2DM	T1DM – T2DM
HFNoise	0,660	0,009	0,660
VAT	0,704	0,009	0,210
QTc	0,000	0,024	0,034
QT_TQ	0,001	0,284	0,022

HFQRS 0,000 0,000 0,000

HFSNR 0,000 0,000 0,000

TA 0,078 0,078 0,697

QRS12energy 0,024 0,541 0,108

QRSE2 0,033 0,639 0,084

QRSw 0,084 0,006 0,878

Pan 0,078 0,128 0,457

RA 0,129 0,129 0,519

SA 0,024 0,484 0,136

Pst 0,000 0,000 0,007

Pfi 0,000 0,001 0,001

QRSst 0,000 0,000 0,001

QRSfi 0,000 0,000 0,000

Tfi 0,000 0,000 0,637

PpeakN 0,000 0,000 0,000

Rpeak 0,000 0,721 0,001

Speak 0,001 0,546 0,016

Tpeak 0,158 0,158 0,048

Toffs 0,192 0,192 0,051

RonsF 0,026 0,026 0,002

RoffsF 0,004 0,188 0,002

SDNN 0,018 0,278 0,222

- The whole version of the predictors with their full version published in previous work https://pmc.ncbi.nlm.nih.gov/articles/PMC9421020/.

Of particular interest are those factors that demonstrate significant differences between the two types of diabetes mellitus, as well as those that effectively differentiate either type of diabetes from the control group. Such factors are visualized in the graph below (Figure 1).

Figure 1: A network of factors demonstrating statistically significant differences in Holm-corrected pairwise comparisons are presented. The largest nodes (depicted in yellow) represent factors that exhibited significant differences across all three groups. Medium-sized nodes correspond to factors differing between any two groups, while the smallest nodes indicate factors significant for only a single group. On the left graph, the nodes are coloured (yellow or orange) according to their ability to differentiate between the types of diabetes. The right graph shows nodes that distinguish the control group from either type of diabetes (significance observed in either "No DM" vs. "T1DM", "No DM" *vs* "T2DM", or across all three classes). The factors that did not appear in both graphs did not demonstrate statistically significant pairwise comparisons after multiplicity correction.

Thus, the factors that demonstrated significant differences between the three classes were QTc, HFQRS, HFSNR, Pst, Pfi, QRSst, QRSfi, PpeakN, and RonsF.

Association building by the type of DM

To identify predictors associated with diabetes and its subtypes, a multinomial logistic regression model was employed. The model was initially adjusted for predefined covariates including age, sex, body mass index, and smoking status. Continuous variables were standardized using z-score normalization (mean-centered and scaled by standard deviation).

The regression model was trained on a randomly selected subset of 519 participants (70% of the total cohort), with validation performed on the remaining 222 participants (30%). Stratified sampling ensured proportional representation of both type 1 and type 2 diabetes cases across both training and validation sets.

Primary predictors selection

Feature selection was performed using L1-regularized multinomial regression to mitigate multicollinearity risks. Model stability was ensured through 10-fold cross-validation. The following predictors were selected: Smoking status (categorized as never smoked, current smoker, or former smoker); QTc; TA; Pan; RA ; SA; Pst; Tfi; RoffsF; Age; Pfi; and PpeakN.

Validation

These predictors were combined into a single regression equation with estimation of the coefficients, their 95% confidence intervals (95%CI), subsequent exponentiation, and calculation of the odds ratio (OR) (Table 2).

Table 2: The primary predictors with their coefficient estimation, 95% confidence intervals, subsequent exponentiation, and odds ratio.

	Type 1 DM			Type 2 DM		
	OR	95%CI	p-value	OR	95%CI	p-value
(Intercept)	0.016	0.005 – 0.048	< 0.001	1.391	1.049 – 1.845	0.022
Smoking	0.156	0.110 – 0.221	< 0.001	0.662	0.100 – 4.401	0.670
QTc	3.810	1.222 – 11.875	0.021	0.351	0.197 – 0.624	< 0.001
TA	4.033	1.819 – 8.941	0.001	11.218	3.778 – 33.312	< 0.001
Pan	1.537	0.917 – 2.577	0.103	4.738	2.943 – 7.630	< 0.001
RA	1.185	0.846 – 1.659	0.324	2.668	1.505 – 4.730	0.001
SA	0.947	0.556 – 1.611	0.840	1.286	0.940 – 1.757	0.115
Pst	0.714	0.533 – 0.957	0.024	0.682	0.442 – 1.053	0.085
Tfi	0.605	0.350 – 1.046	0.072	0.972	0.716 – 1.320	0.854
RoffsF	0.954	0.710 – 1.282	0.755	0.544	0.133 – 2.223	0.397
Age	0.954	0.607 – 1.500	0.839	0.980	0.481 – 1.997	0.956
Pfi	0.725	0.540 – 0.974	0.033	0.732	0.169 – 3.177	0.677
PpeakN	1.510	0.965 – 2.361	0.071	1.946	0.865 – 4.376	0.108

A multinomial logistic regression model with healthy participants as the reference group, the associations between clinical and electrocardiographic parameters and the likelihood of having either type 1 or type 2 diabetes were analyzed.

Type 1 Diabetes Mellitus (compared to healthy controls):

The presence of type 1 diabetes was statistically significantly associated with the following factors:

• Smoking — A reduced likelihood of type 1 diabetes mellitus (T1DM) was observed among smokers (OR = 0.16, 95%CI [0.11; 0.22], $P < 0.001$), which may reflect potential confounding factors or behavioral characteristics.

• Prolonged QTc interval (OR = 3.81, 95%CI [1.22; 11.87], $P = 0.021$)

• Increased T-wave amplitude (TA) (OR = 4.03, 95%CI [1.82; 8.94], $P = 0.001$)

• A decrease in the P-wave terminal force (Ptf) parameter, reflecting atrial electrical activity (OR = 0.71, 95%CI [0.53; 0.96], $P = 0.024$)

• A reduction in the P-wave dispersion index (Pfi) (OR = 0.73, 95%CI [0.54; 0.97], $P = 0.033$)

• A borderline trend towards statistical significance was also identified for the following predictors: Tfi ($P = 0.072$) and PpeakN ($P = 0.071$).

Type 2 Diabetes Mellitus (compared to healthy controls):

For patients with Type 2 Diabetes Mellitus, the following statistically significant predictors were identified:

• QTc interval — An inverse association was observed: A shorter QTc interval was associated with a higher likelihood of type 2 diabetes mellitus (T2DM) (OR = 0.35, 95%CI [0.20; 0.62], $P < 0.001$).

• T-wave amplitude (TA) — Was strongly associated with an increased likelihood of T2DM (OR = 11.22, 95%CI [3.78; 33.31], $P < 0.001$).

• Pan parameter, reflecting the spatial characteristics of the P-wave (OR = 4.74, 95%CI [2.94; 7.63], $P < 0.001$).

• RA (OR = 2.67, 95%CI [1.50; 4.73], $P = 0.001$).

The remaining parameters, including age, Tfi, SA, and RoffsF, did not demonstrate statistically significant differences between the type 2 diabetes mellitus group and healthy controls.

The most stable predictors of diabetes presence (compared to the control group) were abnormalities in QTc interval, TA magnitude, and atrial activity parameters (Pan, RA, Pfi, Pst). Notably, QTc intervals exhibited divergent directional associations:

Prolongation was associated with Type 1 Diabetes Mellitus, while shortening was linked to Type 2 Diabetes Mellitus.

When validated on the holdout dataset of 222 observations, the model demonstrated the following performance metrics (Table 3, Figure 2)

Table 3: The built machine learning model performance in the differentiation of control, T1DM, and T2DM.

Statistic	No DM, mean (95 % CI)	T1DM, mean (95 % CI)	T2DM, mean (95 % CI)
Area under the ROC curve (AUC)	0,82 (0,76; 0,87)	0,84 (0,76;0,91)	0,69 (0,61;0,76)
Sensitivity	0,65 (0,57; 0,72)	0,85 (0,68; 1,00)	0,91 (0,81; 0,98)
Specificity	0,89 (0,81; 0,97)	0,69 (0,63; 0,75)	0,42 (0,34; 0,49)
Positive predictive value (PPV)	0,94 (0,89; 0,98)	0,21 (0,13; 0,32)	0,28 (0,21; 0,36)
Negative predictive value (NPV)	0,51 (0,42; 0,60)	0,98 (0,95; 1,00)	0,95 (0,89; 0,99)

Figure 2: Graphical representation of the diagnostic accuracy of the built model in the diagnosis of diabetes mellitus.

In the one-versus-one classification approach, the highest AUC was observed for differentiating between any type of diabetes and non-diabetic conditions, while the poorest performance was achieved in distinguishing type 1 diabetes from type 2 diabetes (T1D *vs* T2D) (Table 4).

Table 4: The one-versus-one classification built model performance.

Groups comparing AUC	Lower limit 95%CI	Upper limit 95%CI
No DM against T1DM 0.8981013	0.8439558	0.9522468
No DM against T2DM 0.7758087	0.7054986	0.8461189
T1DM against T2DM 0.6366667	0.4914294	0.7819039

The validation of the diagnostic model revealed statistically significant differences in predictive performance across patient groups depending on diabetic status.

The overall diagnostic performance, evaluated by the area under the ROC curve (AUC), demonstrated strong discriminative ability for the absence of diabetes (AUC = 0.82; 95%CI: 0.76–0.87). The model also showed good performance for Type 1 Diabetes Mellitus (AUC = 0.84; 95%CI: 0.76–0.91). For Type 2 Diabetes Mellitus, the

discriminative capability was comparatively limited, though the confidence interval did not include 0.5 (AUC = 0.69; 95%CI: 0.61–0.76). These results indicate the current model has restricted applicability specifically for detecting type 2 diabetes mellitus.

In the non-diabetic group, the model exhibited high specificity (0.89; 95%CI: 0.81–0.97) and high positive predictive value (PPV = 0.94; 95%CI: 0.89–0.98). Among diabetic patients, a pronounced asymmetry in performance characteristics was observed. The model demonstrated high sensitivity in both Type 1 (0.85; 95%CI: 0.68–1.00) and Type 2 diabetes groups (0.91; 95%CI: 0.81–0.98), coupled with high negative predictive values (NPV = 0.98 and 0.95, respectively). This supports its potential utility for ruling out pathology in these cohorts. However, the low specificity in the Type 2 diabetes group (0.42; 95%CI: 0.34–0.49) resulted in correspondingly low PPV values (0.28; 95%CI: 0.21–0.36), indicating a high rate of false positives for this particular class.

Analysis of associations with glycemic levels

Glycemic level is a more labile parameter than some electrocardiographic-derived features. Nevertheless, an attempt was made to identify associations between glycemic levels and several potential predictors.

A linear regression model with combined L1 and L2 regularization (Elastic Net) was employed to identify associations while mitigating multicollinearity risks. The analysis utilized 10-fold cross-validation with mean-centered normalization and scaling by standard deviation for all continuous variables. The table below presents the coefficient estimates of selected factors from the final model, along with their 95% confidence intervals (95%CIs) and statistical significance (Table 5).

Table 5: The coefficient estimates of selected factors from the final model, along with their 95% confidence intervals. A weak to moderate correlation was observed between the true and predicted values (Spearman's rho = 0.488, $P < 0.001$)

Parameter	Estimated coefficient	Lower limit 95%CI	Upper limit 95%CI	P value
(Intercept)	5.852	4.950	6.753	0.0000000
HFSNR	-0.058	-0.159	0.043	0.261
QRSfi	-0.001	-0.003	0.0009	0.253

Tfi 0.0018 0.001 0.003 0.0000114

PpeakN -0.0017 -0.004 0.0009 0.202

The whole version of the predictors with their full version published in previous work https://pmc.ncbi.nlm.nih.gov/articles/PMC9421020/.

However, a graphical representation of the data indicated some degree of correspondence between predicted and observed values up to a glycemic level of 5 mmol/L. Beyond this threshold, the predicted values effectively plateaued, exhibiting minimal dependence on the predictor variables.

Figure 3: Graphical representation of the predicted *vs* true values plot.

Analysis of standard regression quality metrics revealed suboptimal model performance, characterized by a low coefficient of determination (R^2) 0.217 , a moderate mean absolute error (MAE) 1.35, and a substantially elevated maximum error 14.5.

Therefore, the utility of single-lead ECG for predicting glycemic levels appears questionable and should be interpreted with caution, particularly in light of the model's limited explanatory power and elevated maximum error.

DISCUSSION

Discussion

The results demonstrate a significant and clinically relevant association between features derived from a single-lead electrocardiogram (ECG) and the diagnosis of diabetes mellitus (DM), utilizing a machine learning framework. Our findings indicate that the electrophysiological and autonomic nervous system alterations inherent to the diabetic state manifest in measurable, albeit subtle, changes in the ECG signal. These changes are sufficiently distinct to allow for the development of predictive models with promising diagnostic accuracy, particularly for differentiating diabetic from non-diabetic states and for identifying Type 1 Diabetes Mellitus (T1DM).

The core finding is the robust performance of the multinomial logistic regression model. The area under the curve (AUC) values of 0.84 for T1DM and 0.82 for the healthy control group signify a strong discriminative capacity. This performance is

noteworthy given the non-invasive, low-cost, and highly accessible nature of single-lead ECG technology, which is increasingly integrated into consumer wearables and portable health devices. The model's high sensitivity (0.85 for T1DM, 0.91 for T2DM) and negative predictive value (NPV > 0.95 for both DM types) are its most compelling attributes from a clinical screening perspective. This suggests that such a tool could be highly effective as a rule-out test, potentially identifying individuals who are very unlikely to have diabetes and thus reducing the need for more invasive or resource-intensive testing in a large portion of the population.

However, the model's performance for Type 2 Diabetes Mellitus (T2DM) was notably weaker (AUC = 0.69), characterized by low specificity (0.42) and a consequently high false-positive rate (low PPV of 0.28). This asymmetry in performance highlights a critical nuance. The electrophysiological signature of T2DM, as captured by our selected features, appears to be less distinct or more heterogeneous than that of T1DM. This could be attributed to the broader pathophysiological spectrum of T2DM, which often coexists with a cluster of other metabolic and cardiovascular conditions like hypertension and obesity, as also seen in our cohort's higher BMI and hypertension prevalence. These comorbid states likely introduce confounding electrophysiological changes that overlap with those caused by hyperglycemia alone, making it challenging for the model to isolate a unique "T2DM fingerprint." Furthermore, the one-versus-one analysis confirmed the greatest difficulty lies in distinguishing T1DM from T2DM (AUC = 0.64), underscoring that while both types share the common endpoint of hyperglycemia, their underlying cardiac electrophysiological remodeling may follow different trajectories.

The feature selection process yielded profound insights into the specific ECG parameters most affected by diabetes. The identification of factors like QTc interval, T-wave amplitude (TA), and various P-wave parameters (Pst, Pfi, Pan, RA) points towards diffuse involvement of the heart's electrical system. The divergent behavior of the QTc interval is particularly fascinating. QTc prolongation was associated with T1DM, which aligns with existing literature on diabetic autonomic neuropathy leading

to reduced sympathetic tone and potentially prolonged repolarization. Conversely, QTc shortening was associated with T2DM. This counterintuitive finding may be explained by the different autonomic progression in T2DM, often characterized by an early hyperadrenergic state, or by the complex interplay of ischemia, hypertrophy, and electrolyte shifts more common in this population. The strong association of increased T-wave amplitude (TA) with both types of DM, but especially T2DM (OR > 11), is a notable finding that warrants further investigation, as it may reflect underlying myocardial strain or altered ventricular repolarization gradients.

The alterations in P-wave parameters (Pst, Pfi, PpeakN) strongly implicate atrial myopathy in the diabetic process. Diabetes is a known risk factor for atrial fibrillation, and these early subclinical changes in atrial conduction and repolarization, detectable on a simple single-lead ECG, could represent a valuable biomarker for assessing atrial fibrillation risk long before overt arrhythmia occurs. This suggests that the utility of this technology may extend beyond diabetes diagnosis to the stratification of cardiovascular complications within the diabetic population.

In stark contrast to diagnosing the disease state, our attempts to predict real-time glycemic levels using ECG features were unsuccessful. The regression model for glycemia exhibited poor performance ($R^2 = 0.22$, high maximum error), with predictions plateauing beyond 5 mmol/L. This result is, in fact, expected and reinforces a crucial principle: The ECG reflects the end-organ electrophysiological impact of prolonged glycemic exposure and autonomic dysfunction, not the immediate, labile concentration of glucose in the blood. Glycemic levels fluctuate rapidly due to meals, stress, and medication, while the myocardial remodeling and autonomic imbalance that affect ECG parameters develop over months and years. Therefore, the ECG is a biomarker of chronic diabetic disease burden rather than an acute glucometer. This distinction is vital for setting appropriate expectations for this technology.

A deep learning model, IGRNet, was developed to diagnose prediabetes using 12-lead ECGs, achieving an accuracy of 0.781 and an AUC of 0.777. This suggests potential for non-invasive, real-time prediabetes diagnosis[35]. Another study proposed a novel

approach using single-lead ECGs to detect HbA1c levels, achieving an accuracy of 0.9015 and an AUC of 0.9899. This method highlights the potential for non-invasive and fast detection of diabetes-related metrics[36].

The DiaBeats algorithm, using ECG signal data, accurately predicted diabetes and pre-diabetes classes with a precision of 97.1% and an accuracy of 96.8 %. This model utilized leads III, aVL, V4, V5, and V6, indicating the significant role of specific ECG leads in diabetes detection[21]. Combining single-lead ECG with other sensors (*e.g.* glucose, accelerometer) has shown improved accuracy in diabetes prediction. A multisensor combination achieved a prediction accuracy of 98.2%, significantly higher than using single sensors alone[37].

A study utilized multi-resolution analysis of single-lead ECG signals to develop a system for detecting diabetic patients. The system achieved a classification accuracy of 91.5%, demonstrating the effectiveness of ML in identifying diabetes through ECG analysis[38]. Another framework used intrinsic time-scale decomposition and machine learning to screen for diabetes using single-lead ECG signals, achieving an accuracy of 86.9 %. This approach is suitable for resource-limited environments and highlights the potential for widespread screening[25].

The Single lead ECG using Cardio_Qvark studied to diagnose ischemic heart disease and showed an improvement in the diagnostic accuracy comparing to the physical ECG-stress test[39].

Diabetes mellitus induces distinct cardiac alterations through chronic hyperglycemia and insulin resistance, which create a detectable electrophysiological signature on a single-lead ECG. Key pathophysiological pathways include cardiac autonomic neuropathy, which disrupts sympathetic-parasympathetic balance and causes heterogeneous ventricular repolarization, and the accumulation of advanced glycation end-products that promote myocardial fibrosis. These processes directly impair the heart's electrical properties by slowing impulse conduction and destabilizing repolarization.

The integration of these subtle changes—manifested as T-wave flattening (Tfi), prolonged QT interval (QTc), slowed ventricular activation (VAT), and altered P-wave morphology—creates a composite biomarker for diabetes. While individually minor, these features collectively form a distinct pattern that machine learning models can decode from a single-lead ECG, effectively identifying the integrated cardiac impact of diabetes before overt clinical disease develops. (Figure 4)

Figure 4: Pathophysiological pathway of diabetes-induced cardiac electrophysiological changes detectable by single-lead ECG and machine learning. Chronic hyperglycemia initiates four core mechanisms: Autonomic neuropathy, myocardial fibrosis, ion channel dysfunction, and microvascular impairment. These collectively alter cardiac electrophysiology, generating specific ECG biomarkers including T-wave flatness (Tfi↑), prolonged QT interval (QTc↑), and conduction abnormalities (VAT↑, QRSE4). Machine learning integration of these features enables diabetes detection, with optimal performance in high-prevalence, moderate-CVD populations (Cluster 4; AUC = 0.880).

The integration of these subtle changes—manifested as T-wave flattening (Tfi), prolonged QT interval (QTc), slowed ventricular activation (VAT), and altered P-wave morphology—creates a composite biomarker for diabetes. While individually minor, these features collectively form a distinct pattern that machine learning models can decode from a single-lead ECG, effectively identifying the integrated cardiac impact of diabetes before overt clinical disease develops.

Our study has several limitations. Firstly, it is a single-center study with a predominantly Caucasian cohort, which may limit the generalizability of our findings to other ethnicities and healthcare settings. Secondly, the imbalance in group sizes, particularly the smaller T1DM group, can affect the stability of the estimates for that subclass. Thirdly, while we adjusted for key confounders like age, sex, and BMI, residual confounding from unmeasured factors (*e.g.*, duration of diabetes, specific medications, presence of subclinical coronary artery disease) is possible. The diagnosis of DM was not solely based on HbA1c or oral glucose tolerance tests in all cases, relying

partly on medical history, which could introduce misclassification bias. Finally, the model's performance, especially for T2DM, requires significant improvement before clinical implementation can be considered. One of the important limitations that the ECG recording was performed after the diagnosis of DM have been made, which means that these model reflects secondary electrophysiological changes caused by established disease rather than early screening potential. While this makes our model a potent tool for identifying individuals with existing disease, it inherently limits our conclusions regarding its utility for de novo screening or early prediction. The model detects the cardiac sequelae of diabetes, not its prodromal phase. Therefore, our results demonstrate high performance in "diagnosing" the condition in a cross-sectional setting where the disease is already present, but they do not provide evidence that these ECG changes precede the conventional diagnosis. The high sensitivity and negative predictive value are particularly valuable in this context, suggesting the model could be used to "rule out" significant diabetic cardiac involvement or to identify undiagnosed cases in high-prevalence settings, but it would likely miss individuals in the earliest stages of the disease, before substantial electrophysiological alterations have occurred. Longitudinal studies are essential to determine whether subtle ECG alterations can be detected during the prediabetic stage or in at-risk individuals before the onset of overt hyperglycemia. Such research is needed to truly unlock the potential of this technology for primary prevention and early intervention.

Future research directions should include multi-center, multi-ethnic validation studies with larger, balanced cohorts to improve model robustness and generalizability. Incorporating additional data streams from wearables, such as activity level and heart rate variability over time, could enhance predictive power. Exploring more complex deep learning architectures that analyze the raw ECG signal directly might capture features invisible to conventional parameterization. Furthermore, longitudinal studies are needed to determine if these ECG changes can predict the future development of diabetes or its complications, positioning single-lead ECG as a tool for risk stratification and prevention, not just diagnosis.

Diabetic state leaves a discernible imprint on the heart's electrical activity, detectable through machine learning analysis of a single-lead ECG. While not a replacement for standard glycemic tests, this technology holds immense promise as a non-invasive, scalable, and cost-effective screening tool to identify individuals at high probability of having diabetes, particularly T1DM, who can then be referred for definitive testing. It represents a significant step towards leveraging ubiquitous digital health technology for the early detection and management of one of the world's most prevalent chronic diseases.

CONCLUSION

Conclusion

The developed models demonstrate a stronger association between single-lead ECG parameters and the diagnosis of diabetes mellitus. This is likely attributable to the relatively stable and long-term physiological alterations associated with the disease state. In contrast, single-lead ECG indicators do not adequately account for the values or variance in glycemic fluctuations.

116115_Auto_Edited.docx

ORIGINALITY REPORT

3%
SIMILARITY INDEX

PRIMARY SOURCES

1	Xinyan Zhao, Jialing Zhou, Ying Zhang, Yongyin Li et al. "Artificial Intelligence Model for Accurate Grading and Staging of Chronic Hepatitis B: Development and Validation", Springer Science and Business Media LLC, 2025 Crossref Posted Content	42 words — 1%
2	www.frontiersin.org Internet	27 words — < 1%
3	www.ncbi.nlm.nih.gov Internet	27 words — < 1%
4	eprints.whiterose.ac.uk Internet	19 words — < 1%
5	diposit.ub.edu Internet	15 words — < 1%
6	www.nature.com Internet	14 words — < 1%
7	Ali Jafari, Helia Mardani, Faezeh Ghalichi, Fatemeh Talebian, Farzaneh Mokhtary, Fatemeh Razavi, Ghazaleh Eslamian. "The Beneficial Effects of Sesame (Sesamum indicum L.) Products and Their Bioactive Compounds on Cardiovascular Disease Risk Factors in Patients with Diabetes: A GRADE-Assessed Systematic Review and Meta-Analysis", Diabetes & Metabolic Syndrome: Clinical Research & Reviews, 2025 Crossref	13 words — < 1%

8	repository.iphce.org Internet	13 words — < 1%
9	Bingjie Li, Chen Zhu, Zhigang Yao. "Early-life Varicella Infection and Long-term Protective Associations with Chronic Disease Risk: A UK Biobank Cohort Study *", Cold Spring Harbor Laboratory, 2025 Crossref Posted Content	12 words — < 1%
10	Huang Chen Chang, Jun-Peng Chen, Yi-Ming Chen, Wen-Nan Huang Yi-Hsing Chen. "ANTI-C1Q ANTIBODIES AS INDICATORS OF DISEASE ACTIVITY, RENAL INVOLVEMENT, AND NON-SCARRING ALOPECIA IN PATIENTS WITH SLE", The Journal of Rheumatology, 2025 Crossref	12 words — < 1%
11	bmcgeriatr.biomedcentral.com Internet	12 words — < 1%
12	repub.eur.nl Internet	12 words — < 1%

EXCLUDE QUOTES	ON	EXCLUDE SOURCES	< 12 WORDS
EXCLUDE BIBLIOGRAPHY	ON	EXCLUDE MATCHES	< 12 WORDS