Artificial Neural Network for Predicting Cardiovascular Autonomic Reflex Tests from Inflammatory Markers

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Abstract

Cardiac Autonomic Neuropathy (CAN) is a serious complication of diabetes that is associated with multi-organ complications, including cardiovascular, renal, and neurological complications. Cardiovascular Autonomic Reflex Tests (CARTs) are widely accepted as a gold standard measure of autonomic function to diagnose CAN. The aim of this paper is to predict the results of CARTs based on inflammatory biomarkers using a comprehensive dataset collected from a rural diabetes screening clinic at Charles Sturt University (CSU) (DiabHealth) with 2621 patient entries. An Artificial Neural Network (ANN) model optimized by the Sparse Categorical Cross Entropy Loss function is proposed to predict the CART results as normal, borderline, or abnormal. The ANN was compared with various baseline models, where it outperformed all with F1-values of 0.968, 0.904, 949, 0.949, and 0.926 for five autonomic function tests, being LS-HR, DB-HR, VA-HR, LS-BP, and HG-BP respectively. MCP-1, IGF-1, and IL-1Beta were found to be the most significant inflammatory markers for predicting CART results. Utilizing inflammatory markers from urine samples provides an accurate alternative opportunity for the identification of CAN and its progression, in addition to identifying possible treatment pathways based on inflammatory markers.

1. Introduction

Cardiac Autonomic Neuropathy (CAN) is one severe complication of diabetes, resulting from impaired autonomic function, which is frequently left undiagnosed due to symptoms appearing late in disease progression. This condition, if not identified early, leads to irreversible multi-organ dysfunction and a high mortality rate of up to 50% within five to ten years from diagnosis [1]. CAN prevalence ranges from 16-20% in diabetic patients, increasing to 44% with age, and 65% in those with long-standing Type 2 Diabetes [2]. Smoking, body mass index (BMI), lipid levels, systolic blood pressure, glycemic control, and disease duration are significant contributors to the development of CAN [3].

1.1. Diagnosis of CAN

Cardiovascular Autonomic Reflex Tests (CARTs) are widely accepted as the gold standard measure of autonomic function, proposed by Ewing and Clark in 1982 and reviewed by Spallone et al.(2011) [2, 4]. CARTs, as defined by [4], consist of five objective tests that assess the parasympathetic and sympathetic branches of the autonomic nervous system. Parasympathetic functions are evaluated using three heart rate response measures, including lying to standing (LS-HR), deep breathing (DB-HR), and Valsalva (VA-HR) heart rate changes, while sympathetic functions are measured using lying to standing (LS-BP) and handgrip (HG-BP) blood pressure changes. Results of each CART are classified as normal, borderline, or abnormal (Table 1). Based on the combined results of the five tests, Ewing classified the status of CAN into five categories, including Normal, Early, Definite, Severe, and Atypical patterns. CARTs provide valuable information on the progression of CAN, which is crucial for accurate diagnosis and treatment planning.

1.2. Machine Learning Applications

Various data mining models have been proposed for diagnosing cardiac autonomic neuropathy based on inflammatory markers Okdahl et al.(2022) and Hu et al. (2018) found that inflammatory biomarkers are higher in patients with diabetic complications, and autonomic imbalance [5, 6]. Malesevic et al.(2021) and Sempere et al.(2021) found that high-sensitivity C-reactive protein (hs-CRP), Interleukin 6 (IL-6), and IL-18 are significant predictors of Coronary Heart Disease (CHD) in patients with type-2 diabetes [7, 8]. Additionally, a model used by Neves et al. (2020) found that patients with definitive CAN have significantly higher values of Leukotriene B4 (IL-B4) and lower values of Interleukin 10 (IL-10) [9]. Bhati et

Table 1. Diagnostic Values of Cardiovascular Autonomic Functions Tests.

	Normal	**Borderline**	**Abnormal**
Heart rate response to standing (LS-HR)	1.04 or more	1.01 - 1.03	1.00 or less
Heart rate response to deep breathing (DB-HR)	15 beats/min or more	11 - 14 beats/min	10 beats/min or less
Valsalva ratio (VA-HR)	1.21 or more	1.2-1.1	1.1 or less
Blood pressure response to standing (LS-BP)	10 mmHg or less	11-29 mmHg	30 mmHg or more
Blood pressure response to handgrip (HG-BP)	16 mmHg or more	11 - 15 mmHg	10 mmHg or less

al. (2019) reported that low heart rate variability (HRV) is associated with higher levels of IL-6 and lower levels of C-reactive protein (CRP) and that higher levels of CRP are associated with impaired cardiac vagal function [10]. To the best of our knowledge, there have been no studies that aim to predict individual CART results from inflammatory markers.

2. Methodology

2.1. Data Collection and Analysis

The data in this study was obtained from a rural diabetes screening clinic at Charles Sturt University (CSU) (DiabHealth), Albury, Australia, between 2002 and 2015. The study was approved by the CSU Human Research Ethics Committee, and written informed consent was obtained from all participants.

The data set consists of 2621 entries of patients (57% males and 43% females) with an average age of 65 years. Each record has data about the patient's demographics and health status (Gender, BMI, age, screen glucose, blood pressure) and binary variables indicating whether the patient has cardiovascular disease (CVD), diabetes (DM) or hypertension (HPT).Inflammatory markers included Interleukin 6, Interleukin 10, C-reactive protein, Interleukin-1 beta, Monocyte Chemoattractant Protein-1, Insulin-like growth factor 1) and cholesterol profile (Triglyceride, total cholesterol, high-density lipoprotein, and low-density lipoprotein). The dataset also contains values of the autonomic reflex tests obtained from the recommended Ewing tests outlined in Table 1.

Before building any machine learning models to predict the classes of the autonomic function tests from the inflammatory markers, the data was preprocessed by removing any outliers. As the data contains all five classes of cardiac autonomic neuropathy (CAN), only the outliers for the normal class of CAN were removed using the interquartile method, as high values of inflammatory markers can be caused by infection, rheumatologic diseases or other conditions [11]. Additionally, the numerical values in the data were normalized using the robust scaler. The Robust Scaler subtracts the median of all the data points and scales them by the IQR as shown in Equation 1.

$$X_{normalized} = \frac{X - median}{IQR} \tag{1}$$

2.2. Classification Models

The proposed model aims to classify the patient Ewing test results into three categories (normal, borderline, and abnormal). Different multi-class classification models were compared, including Random Forest with 100 estimators, Decision Trees, CatBoost Classifier, Logistic Regression (LR), Artificial Neural Network (ANN), Support Vector Machine (SVM) with RBF kernel and regularization parameter of 1, and XGBoost. Statistical accuracy, precision, recall, and F1-score were used to measure the performance of different models. Ten-fold cross-validation was applied to avoid overfitting. Among the classification models proposed in this section, ANN showed the best results.

The parameters of the ANN were tuned to find which design would result in the best performance. The ANN has four hidden layers with a $Sigmoid$ activation function. The model used the Sparse Categorical Cross entropy loss function illustrated in Equation 2. $Adam$ optimizer was used with 300 epochs and a batch size of 20.

$$Loss = -\frac{1}{N}\sum_{i=1}^{N}\sum_{j=1}^{C} y_{i,j}\log(p_{i,j}) \tag{2}$$

where:

N is the number of samples in the batch, and C is the number of classes. $y_{i,j}$ is the indicator function that takes on the value 1 if the ground truth label of sample i is j, and 0 otherwise. $p_{i,j}$ is the predicted probability that sample i belongs to class j.

3. Results

ANN showed high performance when predicting the individual CART features LS-HR, DB-HR, VA-HR, LS-BP, and HG-BP with F1-values of 0.968, 0.904, 0.949, 0.949 and 0.926 and Area Under the ROC Curve (AUC) values of 0.97, 0.93, 0.96, 0.94, 0.96, respectively. The

performance of the ANN model is shown in Table 2. The confusion matrices of ANN predictions of the LS-HR, DB-HR, VA-HR, LS-BP, and HG-BP are shown in Figures (1,2,3,4,5).

Table 2. Performance of ANN in predicting the results of the Autonomic Function Tests.

	Accuracy	Precision	Recall	F1	AUC
LS-HR	0.969	0.968	0.969	0.968	0.97
DB-HR	0.905	0.905	0.905	0.904	0.93
VA-HR	0.947	0.951	0.947	0.949	0.96
HG-BP	0.926	0.926	0.926	0.926	0.94
LS-BP	0.951	0.949	0.951	0.949	0.96

		Predicted		
		Normal	Borderline	Abnormal
Actual	Normal	2171	8	14
	Borderline	20	115	0
	Abnormal	29	5	108

Figure 1. Confusion Matrix when predicting LS-HR.

		Predicted		
		Normal	Borderline	Abnormal
Actual	Normal	1001	32	35
	Borderline	53	471	43
	Abnormal	47	25	763

Figure 2. Confusion Matrix when predicting DB-HR.

		Predicted		
		Normal	Borderline	Abnormal
Actual	Normal	1244	10	60
	Borderline	0	0	0
	Abnormal	61	1	1094

Figure 3. Confusion Matrix when predicting VA-HR.

		Predicted		
		Normal	Borderline	Abnormal
Actual	Normal	1081	35	28
	Borderline	44	736	20
	Abnormal	33	22	471

Figure 4. Confusion Matrix when predicting HG-BP.

		Predicted		
		Normal	Borderline	Abnormal
Actual	Normal	1939	32	5
	Borderline	60	401	2
	Abnormal	15	6	10

Figure 5. Confusion Matrix when predicting LS-BP.

The current study evaluated the significance of various features, including inflammatory markers, in predicting the classes of the autonomic function tests. To this end, a variable importance analysis was performed, and the results are presented in Figure (6). The importance of inflammatory markers in predicting any of the CARTs is shown in figure (7).

4. Discussion

This study investigates the prediction of the results of the autonomic function tests from inflammatory markers. The model categorizes the features of autonomic function tests into three classes (Normal, borderline, and abnormal). There has been a lack of studies predicting the results of autonomic function tests from inflammatory markers; however, previous studies highlighted the significance of the relationship between inflammatory makers and CAN and its complications. Malesevic et al.(2021), in their proposed model with a sensitivity of 90% and a specificity of 86% in predicting CAN, identified IL-6 and hs-CRP as the most significant prediction factors [7]. Other models found heart rate variability significantly relates to IL-6 and CRP [8, 10].

The feature importance analysis of our model, with the accuracy presented in Table 2, revealed that IGF-1, IL-1Beta, and CRP were the most important inflammatory markers in predicting HG-BP and LS-BP, which conforms with the previous results presented in [6] and indicates their role in long-term changes associated with CAN. These markers may serve as potential biomarkers for identifying individuals at risk of autonomic dysfunction disorders or disease progression. These three biomarkers demonstrated higher importance in predicting sympathetic function tests (HG-BP, LS-BP) compared to parasympathetic function tests (heart rate-based). On the other hand, IL-10 and IL-6 were identified as the least important inflammatory markers when predicting any of the CARTs, which contradicts previous research that highlights the importance of IL-6 in predicting heart rate variability and CAN. The inclusion of additional inflammatory markers as proposed by Sudo et al., [12], may further elucidate the role of inflammation in CAN progression.

The confusion matrices of the proposed model highlight the accuracy of the model in predicting every class of the autonomic function test. However, for use in a clinical context, the percentage of false negatives should be decreased. Also, the confusion matrices highlight the class imbalance between the classes in some of the tests.

5. Conclusion

A multi-class ANN model is proposed to categorize the features of autonomic function tests into three classes (Normal, borderline, and abnormal). The presented model shows high accuracy in predicting results of individual CART results from inflammatory markers obtained from urine samples.

The current study highlights the role of inflammation in cardiac autonomic disease progression. The proposed ANN model has the potential to assist medical practitioners

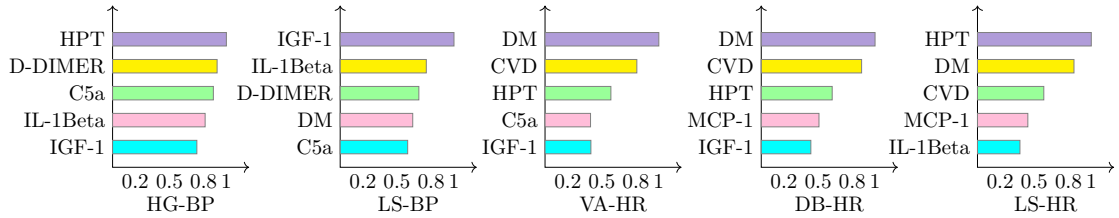

Figure 6. Variable importance of ANN model when predicting the autonomic function tests

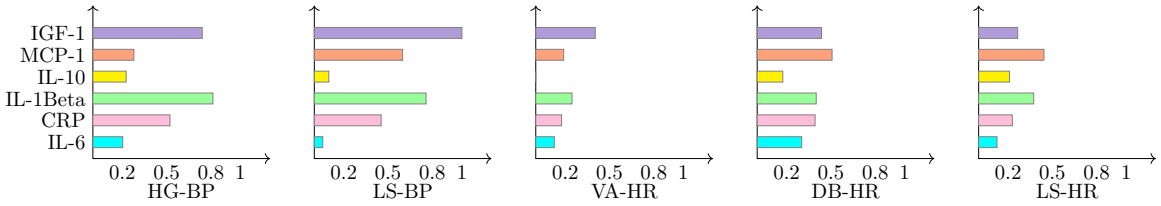

Figure 7. Variable importance of inflammatory markers when predicting the results of autonomic function tests

in the accurate diagnosis of CAN and prompt treatment planning, as it provides an accurate assessment of CAN based on the association of inflammation with disease progression. Future research could be extended to include more inflammatory markers to predict cardiac autonomic neuropathy, especially at the early stage of the disease, and provide information for precision medicine and reduce the risk of CAN progression.

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