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Detecting Diabetic Autonomic Neuropathy from Electronic Health Records Using Machine Learning

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***Abstract*—Diabetes is a disease that affects a large number of people worldwide, and diabetic neuropathy is one of its most common and serious complications. Diabetic autonomic neuropathy (DAN) is a type of diabetic neuropathy that is defined as a disorder of the autonomous nervous system and can affect various organs in the body, including the heart and kidney. DAN is widely under-diagnosed due to reasons such as the cost and unavailability of testing equipment, the difficulty of performing cardiovascular tests, and the oftentimes asymptomatic state of the disease in its early stages. However, a late diagnosis can lead to dangerous health complications in the long run. As such, this paper aims to use machine learning to detect DAN in the kidney and heart in diabetic patients by retrieving their information from electronic health records. For this purpose, a dataset of 1275 patient records was used with a variety of traditional machine learning and deep learning algorithms. The best performing model was TabNet with an F1 score of 85.82 for the heart and 73.37 for the kidney.**

Keywords—machine learning, deep learning, electronic health records, diabetic autonomic neuropathy, cardiovascular autonomic neuropathy

I. Introduction

Diabetes is one of the most common diseases worldwide. In 2021, it was estimated that over 500 million people live with diabetes, and this number is expected to increase by 46% in the next 20 years [1]. Diabetic neuropathy is a common and dangerous complication of diabetes that is frequently overlooked and misdiagnosed. It affects more than 40% of individuals with diabetes over time [2, 3] and plays a major role in morbidity and mortality in patients with type 1 and type 2 diabetes mellitus [4]. Neuropathic pain increases the patient's healthcare costs significantly and creates various limitations in the patient's quality of life, work productivity and physical activity [3]. Diabetic autonomic neuropathy (DAN) is one of the least-understood and least-studied forms of diabetic neuropathy, defined as a disorder of the autonomic nervous system in the setting of diabetes mellitus [5]. It can affect different organ systems such as the cardiovascular, gastrointestinal, urogenital, pupillary, sudomotor and neuroendocrine systems [6]. The focus of this paper is on two different types of DAN; kidney and cardiovascular. The kidney DAN affects the nerves controlling the urinary tract, kidney and bladder. It is associated with various complications including urinary tract infections and several types of bladder dysfunctions such as low uroflowmetry, high post-void residual, and hypotonic bladder [7, 8]. Additionally, it has shown to be a significant predictive factor for kidney stone recurrence in diabetic patients [9]. Cardiovascular autonomic neuropathy (CAN) is the most clinically important form of diabetic neuropathy and can cause various complications such as resting tachycardia, exercise intolerance, orthostatic hypotension, reverse dipping, impaired heart rate variability and delayed ventricular repolarization [5, 10, 11]. CAN affects over 20% of unselected diabetic patients and up to 65% of patients with higher age and diabetes duration [4]. It has shown to be a significant risk factor of cardiovascular mortality [11-13]. CAN can be subclinical for several years, with its associated clinical symptoms occurring late in the disease, however a late diagnosis increases the mortality risk. The progression of CAN from subclinical to clinical is associated with a poor prognosis [14]. As such, it is important for CAN to be discovered during the subclinical stage. The tests frequently used to detect neuropathy in asymptomatic patients include the Electromyogram (EMG), the Nerve Conduction Study (NCS) and the Quantitative Sudomotor Axon Reflex Test (QSART), which are costly, require special equipment and are not widely available [15, 16]. One of the traditional methods for detecting CAN is the Ewing battery test which consists of 5 cardiovascular reflex tests. These tests are time-consuming, require patient effort and are often difficult to perform for elderly patients and those suffering from other medical issues such as heart or lung diseases, proliferative retinopathy, arthritis and mobility challenges [17-19]. Additionally, the diagnostic criteria and staging of CAN using Ewing's test is still debated [20]. Taking these issues into account, our study aims to use routine clinical data to detect early cardiovascular and kidney neuropathy in diabetes mellitus patients in order to determine the patient's need for further testing.

II. Related Work

With the increase in availability of electronic health records (EHR) and the rapid progress in the machine learning and deep learning fields, there has been much research in the usage of EHR and machine learning in medical screening and diagnosis. Previously, several studies have been conducted in detecting CAN with machine learning models using heart rate variability data (HRV) extracted from electrocardiogram (ECG) recordings [21-24]. Abawajy et al. [25] used automated iterative multitier ensembles to predict CAN with a combination of blood biochemistry features and the Ewing battery test results. In [19], Hassan et al. used a combination of ECG, blood chemistry and

Ewing battery test results along with a multistage fusion approach to diagnose CAN. This approach involved the fusion of shared component analyses and a multivariate exponentially weighted moving average. In [26], Petry et al. used random forests to detect CAN using baroreflex sensitivity analysis results. In [18], Hassan et al. proposed a multi-class classifier based on deep learning feature fusion to distinguish between early, normal and severe CAN using ECG recordings, Ewing battery test results, blood chemistry and other health related features. Abdalrada et al. [20] used machine learning and various data including Ewing's battery test results, ECG recordings, blood biochemistry, medical history and peripheral nerve function test results to predict CAN in patients with diabetes.

There is less research available on the prediction and detection of other types of diabetic autonomic neuropathies using machine learning. In [27], Lagani et al. developed risk assessment models for several different diabetes complications including gastrointestinal and urogenital autonomic neuropathies. However, this study defined neuropathy as the presence of bowel, bladder or erectile dysfunctions, which may be caused by other medical conditions and cannot be an accurate marker for DAN without the use of other testing measures.

The contributions of our study are as follows:

- Propose an early kidney DAN and CAN screening model for asymptomatic and symptomatic patients without the need for additional tests such as ECG or blood tests.
- Apply the proposed method on a private dataset collected from UAE population.
- Comparison of the performance of multiple machine learning and deep learning models in neuropathy detection using basic clinical data.

III. Dataset And Methods

A. Data

Clinical data was collected from electronic health records of 1275 diabetes mellitus patients in Dubai, UAE. The clinical data include age, gender, systolic blood pressure (SBP), height, weight and body mass index (BMI). The diagnostic tool used to identify neuropathy in the dataset used in this paper is the Sudoscan test. This test detects clinical and subclinical neuropathy by evaluating the response of the nerve fibers in the sweat glands to electrical stimulus [28-30]. Similarly to the previously mentioned tests, Sudoscan is costly and not widely available, however it is non-invasive and less time-consuming than other testing methods while providing similar reliability in its results, as such it can be used to test patients with comorbidities. Additionally, the Sudoscan kidney DAN score has shown to be an effective screening tool for chronic kidney disease in diabetes patients [31, 32]. Due to these characteristics, we have chosen the Sudoscan test as our neuropathy diagnosis device as opposed to the previously mentioned tests.

The Sudoscan variables in this dataset include the kidney DAN score and CAN score. No personal identifiable information was included. The variables and statistics of the dataset are reported in Table 1.

TABLE I. Statistical details of the features in the dataset: range and mean for numerical features, frequency and percentage for categorical features

Variable	*Range*	*Mean*	*Frequency*	*Percentage*
Age (years)	[15-96]	53.09	-	-
SBP (mm Hg)	[110-160]	131.12	-	-
Diabetes Type	-	-	T2: 1251 T1: 24	T2: 98.11% T1: 1.88%
Gender	-	-	M: 746 F: 531	M: 58.43% F: 41.56%
Weight (kg)	[36-160]	80.75	-	
Height (cm)	[143-194]	167.09	-	
BMI	[15-54]	28.86	-	
Kidney DAN Score	[9-140]	64.37	-	
CAN Score	[5-72]	30.90	-	
Presence of CAN	-	-	Yes: 779 No: 496	Yes: 61.09% No: 38.90%
Presence of Kidney DAN	-	-	Yes: 605 No: 670	Yes: 47.45% No: 52.54%

The results of the Sudoscan test are reported in the form of scores within the range of 0-150 for kidney DAN and 0-100 for CAN. CAN scores of 0-29 represent no neuropathy (38.90% of dataset), 30-59 represent moderate neuropathy (59.84%) and 51-100 represent severe neuropathy (1.25%). Kidney DAN scores of 0-39 represent severe neuropathy (4.31%), 40-59 represent moderate neuropathy (43.14%) and 60-150 represent no neuropathy (52.54%). For the classification task, variables that indicate the existence of neuropathy were created and all values within moderate or severe ranges were labeled as "yes".

B. Pre-processing

We split the dataset into a training set consisting of 70% of the samples and a testing set consisting of 30% of the samples. The dataset contains an imbalance between classes, specifically regarding the presence or absence of CAN, which can negatively affect the performance of the classifiers and result in a model biased towards the majority class. As such, Synthetic Minority Oversampling Technique (SMOTE) [33] was used to generate synthetic examples for the minority class in order to create a balanced dataset. SMOTE operates by synthetizing new samples along the line segments between a minority class sample and any or all of its k-nearest neighbors, depending on the number of samples needed. This technique was performed on the training set only. Additionally, normalization was applied to the quantitative data and one-hot encoding was applied to the categorical data.

C. Models

We created two models, one for detecting the presence of CAN and one for kidney DAN. Three types of algorithms were used for this classification task:

1) Traditional machine learning techniques including support vector machines (SVM), logistic regression (LR) and k-nearest neighbors (KNN).

2) Tree-based ensemble techniques including random forest (RF), extreme gradient boosting (XGB) and CatBoost.

3) Deep learning models including multi-layer perceptron (MLP) and TabNet [34].

Deep learning models such as MLPs have been shown to excel on tabular data when appropriately tuned, however tree-based ensembles are still considered to be the strongest performing models for tabular data. Research has shown that either of the two categories can outperform depending on the dataset, therefore we have chosen to experiment with both [35-36]. We carried out hyperparameter tuning for all models using random search and grid search with the objective of maximizing the cross-validated F1 score. The model was then tested on the testing set, and the F1 score, area under the receiver operating characteristic curve (AUC), accuracy, recall and precision scores were calculated using 5-fold cross-validation. Feature selection was carried out using recursive feature elimination (RFE) which recursively trains the model and removes the least important features. Additionally, we calculated Pearson's correlation coefficients to gauge the correlation of the features with the labels as well as with each other. All analyses were conducted using Python 3.7.

IV. Results

Several machine learning algorithms were used to predict the existence of CAN from the dataset. The performance metrics and receiver operating characteristic (ROC) curves of all CAN models can be seen in Table 2 and Fig. 1 respectively. For CAN, TabNet had the best overall scores, obtaining the highest F1, AUC, accuracy and precision scores. However its recall score was relatively low, indicating a high number of false negatives, which signifies that a relatively large number of CAN patients were not identified by the model. On the other hand, CatBoost achieved the highest recall score and lowest precision score, indicating a high number of false positives; in other words, the majority of the patients with CAN were identified, but a considerable number of patients without CAN were incorrectly labeled as having CAN. The choice of model depends on whether false negatives or false positives are prioritized; a model with a higher number of false positives will identify more CAN patients resulting in a more successful screening, while a model with a higher number of false negatives will result in lower testing costs.

TABLE II. Performance scores of precision, recall, F1, AUC and accuracy for detection of CAN using different machine learning models

Model	*Precision*	*Recall*	*F1*	*AUC*	*Accuracy*
SVM	83.47	86.76	85.01	79.87	81.41
LR	81.38	88.44	84.69	78.18	80.47
KNN	86.01	81.89	83.89	80.46	80.78
RF	83.54	83.82	83.64	78.90	80.78
XGB	81.19	88.45	84.64	78.09	80.39
CatBoost	80.83	**89.72**	85.04	78.13	80.70
MLP	82.99	86.70	84.86	79.19	80.94
TabNet	**86.63**	85.11	**85.82**	**82.17**	**82.82**

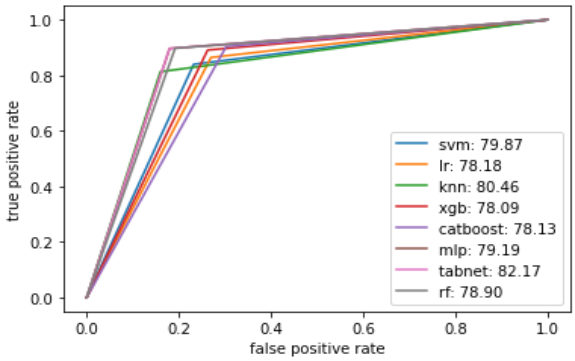

Fig. 1. ROC curves representing the performance of the different machine learning models in the detection of CAN

Similarly, different machine learning models were used to predict kidney DAN from the dataset. The performance metrics and receiver operating characteristic (ROC) curves of all kidney DAN models can be seen in Table 3 and Fig. 2 respectively. As can be noticed, TabNet achieved the highest F1, AUC and accuracy scores, as well as the second highest recall and precision scores. SVM obtained the highest recall but lowest precision score, and MLP obtained the highest precision but second lowest recall score.

TABLE III. Performance scores of precision, recall, F1, AUC and accuracy for detection of kidney DAN using different machine learning models

Model	*Precision*	*Recall*	*F1*	*AUC*	*Accuracy*
SVM	72.36	**73.88**	73.05	74.18	74.19
LR	73.48	72.39	72.91	74.40	74.50
KNN	73.87	66.94	70.21	72.72	73.01
RF	72.73	69.58	71.04	72.85	73.01
XGB	73.19	69.25	71.08	73.06	73.25
CatBoost	73.79	72.23	72.85	74.39	74.50
MLP	**74.61**	68.09	71.17	73.60	73.88
TabNet	73.88	73.05	**73.37**	**74.81**	**74.90**

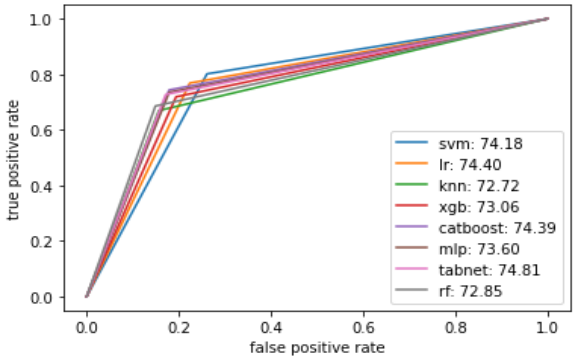

Fig. 2. ROC curves representing the performance of the different machine learning models in the detection of kidney DAN

As mentioned previously, the choice of best model depends on whether the patients and/or physicians prioritize minimizing false negatives or false positives. If minimizing false negatives i.e. identifying as many neuropathy cases as possible is prioritized, the models with the highest recall scores are the best models; CatBoost for CAN detection and SVM for kidney DAN detection. On the other hand, if minimizing false positives i.e. reducing the number of individuals mistakenly classified as neuropathy patients is prioritized, the models with the highest precision scores are the best models; TabNet for CAN detection and MLP for kidney DAN detection. In this paper, we prioritize the highest combined recall and precision scores. This is achieved by TabNet which has the highest F1 score for both CAN and kidney DAN detection. TabNet is a deep learning architecture for tabular data trained using gradient descent-based optimization. It uses sequential attention for instance-wise feature selection at each decision step, therefore we did not apply any feature selection to our data independently before training this model. The hyperparameter values are as follows: clip_value: 1, gamma: 2, lambda_sparse: 0.001, mask_type: entmax, momentum: 0.02, n_a: 5, n_d: 8, n_shared: 3, n_steps: 5, optimizer_params: lr: 0.02. The model was implemented using pytorch-tabnet 3.1.1.

In order to investigate the effect of the limited number of type 1 diabetic patients in our dataset, we ran the experiment using TabNet with only type 2 diabetic patients. The scores achieved through 5-fold cross-validation were the following: For CAN detection, F1 85.88, AUC 81.44, accuracy 82.47, recall 85.65 and precision 86.41. For kidney DAN detection, F1 74.33, AUC 75.20, accuracy 75.24, recall 74.33 and precision 74.44. We observe that the removal of type 1 diabetic patients decreased the average of the performance scores for CAN detection by 0.14% and increased the average of the performance scores for kidney DAN detection by 0.70%.

V. Discussion

Overall, all models performed similarly, with F1 scores in the range [83.64-85.82] for CAN and [70.21-73.37] for kidney DAN. Pearson's correlation coefficients showed the most correlated feature with CAN to be SBP (0.45), followed by age (0.44) and BMI (0.43). In the case of kidney DAN, the most correlated feature was age (0.48) followed by SBP (0.21) and BMI (0.17). The female gender had a positive correlation with both CAN and kidney DAN (0.12 and 0.1 respectively) while the male gender had a negative correlation (-0.12 and -0.1). This suggests that women are more likely to suffer from both CAN and kidney DAN. Lastly, the coefficients were positive for type 2 diabetes (0.16 and 0.12) and negative for type 1 (-0.16 and -0.12), suggesting a prevalence in type 2 diabetics. We also used TabNet's feature_importance_method which showcases the global contribution of each feature to the trained model (Fig. 3 and Fig. 4). The top 3 features in the CAN model were once again age, SBP and BMI. On the other hand, weight and height were more important for the kidney DAN model than SBP. Our findings are line with previous studies which found the female gender and obesity to be a predictive factor of CAN and DAN [37-39]. As such, it can be concluded that it is possible for diabetic patients to lower their risk of being affected by diabetic neuropathy by keeping their BMI within a controlled range. The main advantage of our detection method is that no testing in a clinical setting (such as blood or ECG tests) is needed, providing ease of use for patients.

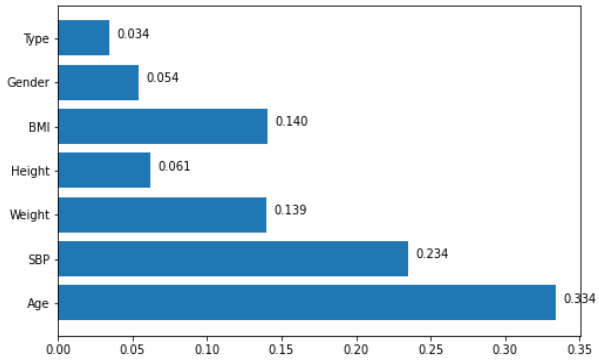

Fig. 3. Importance of each feature in the detection of CAN for the TabNet model reported using the feature_importance method

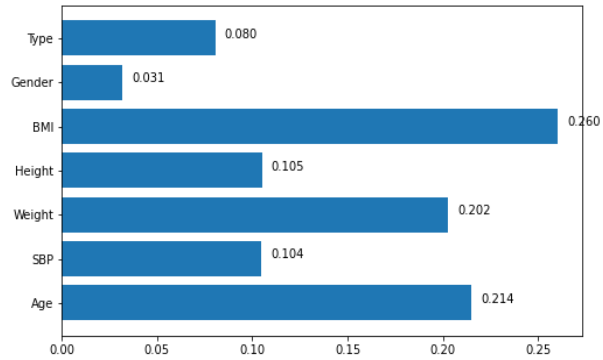

Fig. 4. Importance of each feature in the detection of kidney DAN for the TabNet model reported using the feature_importance method

Due to the extremely limited number of type 1 diabetics in our dataset, our models may not offer a complete representation of type 1 diabetics. As such, further experimentation with a more balanced dataset in terms of diabetes type is needed.

VI. Conclusion

In this paper we trained multiple machine learning, ensemble learning and deep learning models for the detection of CAN and kidney DAN in diabetic patients. The goal was to facilitate initial screening of neuropathy using readily available electronic health records without the need for additional testing. The best performing model was found to be TabNet with F1 scores of 85.82% for CAN and 73.37% for kidney DAN. TabNet's performance shows the potential of deep learning methods for medical screening using tabular data.

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