Classification and Prediction of Hypoglycemia in Patients with Type 2 Diabetes Mellitus Using Data from the EHR and Patient Context

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Abstract: The increase in obesity, a sedentary lifestyle, and population aging are considered the main factors for the increase in Type 2 Diabetes Mellitus (T2DM) worldwide. Global estimates indicate that around 400 million people live with T2DM, reaching 600 million in 2035. This scenario generates a high social and financial cost for the patient and the healthcare system. In this context, this work evaluates machine learning models to classify and predict hypoglycemic crises in patients with T2DM. A dataset with data from a clinical center in southern Brazil is constructed. Patient data involves Electronic Health Records (EHR) and data collected in the patient context through Internet of Things (IoT). This dataset is used to run classification and prediction models. Results show that the proposed approach is promising, achieving an AUC of 0.8200 and a sensitivity of 90.00% for classifying hypoglycemia. In addition, the Clarke Error Grid plot demonstrates an assertiveness of prediction for high blood glucose in clinical terms. These results demonstrate that the proposed method achieves comparable or superior results to related works in the literature. The combined use of EHR, IoT, and Machine Learning can be a promising alternative to improve the monitoring of chronic and long-term diseases, such as T2DM, contributing to a more accurate and effective diagnosis.

1 INTRODUCTION

Currently, Type 2 Diabetes mellitus (T2DM) stands out as an important cause of morbidity and mortality. Global estimates indicate that about 400 million people live with T2DM (8.3%) and, if current trends continue, the number of people with diabetes is expected to exceed 642 million in 2040 (Guariguata et al., 2014; Bertoluci et al., 2021). Furthermore, considering that 50% of people with diabetes do not know they have the disease (Beagley et al., 2014), it is estimated that T2DM could jump from the ninth to the seventh leading cause of death in the world (Bertoluci et al., 2021; Ogurtsova et al., 2017). The increase in the prevalence of obesity, sedentary lifestyle, and population aging are considered the main factors for the increase in the incidence of T2DM in the world (Ogurtsova et al., 2017; Moura et al., 2012). This scenario generates a high social and financial cost for the patient and for the health system in general (Rosa et al., 2014). The World Health Organization (WHO), in January 2020, published the document entitled Global Strategy for Digital Health 2020-2024, conceptualizing Digital Health as the field of knowledge and practice associated with developing and using digital technologies to improve health (WHO, 2020). Digital Health expands the concept of eHealth to include digital consumers with a broader range of smart devices and connected equipment. It also covers other uses of digital health technologies such as the Internet of Things (IoT), Artificial Intelligence, Big Data Analytics and robotics. These technologies can significantly improve health by increasing the efficiency of medical diagnosis, health-based treatments, evidence, and self-care support, strengthening health care. In this sense, a model is being designed to provide patients with knowledge and technologies to play a more active role in health monitoring. This health monitoring can be rigorously defined as: “Repeated or continuous observations or measurements of the patient, their physiological function and the function of life support equipment, in order to guide management decisions, including when to make ther-

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apeutic interventions and evaluation of these interventions" (Hudson, 1985). This model adopts the principles of proactivity, independence, accessibility and economy. They are using a wide range of mobile technologies such as smartphones, tablets and wearable sensors for continuous monitoring of the patient and patient's vital signs (Banos et al., 2014; Gao et al., 2017; Ramazi et al., 2021). The work of (da Costa et al., 2018) presents the concept of the Internet of Health Things (IoHT), which proposes to collect vital signs in a partially or fully automated way to boost health services. This collect would be using handheld devices and smartphones and moving from a conventional hub-based health system to more personalized systems (Pagiatakis et al., 2020). However, transforming advanced IoHT technology into custom systems is still a significant challenge in the field. Some issues include the lack of accurate and cost-effective medical sensors, non-standard IoHT system architectures, heterogeneity of connected wearable devices, the multidimensionality of the generated data, and high demand for interoperability (Baloch et al., 2018; Qi et al., 2017; Pasquier et al., 2018), which are obstacles to its effectiveness. Furthermore, given that the goal of ubiquitous computing in health is to seek context awareness (Dey et al., 2001; Tavares et al., 2016), some challenges stand out, as the idea of using contextualized health awareness is to provide intelligence and focus care on the patient (Mshali et al., 2018; Montori et al., 2018). Therefore, our main contributions with this article are: (i) evaluate Machine learning models based on criteria defined in the literature, using as a dataset data collected in the patient's EHR and data collected in their context through the use of IoT. (ii) evaluate a computational architecture that supports clinical decision-making, using well-known clinical criteria for T2DM, such as the Clarke Error Grid. Furthermore, the use of technological tools in personal health mentioned here is referenced by the WHO's concept of digital health together with the classification of Digital Health interventions (WHO, 2018). Thus, the different ways digital technologies can help health systems are confirmed, aiming to promote an accessible and binding language for health systems planning. The remainder of this paper is organized as follows. Section 2 presents the most significant related works to define the present study. Next, section 3 presents the methodology of the work. The section 4 details the results and discussion. Finally, Section 5 presents the conclusions of the work.

2 RELATED WORK

Early detection of health problems in chronic diseases, such as T2DM, plays a crucial role in diagnosing and treating various comorbidities that arise. One of the critical aspects of any eHealth solution is quality management of urgent situations (Rivera et al., 2019). These situations are currently accessible across a wide range of embedded sensors. The heterogeneity of such sensors and the diversity of user needs require quality service management and adaptation to different critical situations. Considering that the pathophysiology of T2DM is a continuous process, transient critical abnormalities must be detected early (Brisimi et al., 2019; Dworzynski et al., 2019). In this sense, sensor networks capable of providing continuous physiological monitoring data (e.g., glucose, blood pressure, pulse, heart rate) (Ramazi et al., 2019; Abaker and Saeed, 2021), and lifestyle (diet, physical activity, among others.) have great potential to detect these transitions and monitor the progress of the disease (Faruqui et al., 2019). Internet of Things technology can significantly contribute in this direction, allowing the integration of more factors in clinical decision-making related to diabetes management (Shah and Levy, 2021). Due to the multifactorial nature of DM2, multilevel modeling approaches must be applied to consider all the different types of factors strongly associated with the onset and progression of the disease (Pan et al., 2023). New data analysis methods can be used to capture correlated and causal relationships between variables. Examples are classification and regression-based approaches (e.g., linear and logistic regression). Such methods can be applied to identify new biomarkers, which are strongly related to the onset and evolution of DM2 (Massaro et al., 2019; Ellahham, 2020; Lee et al., 2023) Approaches to prediction based on chronic diseases are dependent on large datasets, and the use of Electronic Health Records (EHR) from large hospitals or hospital networks is frequent in the literature. For example, (Brisimi et al., 2019) seeks to predict hospitalizations associated with T2DM within a year from when the patient's EHR is examined, treating the prediction as a classification problem and using data from the Boston Medical Center (BMC). (Dworzynski et al., 2019) seeks to predict the future emergence of comorbidities in patients with T2DM, using data from 200,000 patients from the public health service in Denmark, to prove that early intervention can reduce the appearance of sub-diseases arising from the T2DM. The early identification of risk factors associated with the development of diabetic foot ulcers (DFU) using machine learning techniques was carried out in the work of (Nanda et al., 2022), to discover the association of various clinical and biochemists with DFU and develop a prediction model using different machine learning algorithms. Clinical and laboratory data were analyzed using different algorithms, including Naive Bayes (NB), K-nearest neighbor (KNN), and random forest (RF). In (Pan et al., 2023), the objective is to establish a risk prediction model for diabetic retinopathy (DR) in the Chinese population with T2DM using a few inspection indicators and propose suggestions for the management of chronic diseases. For this purpose, a retrospective dataset from 2,385 patients with T2DM was used. The study aimed to establish a risk prediction model using a few inspection indicators and propose suggestions for managing chronic diseases. Related work aims to classify patients with specific objectives, such as predicting mortality (Brisimi et al., 2019) or more particular health conditions, such as diabetic foot ulcers (Nanda et al., 2022) or cognitive impairment (Chen et al., 2021). Likewise, works in the literature are mainly based on large-scale datasets originating from the EHR of large hospitals or hospital networks for training and testing. Therefore, this work proposes to investigate the effectiveness of machine learning in predicting the emergence of cases of hypoglycemia in patients with DM2, using data originating from the EHR of a clinical center, where the context refers to few resources and data collection in the context of the patient, using IoT.

3 MATERIALS AND METHODS

Our methodology can be divided into four steps: dataset construction (which involves patients' EHR data and data collected in the patients' context), data preprocessing, training, and testing. Preprocessing consists of missing data treatment, normalization, and data balancing. Finally, in the training stage, models and parameters are defined.

3.1 Dataset

We use two datasets to develop the model. One set was collected from historical EHR data from patients treated by a clinical center in Lajeado/RS, and another was collected in the context of these patients. The first set comprises information collected from the patient's EHR, including vital signs, information about addictions, use of medications to control diabetes, and the outcome variable (which, in this case, is the detection of hypoglycemia). The information collected covers the period from 2016 to 2020. The study was approved by the ethics committee under certificate nº 4,235,499. In addition, this document follows the General Data Protection Law (LGPD) recommendations. The second set of data was collected in the context of the patients through an application that collected data on vital signs (diastolic blood pressure, systolic blood pressure, heart rate, body temperature, weight, body mass index, capillary glucose) and the value of the patient's outcome variable. This collected data serves to update the prediction model. The application was installed on the patients' smartphones, and they reported vital sign values according to specialist guidance. Figure 1 shows how the final dataset used in the experiments was constructed. The dataset was constructed from patients' EHR data, comprising structured data on vital signs and data from unstructured fields involving addictions, medication use, and outcome variable corrections. The data collected in the patient's context was collected through an application, collecting data on vital signs and the outcome variable. After data extraction, these data were corrected and integrated, resulting in the final dataset.

3.2 Pre-Processing

We processed both datasets using the same methodology. Due to the origin and nature of the data, there are missing values and erroneous data, leading to irregular sampling. Therefore, preprocessing steps are required to clean the data and make it compatible with the proposed machine learning model. The preprocessing steps considered for this study include handling missing values and normalization (Cenitta et al., 2022). We apply different filling methodologies to deal with missing values, which use imputation methods depending on the missing vital signs and the reason for missing data. The methods were chosen according to the work of (Nadimi-Shahraki et al., 2021), differentiating eventual missing data from a large series of missing data. For large series of missing data, mean imputation was used, which can be defined as:

$$Vt_0 = avg(Vt_1 + ... + Vt_n) \tag{1}$$

where Vt_0 is the missing record, and $avg(Vt_1 + ... + Vt_n)$ is the average of the records present. We use imputation when a missing value was present. We followed the method of (Midroni et al., 2018; Javidi et al., 2022), using the average of the seven days immediately following the missing data to create a new value for the missing value. For specific missing data, an approach based on multiple imputation was used (PEDERSEN et al., 2017; CUMMINGS, 2013; STERNE et al., 2009), which initially imputes the missing data in each variable using the

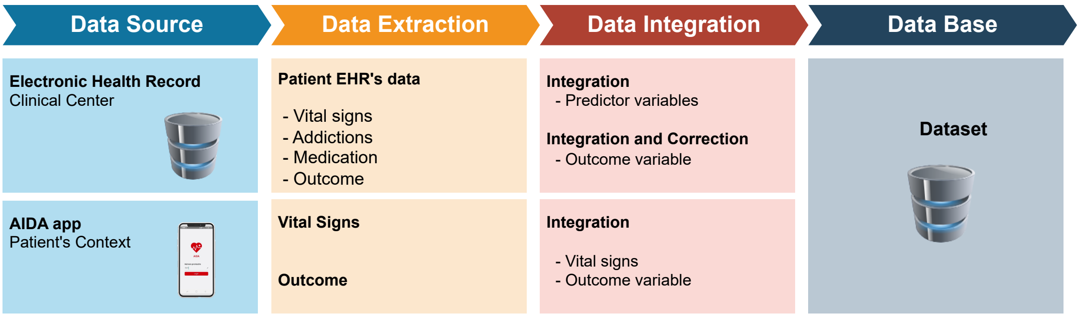

Figure 1: Summary of dataset construction.

mean/mode and then imputes each incomplete variable by a separate model, which explores the previously imputed values of the other variables (BUUREN; GROOTHUIS-OUDSHOORN, 2011; BUUREN, 2018). In Figure 2, we can see a graph with large-scale missing data and specific missing data before imputation (figure A) and after applying the imputation techniques (Figure B).

To avoid harming the algorithms' performance, the data was normalized in two ways. First, in categorical variables, we use *one-hot-encoding* encoding, using simple integers to deal with textual data, as in gender information. Data normalization, to change the values of the data set to a standard scale, without distorting differences in the value ranges, was performed using *min-max scaler* (Rakthanmanon et al., 2013), typically used in health temporal series data (Faruqui et al., 2019; Javidi et al., 2022).

3.3 Training and Test

Typically, a dataset is used to train a machine learning model, and an external dataset is used to validate this model, with this external dataset being collected independently of the dataset used in training (Reddy and Aggarwal, 2015). However, in most practical cases, data is scarce and difficult to collect. To solve this problem, we follow a common strategy to divide the dataset into training and testing sets before tuning a machine learning model and evaluating the best model performance (Joseph, 2022). There still needs to be a consensus on the ideal data split ratio for training and testing. The most commonly used divisions are 60:40, 70:30, or 80:20 (Raschka et al., 2022; Joseph and Vakayil, 2022). In this study, we used the 80:20 ratio split.

3.4 Evaluation

It is essential to compare different learning algorithms to train and select the best-performing model (Raschka et al., 2022). A machine learning model comprises parameters and hyperparameters that affect the speed and accuracy of the learning process. This step uses the training data and hyperparameter optimization approaches to tune the models. The training is divided into multiple sets, and the candidate model was trained and validated using the cross-validation procedure (Joseph and Vakayil, 2022). We used a cross-validation of *K-Folds* with five *folds*. We cannot expect the default hyperparameters of different learning algorithms provided by software libraries to be ideal for our specific task. Therefore, we use Randomized search and Grid search techniques for hyperparameter optimization, which help us tune the performance of our model (Raschka and Mirjalili, 2019). We evaluated the model using the area under receiver operating characteristic (AUC), accuracy, sensitivity, specificity, and F1 score as performance metrics. Furthermore, to consider the clinical impact of prediction error and how it may affect a potential medical decision, we consider the Clarke Grid Error (Clarke et al., 1987), a criterion related to the mean squared error. The Clark error grid is a chart with five main zones of attention (zones A, B, C, D, and E) for interpreting predicted glucose levels. Zone A represents those values within 20% of the reference value that generally leads to adequate treatment of patients. Zone B represents those values outside zone A, but that does not lead to inappropriate treatment of patients. Prediction values falling into zone C lead to inappropriate treatment without dangerous consequences for the patient. Predictive values in zone D lead to failure to detect hypoglycemia or hyperglycemia. Finally, prediction values in zone E lead to inappropriate treatment of hyperglycemia rather than hypoglycemia and vice versa, depending on the zone's location. This way, we can determine an acceptable error for blood glucose prediction compared to the real observation (Faruqui et al., 2019).

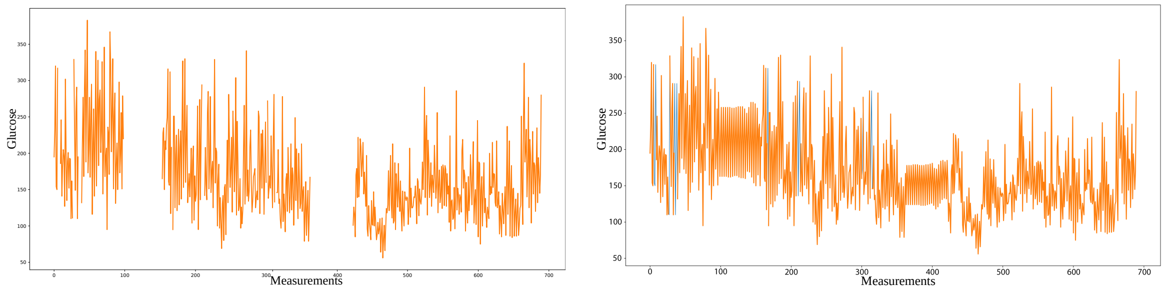

Figure 2: Missing data (A) and with imputation techniques used (B).

4 RESULT AND DISCUSSION

This section presents the results of the proposed method and the comparison with the current literature for detecting hypoglycemia crises. The best weights were chosen automatically based on the validation set error. Table 1 presents the performance obtained for the evaluation metrics in the Lajeado/RS Clinical Center dataset and the respective comparison with the current literature. Few studies in the current literature specifically focus on early detection of hypoglycemia in T2DM. Therefore, direct comparison with related work proves challenging due to disparities in data sets, objectives, and diverse methodologies employed. Therefore, the survey of related works was mainly based on works that detected different comorbidities resulting from T2DM. Most of the studies compared in Table 1 aim to classify patients with specific objectives, such as predicting mortality (Brisimi et al., 2019) or more particular health conditions, such as diabetic foot ulcers (Nanda et al., 2022) or cognitive impairment (Chen et al., 2021). This specificity contributes to the greater precision observed in these studies about the evaluation criteria compared to the results presented in this work. The classification and prediction of conditions more susceptible to subjective interpretations, such as hypoglycemia, generally result in less expressive performance in the evaluation criteria, as evidenced in the studies by (Saravanakumar and Sabibullah, 2022) and (Lee et al., 2023), justifying results more aligned with the metrics presented. Despite the different objectives, the results presented in Tab. 1 show that even without having a well-defined outcome variable objective, such as hypoglycemia, it is possible to achieve results that are very close to or better than comparative studies. At this point, it is essential to highlight the sensitivity (90.00%), demonstrating that the model can identify cases satisfactorily. The proposed method obtained a value of 0.820 for the ROC curve. Compared to related works in the classification literature, our approach is in line with the other works, a little below the results of (Brisimi et al., 2019), (Nanda et al., 2022), and (Lee et al., 2023), but above the others. Furthermore, the data used by related works originates solely from patients' structured EHRs. In our method, the source data of the dataset involves EHR data and data collected in the patient context. Therefore, our method may have been hampered in terms of evaluation criteria due to data gaps and respective imputation methods. On the other hand, we can consider that, as the data are of multiple origins, it may be more susceptible to use as support for decision-making in monitoring patients with T2DM. The predictions were plotted under the Clarke Grid error graph to visualize the predictions in their respective error zones. The plot of the data presented in Figure 3 shows that few predictions were in error zones in the Clarke Grid that denote problems in the treatment. We can see in the graph that only one point was predicted in Zone D, which can lead to a failure to detect hypoglycemia. Most of the predicted points plotted in Figure 3 are in zones A and B, which are either within the reference values for adequate treatment (Zone A) or are outside the reference zone but do not lead to inadequate treatment of the patient (Zone B). The results of our study demonstrate that utilizing data collected in the patient context and merging this data with the EHR can be a practical approach for predicting health decline and potential hypoglycemic crises. Although there is space for improvement in classification and prediction performance metrics, the current results are promising and open possibilities for studies of our model in chronic disease monitoring settings, such as T2DM.

Table 1: Comparison with related works. AUC: area under the receiver operating characteristic. Acc: Accuracy. Sen: Sensibility. Spe: Specificity. F1: F1-score.

Study	Dataset	AUC	Acc	Sen	Spe	F1
(Brisimi et al., 2019)	Private	0.890	-	-	-	-
(Dworzynski et al., 2019)	Private	0.800	-	-	-	-
(Chen et al., 2021)	Private	0.810	79.00	69.57	88.00	76.19
(Nanda et al., 2022)	Private	0.970	-	95.00	93.80	-
(Pan et al., 2023)	Private	0.700	79.00	00.03	-	00.06
(Lee et al., 2023)	Private	0.830	90.00	69.40	-	65.10
Ours	**Private**	**0.8200**	**74.00**	**90.00**	**72.00**	**46.00**

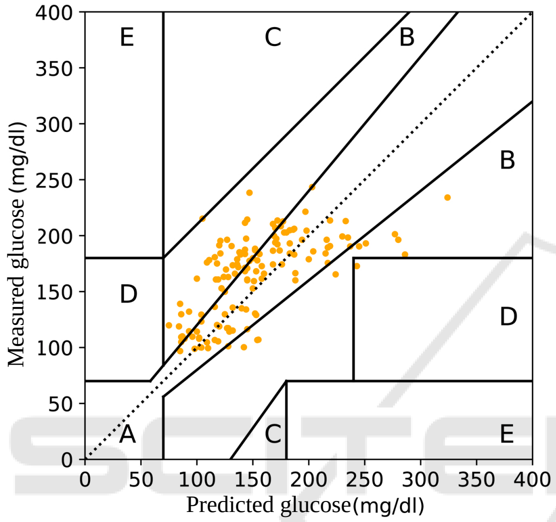

Figure 3: Clarke Grid error for glucose prediction.

5 CONCLUSION

This study explored the use of EHR and patient-context data to support hypoglycemia classification and prediction models in patients with T2DM. The results showed that the proposed approach could sometimes surpass the results of related works that use only data from EHR. Furthermore, using the Clarke Error Grid to evaluate results can help relate the evaluation criteria, showing that the model can be applied in clinical environments. This work has some limitations. The first relates to the union of the dataset originating from the patient's EHR with the data collected in the patient's context and the different data collection failures. Therefore, studying different imputation methods and methods to prevent failures or methodologies for greater patient adherence to technology use are perspectives for future work. Another limiting aspect is the low amount of data collected regarding the patient (since this work presents partial results). In this way, data collection is expected to continue in the patient's context, allowing a possible improvement in the evaluation criteria, especially in the part that refers to the prediction of hypoglycemic crises. The benefits of using technology to monitor chronic patients are significant, allowing faster diagnoses and emerging as a contribution to medical diagnosis, notably in chronic diseases. The proposed method can help save time and resources, especially public healthcare. These advantages make the proposed approach a promising tool for monitoring patients with T2DM in real clinical scenarios.

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