 doi:10.20944/preprints202208.0098.v1

Article

One-Class Machine-Learning Model to Screen for Dysglycemia Using Single Lead ECG in ICU, toward Noninvasive Blood Glucose Monitoring

I-Min Chiu[1,2], Chi-Yung Cheng[1,2,*], Chang Pokai[1], Chao-Jui Li[2], Fu-Jen Cheng[2], Chun-Hung Richard Lin[1,*]

[1] Department of Computer Science and Engineering, National Sun Yat-Sen University, Kaohsiung 804, Taiwan
[2] Department of Emergency Medicine, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung 833, Taiwan
* Correspondence: C.H.L, lin@cse.nsysu.edu.tw; Tel.: 886+7-5252000 ext. 4339; C.Y.C, qzsecawsxd@cgmh.org.tw; Tel.:886+978839806

Abstract: Blood glucose (BG) monitoring is an important issue for critically ill patients. Previous studies reported that poor sugar control was associated with increased mortality in admitted patients. However, repeated blood glucose monitoring can be resource-consuming and cause a healthcare burden in clinical practice. In this study, we aimed to develop a personalized machine-learning model to predict dysglycemia based on electrocardiogram (ECG) findings. The study included patients with more than 20 ECG records during single hospital admission in the Medical Information Mart for Intensive Care III database, focusing on the lead II recordings, along with the corresponding blood sugar data. We processed the data and used ECG features from each heartbeat as inputs to develop a one-class support vector machine (SVM) algorithm to predict dysglycemia. The model prediction for dysglycemia using a single heartbeat had an AUC level of 0.92 ± 0.09, with a sensitivity of 0.92 ± 0.10 and specificity of 0.84 ± 0.04. Based on 10 s majority voting, the model prediction for dysglycemia improved to an AUC of 0.97 ± 0.06. In this study, we found that a personalized machine-learning algorithm could accurately detect dysglycemia using a single-lead ECG.

Keywords: machine learning; dysglycemia; blood glucose, ECG, personalized medicine, noninvasive blood glucose monitor

1. Introduction

Blood glucose (BG) monitoring and control are among the most important issues in global healthcare. With hyperglycemia common in critically ill patients, previous studies have reported that poor sugar control is associated with increased mortality in admitted patients[1–4]. In critically ill patients, continuous glucose monitoring can prevent acute complications such as severe hypoglycemia[5,6]. BG is typically measured with a glucose meter after using a lancing device and a test strip to obtain a blood sample. Repeated blood glucose monitoring can be resource-consuming and cause a healthcare burden in clinical practice. It is also a painful and distressing experience, leading to low adherence to general practice in home healthcare[7,8].

The idea of using electrocardiogram (ECG) features to determine BG levels has previously been proposed. Previous research has suggested that hyperglycemia and hypoglycemia are both correlated with a prolonged QT interval and decreased heart rate variability in an ECG[9–11]. However, it is still difficult to identify dysglycemia based on an ECG because numerous differential diagnoses should be considered when interpreting ECG findings.

 doi:10.20944/preprints202208.0098.v1

Because of increases in storage ability and computing power, machine learning has recently begun to evolve in the medical field. Machine learning-assisted ECG interpretation has shown promising results in distinguishing cardiac arrhythmia and predicting certain metabolic illnesses such as hyperkalemia[12–14]. In the past few years, there has also been a trend to use machine learning to predict hypoglycemic episodes from an ECG, which has demonstrated potential[15]. However, a recent meta-analysis showed that machine learning had a sensibility of only 0.72–0.86 in predicting hypoglycemia in patients with diabetes mellitus, which is still insufficient for clinical application[16].

In this study, we aimed to develop a personalized machine-learning model to predict dysglycemia, including hyperglycemia and hypoglycemia, based on ECG data. We believe this model can be used to improve the clinical practice of blood glucose monitoring, optimize the use of human resources, and improve the quality of life for patients.

2. Materials and Methods

The data collected and protocols used in this study were approved by the institutional review board of the Chang Gung Medical Foundation (202100362B0). The data supporting this study's findings are openly available in the MIMIC-III Waveform Database Matched Subset (http://doi.org/10.13026/c2294b)[17].

Dataset collection and inclusion criteria

This study used data from the Waveform Database Matched Subset of the Medical Information Mart from Intensive Care III (MIMIC-III). The dataset contains 22,317 waveform records and 22,247 numeric records for 10,282 distinct ICU patients admitted to the critical care units of medical centers in the United States between 2001 and 2012[18]. These recordings typically include digitized signals such as ECG, arterial blood pressure, and respiration data, as well as periodic measurements such as heart rate, oxygen saturation, and blood pressure values. The ECG signals contained in the dataset are usually lead I, lead II, or lead V signals. This subset represents records for which the patients have been identified, and their corresponding clinical records are available in the matched clinical database.

In this study, we considered patients in the MIMIC-III database for which 20 ECG recordings were made during a single hospital admission, focusing on the lead II records, along with their corresponding blood sugar data. Patients with atrial fibrillation or an implanted pacemaker were excluded from the study. Patients who had less than five dysglycemia data points during single hospital admission were also excluded. We defined two classes of BG levels: dysglycemia for BG > 200 mg/dL or BG < 70 mg/dL and euglycemia for BG between 80 and 180 mg/dL. ECG signals corresponding to BG values in the ranges of 70–80 and 180–200 were not considered during training in this study to ensure that no consecutive heartbeats would be considered as both hypoglycemia and euglycemia, or both euglycemia and hyperglycemia.

Training and validation dataset

Of all the included patients, we randomly selected the euglycemic BG data for 10, along with their corresponding lead II ECG records, as the training dataset for developing a one-class machine-learning model. We then randomly selected five euglycemia and five dysglycemia BG data points from the rest, along with their corresponding ECG records, as the validation dataset. We defined a corresponding ECG of one BG data point as the signal within a 10 min period before the storage time of the BG record.

 doi:10.20944/preprints202208.0098.v1

ECG segmentation and feature extraction

After retrieving the corresponding ECG signals, we segmented each ECG record into multiple heartbeats with 1 s segments based on the R-peak position with a 2:3 ratio. Because the ECG records in the MIMIC-III database were one-dimensional digital signals at 125 Hz, each heartbeat segment contained 50 samples before and 75 samples after the R-peak position. The segmented heartbeat first underwent manual inspection to exclude those containing a high level of ECG signal noise. This process helped to reduce the overfitting of the model and deviation as a result of noisy data.

After the heartbeat segmentation, ECG features related to P-Q-R-S-T point position correlations were extracted, which included the amplitude, interval, and slope gradient between two of the five points in one heartbeat ECG cycle. A total of 10 interval features (Figure 1A) and 15 amplitude features (Figure 1B, 1C) were extracted. The R-peak interval to the next heartbeat was also collected as an input feature.

Machine-learning algorithm

In this study, we developed a one-class support vector machine (Oc-SVM) algorithm to predict dysglycemia based on ECG features. SVM is a machine-learning algorithm that can create a nonlinear decision boundary by projecting data through a nonlinear function to a space with a higher dimension. This means that data points that cannot be separated by a straight line in their original space are shifted to a feature space, where there can be a straight hyperplane that separates the data points of one class from those of another. When that hyperplane is projected back to the input space, it has the form of a nonlinear curve. The one-class version of SVM is mostly applied to specific tasks such as anomaly detection or fault detection, where positive cases are difficult to collect during the training process. In our study, 10 normal BG datasets with their corresponding ECG heartbeats were used to train the Oc-SVM model.

Statistical analysis

Data were presented as mean (standard deviation [SD]) values for continuous variables, proportions for nominal variables, and median (interquartile range) values for ordinal variables. The performance measures used for the model assessment were accuracy, sensitivity, specificity, and AUC. In addition, from a clinical perspective, the sensitivity was considered more relevant than the specificity because it showed how well the hypoglycemia and hyperglycemia events were identified. Thus, when comparing different models, the sensitivity was considered more important.

When training the model, the inputs of the SVM model and its output prediction were based on segmented heartbeats. In clinical applications, predicting dysglycemia for every single heartbeat is undesirable, and the result may fluctuate, which makes it difficult to follow. Generating a prediction every 10 s, which is represented by a standard ECG, is more feasible. For this reason, we also evaluated the model's performance in a 10 s window of time by taking the majority class of the heartbeat predictions in that specific timeframe.

3. Results

In this study, we included 50 patients from the MIMIC-III database for the analysis(Appendix 1). Their median age was 64 (55–72) years old, with 27 (54.0 %) being males, and most of them were white (58.0 %). Most of the main diagnoses on ICU admission were cardiovascular disease (26.0 %), followed by neurological disease (22.0 %), respiratory

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 4 August 2022 doi:10.20944/preprints202208.0098.v1

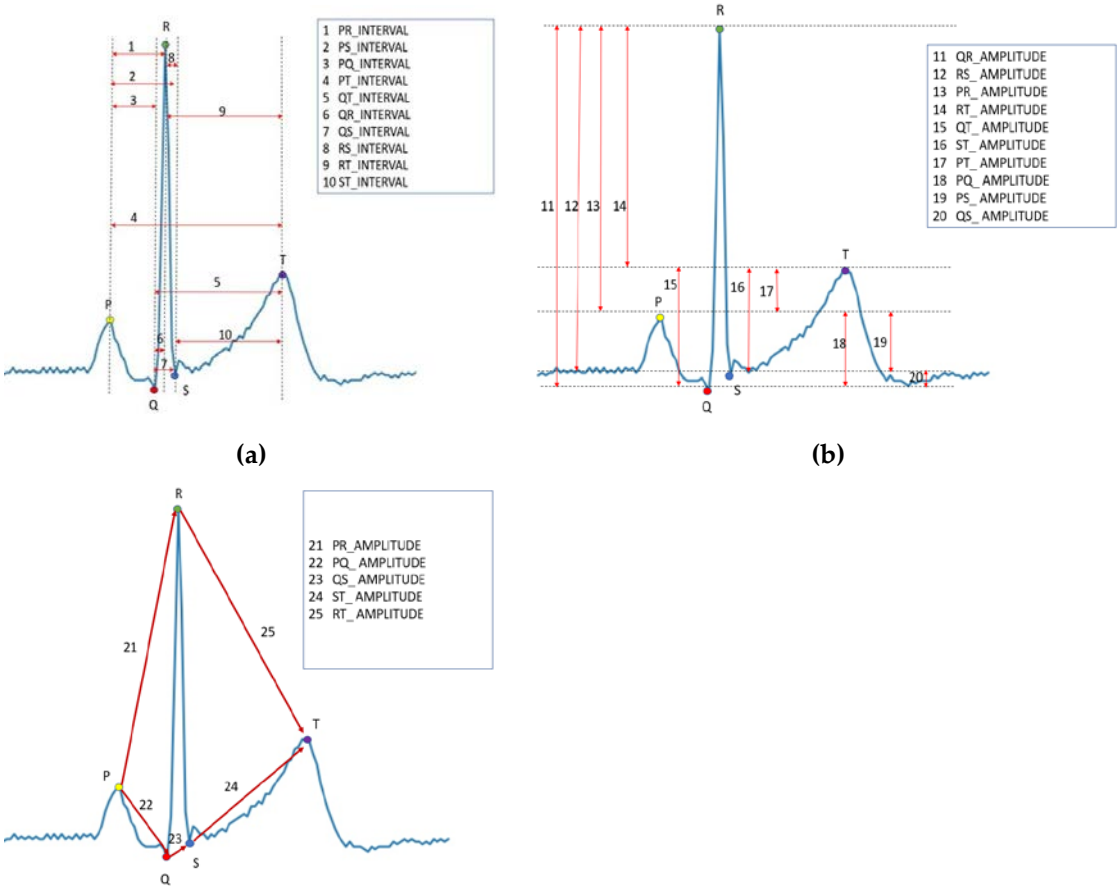
disease (14.0 %), infectious diseases (12.0 %), gastrointestinal disease (8.0 %), metabolic disease (8.0 %), and others. The other demographic characteristics are presented in Table 1.

During training, each patient was given their model weight based on their training data. Individual Oc-SVM models were developed for the included patients with the same hyperparameters, in which the kernel function selected was a linear SVM, and the "ν" argument was set to 0.75 to provide better sensitivity for dysglycemia during the prediction.

The prediction performances of the developed models for all the patients are presented in Appendix 2. Appendix 2A demonstrates the prediction performance for a single heartbeat, and Appendix 2B demonstrates the performance for a 10 s strip. The model prediction for dysglycemia from a single heartbeat had an AUC level of 0.92 ± 0.09 (Figure 2A), with a sensitivity of 0.92 ± 0.10 and specificity of 0.84 ± 0.04. The positive predictive value (PPV) for a single heartbeat was 0.85 ± 0.03, and the negative predictive value (NPV) was 0.92 ± 0.09. Based on 10 s majority voting, the model prediction for dysglycemia improved to an AUC of 0.97 ± 0.06 (Figure 2B). Other performance measurements are listed in Table 2.

Table 3 demonstrates the feature importance of the developed Oc-SVM model based on the average model weights of all the included patients. The most important ECG feature for predicting dysglycemia was the R-R interval, followed by the R-S, P-T, Q-R, Q-R, S-T, R-T, and R-S intervals.

Figure 1. The extracted features from one heartbeat ECG cycle.



 doi:10.20944/preprints202208.0098.v1

(c)

Table 1. Demographics of included patients.

Variables	Median(IQR)/N(%)
Age, median (IQR)	64 (55-72)
Male, n (%)	27 (54.0)
Race	
White	29 (58.0)
Black	10 (20.0)
Asian	2 (4.0)
Latino	2 (4.0)
Height (cm), median (IQR)	172 (163-180)
Weight (Kg), median (IQR)	83.6 (70.2-96.3)
BMI, median (IQR)	27.9 (25.4-29.7)
Diagnosis at admission	
Cardiovascular	13 (26.0)
CNS	11 (22.0)
Respiratory	7 (14.0)
Infectious	6 (12.0)
Gastrointestinal	4 (8.0)
Metabolic	4 (8.0)
Others	5 (10.0)

[1] IQR: Interquartile Range, BMI: Body Mass Index, CNS: Central Nervous System

Table 2. Performance of model prediction based on single heartbeat and 10 second majority voting

Oc-SVM	AUC	sensitivity	specificity	PPV	NPV
Single heartbeat	0.92 ± 0.09	0.92 ± 0.10	0.84 ± 0.04	0.85 ± 0.03	0.92 ± 0.09
10 second	0.97 ± 0.06	0.97 ± 0.09	0.96 ± 0.04	0.96 ± 0.04	0.97 ± 0.09

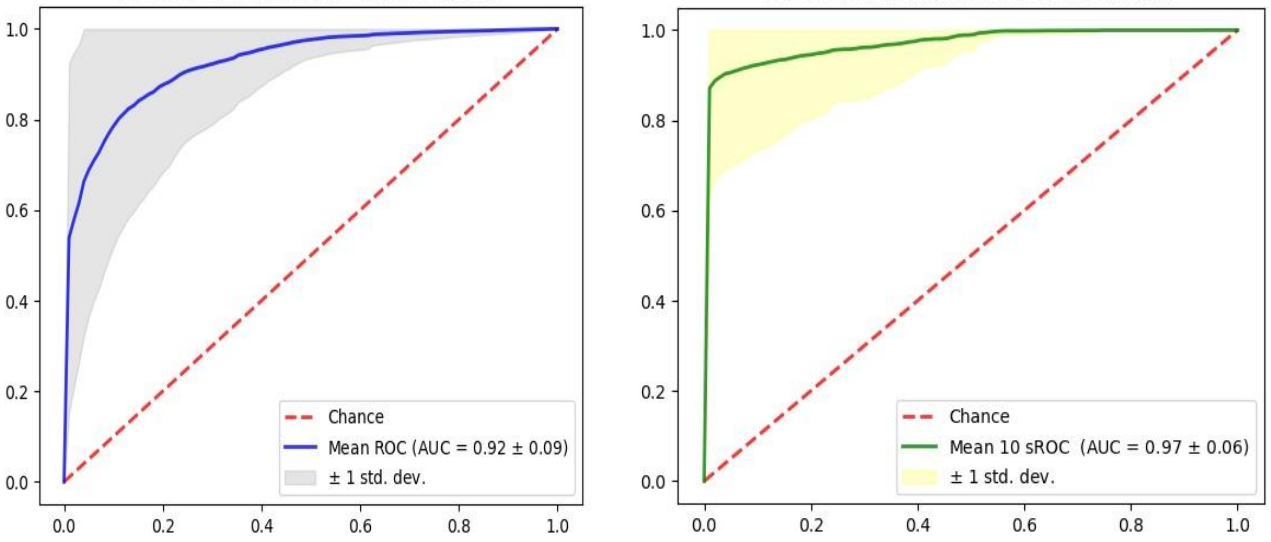
[1] AUR: Area Under the Receiver operating curve, PPV: Positive Predictive Value, NPV: Negative Predictive Value

Table 3. Feature importance of Oc-SVM model in predicting dysglycemia

ECG features	F-score
R-R interval	591
R-S amplitude	271
P-T amplitude	153
Q-R amplitude	150
Q-R interval	98

 doi:10.20944/preprints202208.0098.v1

S-T slope	97
R-T amplitude	76
R-S interval	76
P-S amplitude	72
P-Q amplitude	69
P-R slope	69
R-T slope	69



(**a**) (**b**)

Figure 2. Receiver Operating Curve of model prediction based on single heartbeat and 10 second majority voting

4. Discussion

In this study, we aimed to develop a personalized machine-learning algorithm to recognize dysglycemia from an EKG recording using only the lead II ECG record. Using personalized data, we found that the Oc-SVM model could accurately predict dysglycemia from a single heartbeat with a high AUC level of 0.92. When using 10 s majority voting, the model performance improved to an AUC of 0.97.

The most common method for blood glucose testing is finger stick glucose monitoring. However, this is not only invasive but also cumbersome and expensive, leading to poor patient compliance for glucose measurements[19]. In addition, it does not allow for continuous monitoring. Several noninvasive continuous glucose monitoring techniques have been developed, including methods that utilize Raman spectroscopy, fluorescence technology, mid-infrared spectroscopy, near-infrared spectroscopy, optical coherence tomography, and optical polarimetry[20,21]. Although such devices have shown promising results, the equipment should be improved to make them more accurate, convenient, comfortable to wear, and available for personalized use at home.

 doi:10.20944/preprints202208.0098.v1

In the past decade, wearable noninvasive sensors have been developed for tracking cardiac signals. A method was then proposed to use an ECG to detect dysglycemic events. Based on an ECG, Ling et al. proposed a hybrid neural logic approach that detected hypoglycemic events with an average sensitivity of 79.07 % and a specificity of 53.64 %[22]. Using a deep belief network for the detection of hypoglycemic episodes in diabetes patients, San et al. achieved sensitivity and specificity values of 80.00 and 50.00 %, respectively[23]. Cordeiro et al. evaluated ECG data from 1,119 patients and found that a 10-layer deep neural network was effective in detecting hyperglycemia, with a value of 94.53 % for the area under the curve (AUC), 87.57 % sensitivity, and 85.04 % specificity[24].

However, the focus of the current research is on detecting hypoglycemia or hyperglycemia only. Very few studies have detected ECG changes in combination with the hypoglycemic and hyperglycemic states. Although Nguyen et al. revealed that ECG parameters could be used to identify hypoglycemia and hyperglycemia in patients with type 1 diabetes, they did not develop an AI model to detect dysglycemic events[25]. Furthermore, most of the studies described above attempted to detect dysglycemia through noninvasive monitoring using features extracted from the ECG signal among generalized data. To date, only a limited number of studies have been conducted to detect dysglycemia using personalized ECG signals. Porumb et al. demonstrated that using personalized raw ECG signals recorded with noninvasive wearable devices, a model based on a convolutional neural network could detect hypoglycemic events with a sensitivity of 87. 5% and specificity of 81.7 %[26]. To the best of our knowledge, our study was the first to develop a personalized model to detect both hyperglycemia and hypoglycemia events simultaneously. With ECG signal detection using a 10 s window, the model performance reaches high AUC, sensitivity, and specificity values of 0.97, 0.97, and 0.96, respectively. Additionally, instead of using a multiple-lead ECG, we used only a single-lead ECG for signal acquisition. Because consumer wearable devices with ECG reading capabilities, such as smart watches, are becoming easily accessible to everyone, this technique can be useful for the general public.

The blood glucose concentration is known to affect the electrical activity of the heart[27]. Blood heart rate variability (HRV), as a representative of cardiovascular autonomic function, is considered to be significantly modulated by the blood glucose level. Bekkink et al. demonstrated that hypoglycemic events were related to an increase in the low frequency (LF)/high frequency (HF) ratio and a decrease in the square root of the mean standard differences of successive R-R intervals[28]. Amanipour et al. found that hyperglycemia was related to a 6-fold decrease in the LF/HF ratio[29]. The QT interval is also recognized as one of the most common features of cardiopathy assessment in dysglycemia[30]. Robinson et al. demonstrated that hypoglycemia could lead to QTc and QTd lengthening from baselines of ~75 and 55 ms, respectively[31]. Among 8,277 participants, Arnaud et al. found that severe hypoglycemia was associated with an increased risk of QTc prolongation, independent of other risk factors such as cardiac autonomic neuropathy[32]. Pickham et al. revealed that elevated glucose levels of 140–180 mg/dL had 2.1 odds of QTc interval prolongation, while glucose levels above 180 mg/dL had 3.8 odds of QTc interval prolongation[33]. In a population-based study, impaired fasting serum glucose led to significant QTc lengthening and RR interval shortening, and both phenomena were associated with an increased risk of sudden cardiac death[34]. ECG changes in response to hypoglycemia included an increased QTc interval, decreased PR interval, increased R-wave amplitude, decreased T-wave amplitude, and ST depression[35]. In cases of hyperglycemia, other ECG abnormalities such as significant increases in the PR interval and shorter mean RR intervals have been reported[36,37]. For additional information, we ranked the results of the variables by importance. This

 doi:10.20944/preprints202208.0098.v1

would enable a clinical physician to recognize which part of the ECG signal is significantly associated with dysglycemia. In our study, the most important ECG feature for predicting dysglycemia was the R-R interval, followed by the R-S amplitude, P-T amplitude, Q-R amplitude, Q-R interval, S-T slope, R-T amplitude, and R-S interval.

Our study had certain limitations. First, we used 10 euglycemic BG data points, five euglycemia data points, and five dysglycemia BG data points to develop a personalized Oc-SVM model. Real-world applications will require several samples of dysglycemic ECG signals from a user. Second, collecting ECG signals might be a challenging task because they could be sensitive to diverse environmental stresses, which would affect the quality of the data. However, wearable devices have been proven to reach high levels of accuracy for diagnoses[38]. Further research should be conducted using ECG signals from wearable devices.

5. Conclusions

A personalized machine-learning algorithm with Oc-SVM can detect both hypoglycemia and hyperglycemia using only lead II ECG records. As a noninvasive continuous monitoring method, this ECG-based dysglycemia identification method provided a high AUC of 0.97. Because only a single-lead ECG for signal acquisition is used, the technique is expected to be easily accessible to the general public. In addition, ranking ECG features using the Oc-SVM model would allow clinical physicians to recognize which part of the ECG signal is significantly associated with dysglycemia.

Author Contributions: Conceptualization, I.M.C. and C.Y.C.; methodology, I.M.C.; validation, C.Y.C., C.H.L. and C.J.L.; formal analysis, B.K.C.; investigation, I.M.C; data curation, B.K.C.; writing—original draft preparation, I.M.C; writing—review and editing, F.J.C.; supervision, C.Y.C. and C.H.L.

Funding: This study was funded by the Chang Gung Medical Foundation, grant number CMRPG8L1171.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the institutional review board of the Chang Gung Medical Foundation (202100362B, date of approval: 29/03/2021).

Informed Consent Statement: Not applicable.
Data Availability Statement: The data supporting this study's findings are openly available in the MIMIC-III Waveform Database Matched Subset (http://doi.org/10.13026/c2294b)

Conflicts of Interest: The authors declare no conflict of interest.

Appendix A

Demographics and diagnosis of all included patients.

Appendix B

The prediction performances of the developed models for all the patients

References

1. Capes SE, Hunt D, Malmberg K, Gerstein HC. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. The Lancet 2000;355:773-8.
2. Sung J, Bochicchio GV, Joshi M, Bochicchio K, Tracy K, Scalea TM. Admission hyperglycemia is predictive of outcome in critically ill trauma patients. J Trauma 2005;59:80-3.
3. Krinsley JS. Association between hyperglycemia and increased hospital mortality in a heterogeneous population of critically ill patients. Mayo Clin Proc 2003;78:1471-8.

4. Falciglia M, Freyberg RW, Almenoff PL, D'Alessio DA, Render ML. Hyperglycemia-related mortality in critically ill patients varies with admission diagnosis. Crit Care Med 2009;37:3001-9.
5. Armstrong C. ADA Updates Standards of Medical Care for Patients with Diabetes Mellitus. Am Fam Physician 2017;95:40-3.
6. Battelino T, Phillip M, Bratina N, Nimri R, Oskarsson P, Bolinder J. Effect of continuous glucose monitoring on hypoglycemia in type 1 diabetes. Diabetes care 2011;34:795-800.
7. Karter AJ, Ferrara A, Darbinian JA, Ackerson LM, Selby JV. Self-monitoring of blood glucose: language and financial barriers in a managed care population with diabetes. Diabetes care 2000;23:477-83.
8. Vincze G, Barner JC, Lopez D. Factors associated with adherence to self-monitoring of blood glucose among persons with diabetes. The Diabetes Educator 2004;30:112-25.
9. Singh JP, Larson MG, O'Donnell CJ, et al. Association of hyperglycemia with reduced heart rate variability (The Framingham Heart Study). Am J Cardiol 2000;86:309-12.
10. Laptev DN, Riabykina GV, Seid-Guseĭnov AA. [24-hours monitoring of ECG and glucose level for detection of relations between glycemia and QT interval duration in patients with type 1 diabetes]. Ter Arkh 2009;81:28-33.
11. Tobore I, Li J, Kandwal A, Yuhang L, Nie Z, Wang L. Statistical and spectral analysis of ECG signal towards achieving non-invasive blood glucose monitoring. BMC medical informatics and decision making 2019;19:1-14.
12. Hannun AY, Rajpurkar P, Haghpanahi M, et al. Cardiologist-level arrhythmia detection and classification in ambulatory electrocardiograms using a deep neural network. Nature medicine 2019;25:65-9.
13. Attia ZI, Noseworthy PA, Lopez-Jimenez F, et al. An artificial intelligence-enabled ECG algorithm for the identification of patients with atrial fibrillation during sinus rhythm: a retrospective analysis of outcome prediction. The Lancet 2019;394:8617.
14. Galloway CD, Valys AV, Shreibati JB, et al. Development and validation of a deep-learning model to screen for hyperkalemia from the electrocardiogram. JAMA cardiology 2019;4:428-36.
15. Mujahid O, Contreras I, Vehi J. Machine Learning Techniques for Hypoglycemia Prediction: Trends and Challenges. Sensors 2021;21:546.
16. Kodama S, Fujihara K, Shiozaki H, et al. Ability of Current Machine Learning Algorithms to Predict and Detect Hypoglycemia in Patients With Diabetes Mellitus: Meta-analysis. JMIR Diabetes 2021;6:e22458.
17. Moody B, Moody, G., Villarroel, M., Clifford, G., & Silva, I. MIMIC-III Waveform Database Matched Subset (version 1.0). PhysioNet.2020.
18. Johnson AEW, Pollard TJ, Shen L, et al. MIMIC-III, a freely accessible critical care database. Scientific Data 2016;3:160035.
19. Wagner J, Malchoff C, Abbott G. Invasiveness as a barrier to self-monitoring of blood glucose in diabetes. Diabetes Technol Ther. 2005;7:612-9.
20. Chen C, Zhao XL, Li ZH, Zhu ZG, Qian SH, Flewitt AJ. Current and Emerging Technology for Continuous Glucose Monitoring. Sensors (Basel). 2017;17:182.
21. So CF, Choi KS, Wong TK, Chung JW. Recent advances in noninvasive glucose monitoring. Med Devices (Auckl). 2012;5:45-52.
22. Ling, S. H., San, P. P., Lam, H. K. & Nguyen, H. T. Hypoglycemia detection: multiple regression-based combinational neural logic approach. Soft Comput. 2017;21: 543-553
23. Phyo Phyo San, Sai Ho Ling, Nguyen HT. Deep learning framework for detection of hypoglycemic episodes in children with type 1 diabetes. Annu Int Conf IEEE Eng Med Biol Soc. 2016 Aug;2016:3503-3506.
24. Cordeiro R, Karimian N, Park Y. Hyperglycemia Identification Using ECG in Deep Learning Era. Sensors (Basel). 2021;21:6263.
25. Nguyen LL, Su S, Nguyen HT. Identification of hypoglycemia and hyperglycemia in type 1 diabetic patients using ECG parameters. Annu Int Conf IEEE Eng Med Biol Soc. 2012;2012:2716-9.
26. Porumb M, Stranges S, Pescapè A, Pecchia L. Precision Medicine and Artificial Intelligence: A Pilot Study on Deep Learning for Hypoglycemic Events Detection based on ECG. Sci Rep. 2020;10:170.
27. Lipponen JA, Kemppainen J, Karjalainen PA, et al. Dynamic estimation of cardiac repolarization characteristics during hypoglycemia in healthy and diabetic subjects. Physiol Meas. 2011;32:649-660.
28. Olde Bekkink M, Koeneman M, de Galan BE, Bredie SJ. Early Detection of Hypoglycemia in Type 1 Diabetes Using Heart Rate Variability Measured by a Wearable Device. Diabetes Care. 2019;42:689-692.
29. R. Amanipour, H. Nazeran, I. Reyes, M. Franco and E. Haltiwanger, The effects of blood glucose changes on frequency-domain measures of HRV signal in type 1 diabetes, CONIELECOMP 2012, 22nd International Conference on Electrical Communications and Computers, 2012;50-54
30. Gordin D, Forsblom C, Rönnback M, Groop PH. Acute hyperglycaemia disturbs cardiac repolarization in Type 1 diabetes. Diabet Med. 2008;25:101-5.
31. Robinson RT, Harris ND, Ireland RH, Lee S, Newman C, Heller SR. Mechanisms of abnormal cardiac repolarization during insulin-induced hypoglycemia. Diabetes. 2003;52:1469-74.
32. Kaze AD, Yuyun MF, Erqou S, Fonarow GC, Echouffo-Tcheugui JB. Severe Hypoglycemia and Incidence of QT Interval Prolongation Among Adults With Type 2 Diabetes. J Clin Endocrinol Metab. 2022;107:e2743-50.
33. Pickham D, Flowers E, Drew BJ. Hyperglycemia is associated with corrected QT prolongation and mortality in acutely ill patients. J Cardiovasc Nurs. 2014;29:264-70.

 doi:10.20944/preprints202208.0098.v1

34. van Noord C, Sturkenboom MC, Straus SM, Hofman A, Kors JA, Witteman JC, Stricker BH. Serum glucose and insulin are associated with QTc and RR intervals in nondiabetic elderly. Eur J Endocrinol. 2010;162:241-8.
35. Laitinen T, Lyyra-Laitinen T, Huopio H, Vauhkonen I, Halonen T, Hartikainen J, Niskanen L, Laakso M. Electrocardiographic alterations during hyperinsulinemic hypoglycemia in healthy subjects. Ann Noninvasive Electrocardiol. 2008;13:97-105.
36. Marfella R, Nappo F, De Angelis L, Siniscalchi M, Rossi F, Giugliano D. The effect of acute hyperglycaemia on QTc duration in healthy man. Diabetologia. 2000;43:571-5.
37. Bathula R, Hughes AD, Panerai R, et al. Indian Asians have poorer cardiovascular autonomic function than Europeans: this is due to greater hyperglycaemia and may contribute to their greater risk of heart disease. Diabetologia. 2010;53:2120-8.
38. Bouzid Z, Al-Zaiti SS, Bond R, Sejdić E. Remote and wearable ECG devices with diagnostic abilities in adults: A state-of-the-science scoping review. Heart Rhythm. 2022 Jul;19(7):1192-1201.