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Diabetic Sensorimotor Polyneuropathy Severity Classification Using Adaptive Neuro Fuzzy Inference System

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ABSTRACT Diabetic sensorimotor polyneuropathy (DSPN) is an early indicator for non-healing diabetic wounds and diabetic foot ulcers, which account for one of the most common complications of diabetes, leading to increased healthcare cost, decreased quality of life, infections, amputations, and death. Early detection and intelligent classification tools for DSPN can allow correct diagnosis and treatment of painful diabetic neuropathy as well as a timely intervention to prevent foot ulceration, amputation, and other diabetic complications. Hence, to successfully mitigate the prevalence of DSPN, this study aims to depict an intelligent DSPN severity classifier using Adaptive Neuro Fuzzy Inference System (ANFIS). Michigan Neuropathy Screening Instrumentation (MNSI) was considered as the input for identification and stratification of DSPN. Patients have been classified into four classes: Absent, Mild, Moderate, and Severe. The model accuracy was validated with the results from different machine learning algorithms. The Accuracy, sensitivity, and specificity of the ANFIS model are 91.17±1.18%, 92±2.26%, 96.72±0.93%, respectively. The proposed classifier was used to classify the Epidemiology of Diabetes Interventions and Complications (EDIC) clinical trial patients and observed that in the first, eighth, and nineteenth EDIC years 18.31%, 39.45%, and 59.14% patients had different levels of DSPN. This study also investigates the changes in muscle activity during gait from three different lower limb muscles (vastus lateralis (VL), tibialis anterior (TA), and gastrocnemius medialis (GM)) electromyography (EMG) of DSPN patients with different severity levels classified by the proposed classifier and observed that VL and GM muscles show an increase in delay for activation peak and decrease in peak magnitude during gait with the progression of DSPN severity. Based on this observation, the ANFIS model was trained using the extracted EMG features for DSPN severity stratification and showed promising results. Our proposed ANFIS based severity classifier using both MNSI variables and EMG features will help health professionals to diagnose and stratify DSPN severity based on both signs and symptoms and electrophysiological changes due to DSPN.

INDEX TERMS ANFIS, DSPN, diabetic neuropathy, fuzzy system, classifier.

I. INTRODUCTION

According to the 9th International Diabetic Federation Diabetes Atlas, 463 million people worldwide were affected by diabetes in 2019. Diabetic sensorimotor polyneuropathy (DSPN) is the most common form of diabetic neuropathy, involving signs and symptoms of impairment of the peripheral nerve functions which affects over 50% of diabetic patients [1]–[4]. DSPN has many long-term complications; especially in lower limbs and is crucial for cases like foot ulceration and amputation [5]. According to the American Diabetic Association (ADA), position statement [5], almost

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50% of DSPN patients show no symptoms of such diseases. Thus, early detection is essential in order to prevent long-term complications and foot injuries; and to improve the quality of the healthcare facilities for diabetic patients.

For the assessment of DSPN, a large number of specialized screening and diagnostic tests are available, which can be easily deployed [5], [6]. In most cases, the neurological history, physical examination, and electrophysiological tests are combined for accurate conventional assessment of DSPN [5]–[7]. Some of the popular clinical diagnostic methods for DSPN are- Vibration sensation test using a 128 Hz tuning fork [5], Monofilament test [5], Quantitative sensory testing (QST) [8], Skin biopsy [9], Nerve Conduction Studies (NCS) [10], Corneal confocal microscopy (CCM) [11], Electromyography (EMG) [12], etc. Although many screening and clinical tests are available for DSPN, most of them are expensive, painful, and require specialized personnel and equipment. Some of them are invasive methods, and some produce inconsistent results even after using similar methods. Present DSPN measure lacks uniformity and agreement in clinical research, to correctly identify the patients' severity [5].

Over the years, researchers tried to introduce intelligent systems in medical fields for the enhancement of the health care systems [13]–[16]. Intelligent diagnosis system for DSPN becoming a focus of interest for researchers due to its effect on the long term and severe complications. CCM is a new rapid, regenerable, and non-invasive method for accurately detecting DSPN from the in-vivo corneal images. Researches are being emphasized to automated CCM systems for accurate and reproducible identification of DSPN using artificial intelligence [17]–[19]. However, this method is expensive, requires specialized equipment and personals, and is not available in regular clinics. In the initial stage, DSPN is diagnosed using different screening methods like neuropathy disability score (NDS), Michigan neuropathy screening instrumentation (MNSI), etc., based on the symptom and signs of the patients [6]. These tests are used for assessing pain, touch, vibration, and temperature sensation loss due to DSPN [6]. For reliable, accurate, reproducible diagnosis using these scoring methods for DSPN, intelligent systems can be a potential solution. In the existing literature, the Fuzzy Inference System (FIS) is the most commonly used system for screening and classifying the severity of DSPN [20]–[22]. As the fuzzy system works based on if-then rules, there is always a chance to have a human error in defining the rules for identifying DSPN, thus the accuracy of the classification is questionable. One study has been conducted to identify the different levels of DSPN severity by Kazemi *et al.* [23] using a multicategory support vector machine with NDS as the input of their model. However, the model performance accuracy was only 76%.

In such a scenario, the adaptive neuro-fuzzy inference system (ANFIS); which has learning capability incorporating the benefits of fuzzy inference system to approximate nonlinear functions, can be an advantageous method for dealing with the nonlinear characteristics of the DSPN. ANFIS has been chosen as a universal estimator due to its dual applicability to predict the future condition by utilizing a present dataset and approximation of non-linear characteristics by setting the rules of the Fuzzy system [24]. Due to this advantage of ANFIS, it is becoming very popular in decision-making and prediction systems for biomedical applications [24]–[27]. This study states an intelligent severity classifier for DSPN using ANFIS. A combination of clinical history and examination are highly useful for the clinical diagnosis of DSPN. Michigan Neuropathy Screening Instrumentation (MNSI) is a validated screening method [5]. According to ADA position statement [5] for the screening of DSPN, history questionnaire, pinprick sensation for small fiber function and vibration sensation for large fiber function with the addition of the 10-g monofilament tests to access the risk of amputation and ulceration should be included. MNSI is a very simple, inexpensive, and most commonly used screening method for DSPN, which does not require specialized personnel. Moreover, it can be carried out in any regular healthcare system. MNSI is the most widely used questionnaire for screening of DSPN [28], [20]. MNSI was used as inputs for training the DSPN severity classifier system using the ANFIS algorithm. Feldman *et al.* [28] indicated that MNSI can play an important role in early diagnosis and staging of diabetic neuropathy and is highly correlated with NDS.

Diabetic neuropathy denotes the progressive deprivation of sensitivity in the somatosensory system; especially in the lower limbs, which leads to dysfunctional gait dynamics; predominantly associated with abridged joint movement, reduction in active muscle power, and changes in gait mechanics [28]. DSPN patients have shown greater stance phase time, reduced amplitude, and prolonged activation peak in the lower limb muscle activity [29]–[31]. In particular, the following three lower limb muscles: vastus lateralis, tibialis anterior, and gastrocnemius medialis are commonly studied to observe the changes in muscle dynamics with the progression of neuropathy [22], [29]–[33]. Therefore, to diagnose DSPN and to observe the biomechanical changes in different muscle activity due to DSPN, electromyography (EMG) [22], [29]–[33] has been widely used in different clinical research and trials; to observe the muscle activities and identify DSPN severity. In this research, we have investigated the changes in muscle activation delay during the gait cycle of three lower limb muscles from the patients with different degrees of DSPN severity using ANFIS. EMG parameters during the gait cycle have been considered as input to classify the DSPN patients' severity level using the proposed ANFIS model.

The novelty of this research work is to develop an ANFIS based intelligent classifier that will be able to classify DSPN severity levels using Michigan neuropathy screening instrumentation scores as well as lower limb muscle EMG parameters during gait. The benefit of this classifier is, it will be able to classify patient's severity levels using two different screening methods and provide reliable, accurate, and early

identification to enhance the health care facility for the DSPN patients. Another major contribution of this study is to investigate the progression of DSPN severity over time among the patients from the Epidemiology of Diabetes Interventions and Complications (EDIC) clinical trials. As per our knowledge, this is the first study that has observed the DSPN severity of EDIC patients using a machine learning algorithm. We have investigated the changes in different lower limb muscle activities with the progression of DSPN severity using ANFIS and used those properties to classify the DSPN patients using the proposed model. This study exhibits the potential of the proposed intelligent DSPN severity classifier based on the ANFIS algorithm, using both the MNSI scoring system and EMG parameters in DSPN severity classification. In the current state-of-the-art, the clinical practice is to acquire data and post-process by the experts to interpret the results. Both the DSPN severity classifier system can contribute to enhancing the healthcare facilities for DSPN patients by providing early, reliable, accurate identification and stratification of the DSPN. This study can help the health professionals with making an accurate decision as for diagnosis of DSPN, initial screening can be done using MNSI and electrophysiological changes can be observed from EMG features and will be able to classify the patient's severity based on these results from our proposed severity classifier. So, this research aims to develop an intelligent classifier using ANFIS for screening and stratification of DSPN severity, which will be able to work as a stand-alone system and will assist the healthcare professionals to improve the healthcare facilities for DSPN patients.

The rest of the study is divided into following sections: Section 2 discuss the Adaptive Neuro Fuzzy Inference system architecture, Section 3 showcase the methodology of this study which describes following processes: data collection, augmentation, imputation, input feature ranking, preparation of MNSI dataset, ANFIS model development, and three lower limb muscles EMG signals processing for feature extraction and severity classification using EMG features. In the 4^{th} section, the findings of this study have been discussed. This section has been divided into two sub-sections, study one discusses the MNSI dataset preparation from the EIDC trials, proposed ANFIS models performance analysis, and validating the ANFIS model with different conventional machine learning algorithms and FIS models. Study two discuss the progression of DSPN severity with time in the EDIC patients, observed from the MNSI data and the change of lower limb muscle activities with the progression of DSPN severity from muscle EMG's and use those features to classify DSPN severity using the proposed ANFIS classifier. In the fifth section, the overall results were discussed, and the sixth section includes a conclusion with future work.

II. ADAPTIVE NEURO FUZZY INFERENCE SYSTEM (ANFIS)

ANFIS is an artificial neural network (ANN), was first introduced by Jyh-Shing Roger Jang [24] in 1993. It is a fuzzy inference system implemented in the framework of adaptive networks, which can serve as a basis for constructing a set of fuzzy IF-THEN rules with appropriate membership functions to generate the stipulated input/output (I/O) pairs. ANFIS is a fuzzy mapping algorithm based on the Tagaki-Sugeno-Kang fuzzy inference system (1985) to develop a systematic approach to generating fuzzy rules from a given I/O dataset [25], [26]. Based on both human knowledge (in the form of fuzzy IF-THEN rules and hybrid learning algorithm); ANFIS can construct mapping using given input/output I/O data values [27]. The ANFIS model generates outputs similar to the system outputs with a minimum root mean square error (RMSE) and maps the relationship between an input and output dataset to identify the optimal distribution of membership functions [27]. The ANFIS model was implemented in MATLAB, which includes Fuzzification by determining the type and the number of membership functions.

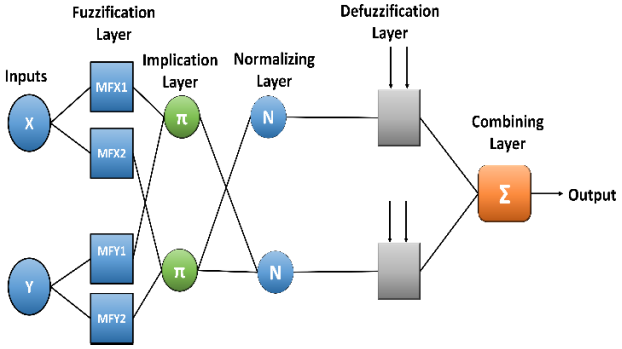


FIGURE 1. Two input ANFIS Architecture.

ANFIS architecture consists of five layers with directional links and nodes. It uses Hybrid Learning Algorithm, which consists of two passes: a) forward pass where functional signals go forward till layer 4 and the consequent parameters are identified by the least squares estimate, and b) backward pass where the error rates propagate backward, and the premise parameters are updated by the gradient descent. Figure 1 is showing two input ANFIS architecture.

The function of each layer of the ANFIS architecture is described below [25]:

Layer 1: The first layer takes the input value and determines the membership function and belonging to them. Every node i in this layer is a square node with a node function

$$\boldsymbol{O}_i^{\mathbf{1}} = \boldsymbol{\mu}_{A_i}(\boldsymbol{x}), \quad i = 1, 2 \ldots \tag{1}$$

where, x is the input to node i, and $\mathbf{A}_i$, is the linguistic label (small, large, etc.) associated with this node function. Parameters in this layer are referred to as premise parameters. Node output is the membership value of the input.

Layer 2: The second layer is responsible for generating the firing strengths for the rules. Every node in this layer is a circle node labeled π, which multiplies the incoming signals and sends the product out. For instance

$$O_i^2 = w_i = \mu_{A_i}(x) * \mu_{B_i}(x), \quad i = 1, 2 \ldots \tag{2}$$

Node outputs are the firing strength of the rules.

Layer 3: The role of the third layer is to normalize the computed firing strengths by diving each value with the total firing strength. Every node in this layer is a circle node labeled N. The i^{th} node calculates the ratio of the i^{th} rule's firing strength to the sum of all rules' firing strengths:

$$O_i^3 = \overline{w}_i = \frac{w_i}{w_1 + w_2}, \quad i = 1, 2 \ldots \tag{3}$$

Node outputs are the normalized firing strengths of the rules.

Layer 4: The fourth layer takes the normalized values as inputs and the consequence parameter set $\{p_i, q_i, r_i\}$. Every node i in this layer is a square node with a node function,

$$O_i^4 = \overline{w}_i f_i = \overline{\omega}_i (p_i x_1 + q_i x_2 + r_i) \tag{4}$$

where $(\overline{w_i})$ is the output of layer 3. Node outputs are the evaluation of right-hand side polynomials of equation 4.

Layer 5: The values returned by the 4th layer are the defuzzified ones and those values are passed to the last layer to return the final output as the summation of all incoming signals, i.e.,

$$O_i^5 = \sum_i \overline{w}_i f_i = \frac{\sum_i w_i f_i}{\sum_i w_i} \tag{5}$$

Node outputs are the weighted evaluation of right-hand side polynomials.

III. METHODS

This research is divided into two studies. The first study discusses the process of dataset preparation, design of the ANFIS based DSPN severity classifier, and validation of the classifier. The second part of the study discusses the classification of EDIC patients using the ANFIS based classifier to observe the progression of DSPN severity over time, the change in lower limb muscle activities during gait among DSPN patients with different levels of severity, EMG feature extraction process, and used the extracted features to train the proposed DSPN severity classifier. In the sections below methodology for both studies has been discussed in detail.

A. STUDY-1

1) DATA COLLECTION

For the design, train, and validation of the ANFIS based DSPN severity classifier, the MNSI dataset from Epidemiology of Diabetes Interventions and Complications (EDIC) [34], [35] clinical trials have been used in this study. EDIC clinical trials were designed by the National Institute of Diabetes, Digestive and Kidney Diseases to annually assess DSPN among type1 diabetic patients using MNSI. This clinical study was started in 1994 with 1,375 patients from 29 different medical centers, and the study is still an ongoing process. For training and cross-validation purposes 8 EDIC years MNSI data with 10543 samples were collected. To observe the progression of DSPN severity over the years among the EDIC patients, first, eighth, and nineteenth EDIC years MNSI data were used.

2) DATA IMPUTATION

Eight years of MNSI data with 10543 samples could have been retrieved from the EDIC trials. However, the dataset was imbalanced and have missing data. Among the 10543 samples, there were 363 blank entries with no MNSI data. After removing the blank entries, 10180 samples were recovered. Among the 10180 data, there were missing values in the dataset. The K-nearest neighbor [36] data imputation technique had been used to fill the missing data.

3) DATA AUGMENTATION

The imputed EDIC dataset with 10180 samples was imbalanced and had 8819, 1075, 245, and 40 samples in absent, mild, moderate, and severe classes, respectively. In order to deal with imbalanced data in different DSPN severe groups, data augmentation techniques had been used to balance the dataset so that the dataset has an equal number of samples in each class. Two techniques Random Over Resampling and Synthetic Minority Oversampling Technique (SMOTE) had been checked to balance the dataset. No difference was found in the augmented datasets using both techniques. As the MNSI dataset consists of values in between 0 to 2, both the technique are exhibiting the similar performance for resampling the dataset. It was made sure that there was no overfitting in the augmented data. Python 3.7 in-house written code was used for data imputation and data resampling.

4) DSPN SEVERITY SCORING FOR MNSI DATASET

MNSI scoring system consists of two parts: history questionnaire and clinical tests. In history questionnaire, there are 15 yes/no questions related to the patient's symptoms where each question is scored as 1 point depending on the patients' response. In EDIC trials, all the results from the questionnaire are added together and consider as one single estimator for identifying DSPN symptoms. Hence, we have considered the questionnaire as one parameter. In the clinical examination part of MNSI, there are five tests: the appearance of the foot, ulceration, ankle reflection, vibration perception, and tactile sensitivity are included in the clinical tests. Each clinical test is scored as 1 for each leg and a total of 2 for both legs. In this study, history questionnaire had been chosen as one parameter and the rest 5 clinical tests as 5 individual parameters in identifying DSPN severity. Total 6 MNSI variables data were used from EDIC trials for this study. After processing the MNSI dataset from EDIC trials with imputation and augmentation methods, patients MNSI data were assigned with "Neuropathy degree score" proposed by Watari *et al.* [22] after reviewing other existing literature [22], [24], [27], and the final score was ranged from 0 to 10. The neuropathy degree score was used to classify the patients with different degree of severity as follows:

(i) $x \leq 2.5$: Absent neuropathy
(ii) $2.5 < x < 5.0$: Mild neuropathy
(iii) $5.0 \leq x \leq 8.0$: Moderate neuropathy
(iv) $x \geq 8.0$: Severe neuropathy
where x is the neuropathy score.

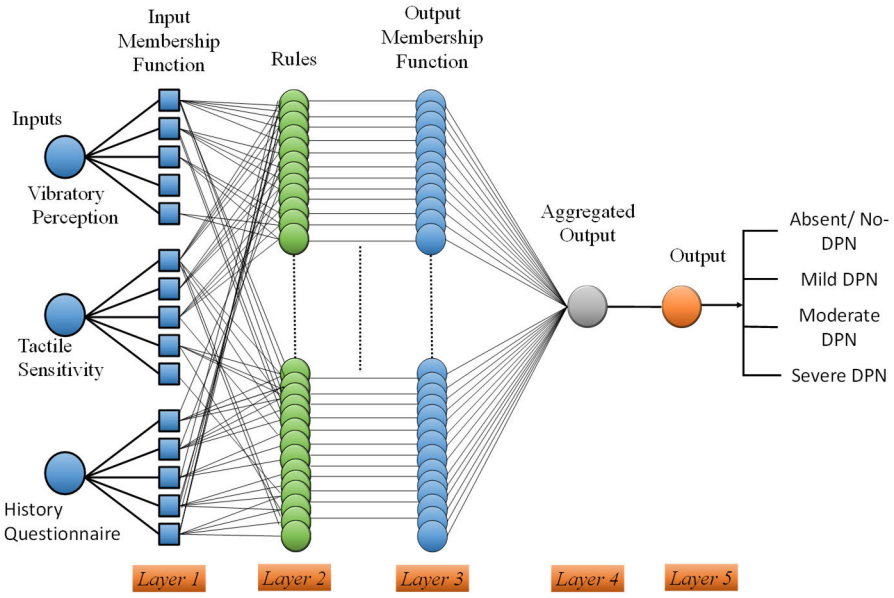


FIGURE 2. ANFIS Architecture for DSPN Severity Classification using MNSI.

A second MNSI dataset was collected which was collected from Watari *et al.* [22] for the validation and EMG feature analysis. In their study, Patients' DSPN severity level was classified from the MNSI dataset by a Fuzzy Inference System (FIS). The purpose of this dataset was to classify the DSPN severity of the patients using the proposed ANFIS severity classifier and validate the results with the original severity classes, classified using FIS by Watari *et al.* [22].

5) FEATURE RANKING

To understand the effects of all the 6 MNSI parameters in identifying DSPN, MNSI features were ranked using the eXtreme Gradient Boosting (XGBoost) algorithm. XGBoost is a decision-tree-based ensemble Machine Learning algorithm that uses a gradient boosting framework. XGBoost can estimate feature importance from a trained predictive model by providing a score to each feature that was used in the construction of the boosted decision trees within the model. Imputed and augmented EDIC dataset was used for feature ranking. The hyperparameters of the XGBoost model were tuned by fixing the maximum depth of the tree to 4, subsample ratio of the training instance and subsampling of columns were fixed at 0.9, to avoid overfitting and learning rete was used to 0.2 for the conservative boosting process. The designed XGBoost model was trained to evaluate the feature importance of the MNSI variables. Based on the results from the feature ranking top three features with a comparatively high importance index in identifying DSPN had been selected as inputs for the ANFIS model. Python 3.7 in-house written code was used for feature ranking.

6) ANFIS MODEL DEVELOPMENT USING MNSI DATA

An ANFIS model was designed using MATLAB ver. R2020a, (The MathWorks, Inc., Natick, Massachusetts, United States) with three inputs and an output. For designing the ANFIS model, 5 input membership functions were considered for the three input parameters from the feature ranking. All the membership functions were Gaussian type. Initial FIS was generated using the Matlab function *Genfis*. The grid partition method was used to generate the initial FIS. We have considered the hybrid learning algorithm for minimizing the error and to adjust the shape of membership functions of the ANFIS model. This allows the fuzzy inference systems to learn from the data that is being modeled. Stratified 10-fold cross-validation was used to train and test the designed ANFIS model. 10- fold stratified Cross-validation was achieved by *Cvpartition* Matlab function. Matlab function *Evalfis* was used to evaluate the ANFIS model using the test data. In the ANFIS architecture, there were 286 nodes with 500 linear and 30 nonlinear parameters with 125 IF-THEN rules. Figure 2 is showing the proposed ANFIS architecture for DSPN severity Classification. Confusion matrices were generated to evaluate the performance of the designed ANFIS model in classifying DSPN.

B. STUDY-2

1) DATASET PREPARATION FOR LONGITUDINAL STUDIES ON EDIC PATIENTS

To observe the progression of the DSPN severity over time among the EDIC patients, this study has observing first, eighth, and nineteenth EDIC years MNSI data. All three years MNSI data was collected from the EDIC trials and made three different datasets for observation. Missing data were treated

with the K-NN data imputation method. On the first, eighth, and nineteenth EDIC years 1222, 1374, 1280 patients MNSI data were collected, respectively. These datasets were used to classify the EDIC patients DSPN severity levels using the designed ANFIS classifier.

2) EMG SIGNAL PROCESSING AND FEATURE EXTRACTION

Diabetic neuropathy leads to a progressive loss of somatosensory sensitivity, especially in the lower limbs, which may cause functional gait variations; predominantly related to reduced range of movement of joints, reduced active muscle power, and changes in gait mechanics [20]. EMG has been widely used by researchers to observe muscle activities and diagnose DSPN in patients [22], [28], [30], [33]. In this research, we wanted to investigate the changes in muscle activity for three lower limb muscles (vastus lateralis (VL); tibialis anterior (TA); and gastrocnemius medialis (GM)) during the gait cycle in different DSPN severity groups. Based on these investigations, we want to extract EMG features and apply them to classify DSPN patient's severity levels using the proposed ANFIS based classifier.

With that purpose, a second MNSI dataset from Watari *et al.* [22] was also collected to analyze the EMG signals of the patients based on DSPN severity. This dataset was composed of 132 real case adult volunteers of both genders and divided into a control group of non-diabetic subjects (n = 30) and diabetic subjects (n = 102). Corresponding MNSI dataset, three lower limb muscles EMGs, and vertical ground reaction force (vGRF) signals were collected for each DSPN patients for the EMG signal analysis. The patients were classified into four DSPN severity classes based on their corresponding MNSI data using the proposed ANFIS based classifier. The patients' severity levels classified from the ANFIS model were verified from the results reported by Watari *et al.* [22]. For the acquisition of the muscle EMG's, Watari *et al.* [22]. had used an EMG system with 1000 factor signal amplification and 10 mm circular Ag/AgCl electrodes. Three different lower limb muscles were considered for EMG signal acquisition during gait: VL, TA, and GM. EMG raw data were collected from [22] for signal analysis and feature extraction. A total of 102 DSPN patients' raw EMG signals from three different lower limb muscles were collected and used for muscle characteristics observation. EMG signals were sampled at 2000Hz sampling frequency. Baseline wondering was removed from the raw EMG signal. The signal was in digital form and we processed the EMGs by in-house built Matlab code. EMG signals were filtered through a zero-lag 4th order Butterworth filter with a 50-500 Hz passband followed by a low pass filter with a cutoff frequency of 5 Hz for noise elimination and full-wave rectified. From the vertical GRF, the corresponding gait cycle was detected for all the EMG signals. From the processed signals peak amplitude and % stance phase time to get the activation peak was observed for different DSPN severity group patients.

A new dataset was prepared from the observed 102 patients' EMG parameters consisting of peak amplitude and time to get the activation peak for three (TA, VL, GM) lower limb muscles. The dataset was resampled to have 930 samples and was made sure that there is no repetition in the data. Using the developed ANFIS model and the EMG dataset, two different models were trained, and performance was observed for DSPN severity classification. In model 1, we have considered only the peak amplitude from three lower limb muscles for different severity groups as an input of the ANFIS model, whereas in model 2, we have considered both peak amplitude and time to get the peak activation of three muscles as inputs.

C. STATISTICAL ANALYSIS

Statistical analyses were performed using SPSS software (version 21.0; SPSS Inc., Chicago, IL, USA). Data were compared among neuropathic and non-neuropathic groups. Descriptive statistics were used to find out the mean and standard errors and data were expressed as mean $\pm$ standard deviation (SD). Analysis of variance (ANOVA) was used to find out the statistical significance of the variables. An independent t-test was used to find out the 95% confidence intervals (95% CI). All statistical tests were one-sided, and the statistical significance was considered at $p<0.05$.

IV. RESULTS

The results section has been divided into two subsections. In study-1, ANFIS model development and performance analysis were discussed for DSPN severity classification. In study-2, using the validated ANFIS based DSPN severity classifier, two observational studies have been conducted. The studies and their outcomes are discussed in detail in the following sections.

A. STUDY-1

1) MNSI DATASET

Demographic variables such as age, sex, body-mass-index (BMI), DM duration, HBA1C, etc. have been observed to understand the EDIC patient's characteristics. Table 1 is showing the baseline characteristics of the patients during the first year of the EDIC trials. It is visible that HDL cholesterol and BMI show no statistical significance ($p > 0.05$) among neuropathic and non-neuropathic groups. In our dataset, we have considered 1200 samples per DSPN class, a total of 4800 samples. An imputed and augmented dataset was used in feature ranking to find the importance of the MNSI variables. Figure 3 is showing all the six MNSI variables' impact in identifying DSPN severity by the XGBoost feature ranking method. It was found that the Questionnaire, vibratory perception, and tactile sensitivity among all the other MNSI variables have more impact in identifying the severity of DSPN. Therefore, in this study, we have selected these three parameters as inputs. So the final dataset was consists of three inputs: vibration perception (range 0 to 2), tactile sensitivity (range 0 to 2), questionnaire (range 1 to 22) range, and one output: DSPN severity

TABLE 1. Baseline characteristics of the EDIC patients.

(N=1370)		Mean	Std. Error	95% Confidence Interval of the Difference		F	p
				Lower	Upper		
Age (years)		35.93±6.945	0.188	35.56	36.3	41.344	0.000
Sex	F	653					
	M	718					
Diabetic Duration (years)		14.56±4.906	0.133	14.3	14.82	24.850	0.000
BMI (kg/m^2)		26.28±4.035	0.109	26.06	26.49	1.234	0.267
HBA1C (%)		8.25±1.374	0.037	8.18	8.33	20.108	0.000
HDL Cholesterol (mg/dl)		54.11±13.844	0.38	53.36	54.85	0.008	0.928
LDL Cholesterol (mg/dl)		114.39±30.618	0.844	112.73	116.04	5.958	0.015
Hypertension (%)		0.23±0.418	0.011	0.2	0.25	34.409	0.000

TABLE 2. Performance evaluation of the proposed ANFIS model.

	Sensitivity (%)	Specificity (%)	Accuracy (%)	F1 Score (%)	Classification Rate (%)	Fold Error (%)
ANFIS	92. 06±2.26	96.72±0.93	91.17±1.18	91.15±1.20	91.26±1.11	0.09±0.01
Ensemble	90.07±4.02	96.22±0.93	89.98±1.83	90.31±0.02	89.98±1.83	0.10±0.02
SVM	89.07±4.74	96.39±0.85	89.69±1.75	89.79±0.02	89.69±1.75	0.10±0.02
KNN	88.09±0.02	92.67±1.36	87.81±2.14	87.95±0.02	87.81±2.14	0.12±0.02
Naïve Bayes	87.93±0.01	94.47±0.73	87.81±1.17	87.87±0.01	87.81±1.17	0.12±0.01
DAC	87.24±0.02	95.86±0.83	87.21±1.53	87.22±0.02	87.21±1.53	0.13±0.02

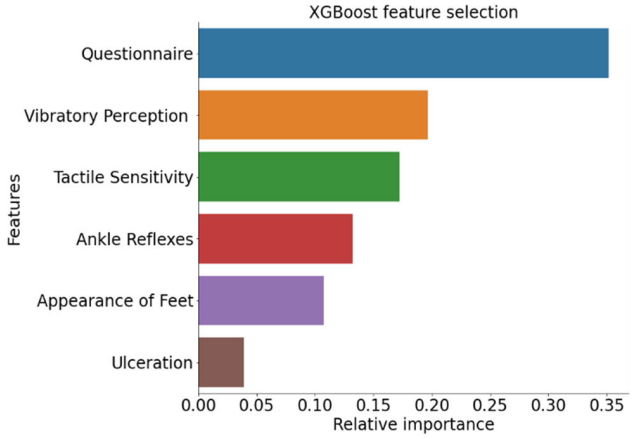


FIGURE 3. Feature ranking of the MNSI parameters.

level (grade 0: absent or non-neuropathic, grade 1: mild neuropathic, grade 2: moderate neuropathic, grade 3: severe neuropathic).

2) ANFIS MODEL

The preprocessed MNSI dataset was used for 10-fold stratified cross-validation to evaluate the ANFIS model's performance. The dataset was divided into 4320 samples for the training set and 480 samples for the testing set. The training set had 1080 samples and the testing test had 120 samples in each DSPN severity class. The ANFIS model was trained for 10 epochs; the training root mean square (RMS) error was 0.235. Figure 4 shows the confusion matrix for DSPN severity classification using the ANFIS model. Seven absent, sixteen mild, and eight moderate patients were miss-classified by the ANFIS model however, no severe patient was miss-classified.

3) PERFORMANCE EVALUATION

The performances of the DSPN severity classification system were compared with different conventional machine learning (ML) algorithms such as Ensemble classifier, support vector machine (SVM), K-nearest neighbor (KNN), naïve Bayes, and discriminant analysis classifier (DAC) for the validation of the proposed model. Customized in-house MATLAB codes were written for all ML classifiers. The dataset with 10-fold stratified cross-validation was used to train and validate the ML models. Table 2 shows the comparative performance analysis of ANFIS with different ML algorithms for DSPN severity classification. Accuracy, sensitivity, and specificity of the ANFIS model are 91.17±1.18%, 92.17±2.26%, 96.72±0.93% respectively. It is evident from Table 2 is that ANFIS is outperforming the ML models with a significant performance difference.

B. STUDY-2

1) LONGITUDINAL STUDY ON EDIC TRIALS FOR DSPN SEVERITY CLASSIFICATION

The validated ANFIS model was used to classify the EDIC patients' severity levels to observe the progression of DSPN with time. First, eighth, and nineteenth years' MNSI data

	Absent	Mild	Moderate	Severe
Absent	113	7	0	0
Mild	5	104	11	0
Moderate	0	6	112	2
Severe	0	0	0	120

FIGURE 4. Confusion matrix for the ANFIS model using 10-fold cross-validation.

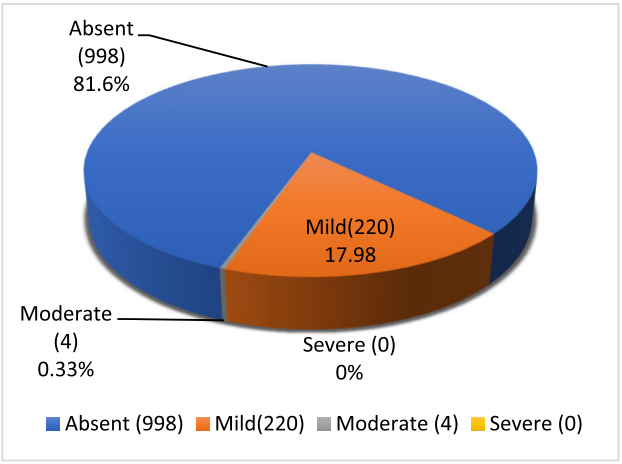
from EDIC trials were used to observe the change in severity level of the DSPN patients. Figure 5 shows the DSPN severity condition of the patients for the first, eighth, and nineteenth EDIC years. It can be observed that there are no severe neuropathic patients in the first year and the number of non-neuropathic patients was 81% of the total patients. In year 8, the number of neuropathic patients increased, and 6 patients got severe neuropathy. By the end of 8 years, 20% of the total patients became neuropathic. In the 19th year, almost 59% of the total patients became neuropathic. Initially, there were no severe DSPN patients, which increased to 39 in the 19th year. From this observation, we can conclude that, with time, all diabetic patients have higher risks to have DSPN and therefore, early detection is very crucial for diabetic patients to provide medication to prevent the consequences of severe DSPN.

TABLE 3. Validation of the DSPN severity classifier with existing literature.

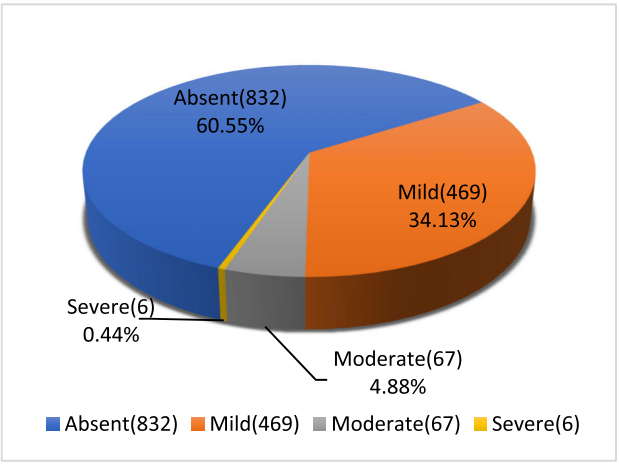
Neuropathy Severity	Classification By ANFIS Model	% of total patients	Classification by FIS model [22]
Absent	43	42.16	43
Mild	24	23.53	30
Moderate	14	13.73	16
Severe	21	20.59	28
Total	102	-	117

2) EMG BASED DSPN SEVERITY STRATIFICATION USING ANFIS MODEL

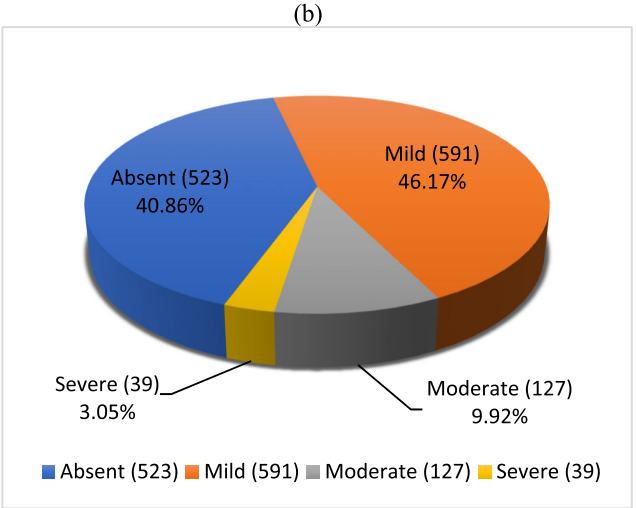
With the trained and cross-validated ANFIS model, we have classified the MNSI data collected from Watari *et al.* [22]. The objective of this classification was to stratify the DSPN severity for the patients reported in [22]. Table 3 shows the number of patients in different DSPN severity classes classified using the ANFIS model and the result reported in [22]. There were some missing data in the dataset which caused some mismatch in the number of patients. In our investigation, we have used 102 patients while Watari *et al.* [22] reported results on 117 patients. Classified patient's EMG signals were analyzed to observe the change in muscle activity due to DSPN.



(a)



(b)



(c)

FIGURE 5. DSPN severity groups of EDIC patients (a) year 1, (b) year 8, and (c) year 19.

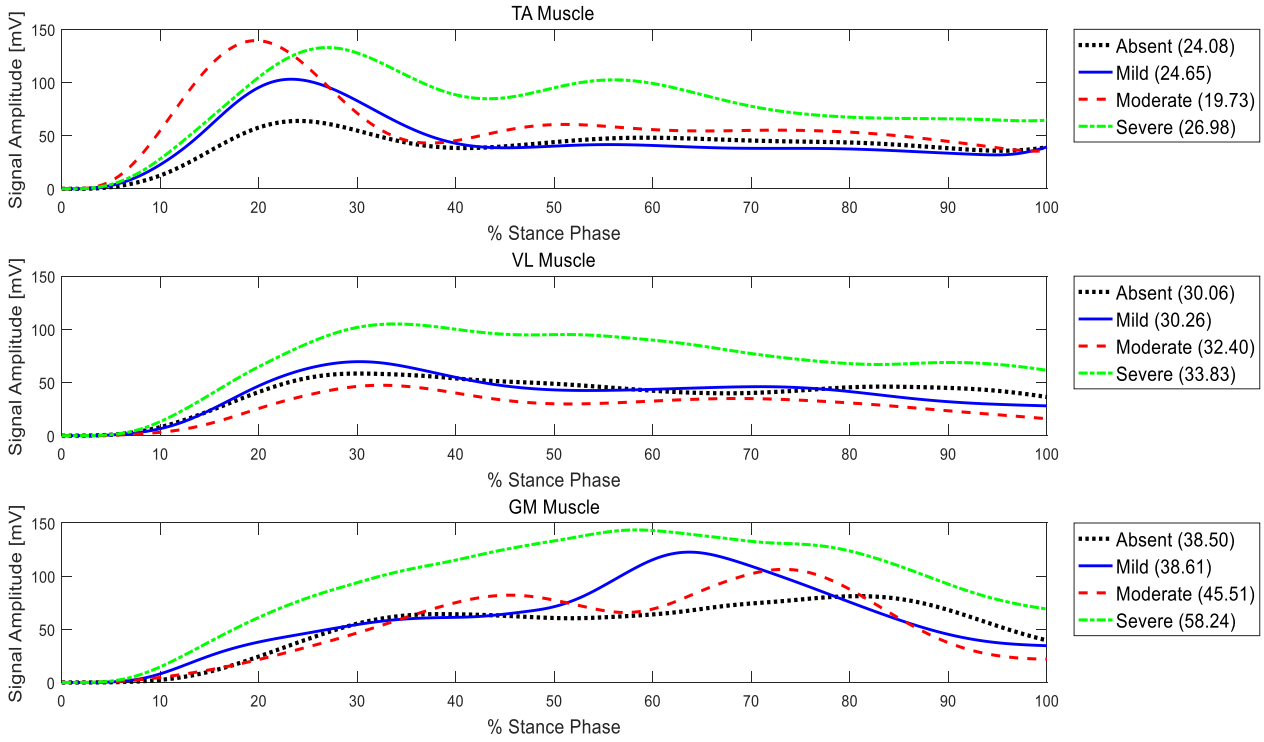


FIGURE 6. Change in muscle activity for different DSPN severity groups three different lower limb muscles (TA [top], VL [middle], GM [bottom]) during gait. [Time to get the first activation peak corresponds to each severity groups for all three muscles are indicated in the legend of each graph].

TABLE 4. Peak magnitude and Time for peak activation for vastus lateralis (VL), tibialis anterior (TA), and gastrocnemius medialis (GM) muscles during the gait cycle.

		Absent	Mild	Moderate	Severe
TA	Peak Magnitude (μV)	345.12±151.37	305.01±160.94	303.22±105.30	230.04±125.46
	Time to peak (% stance phase)	24.08±2.5	24.65±2.4	19.73±2.0	26.98±2.6
VL	Peak Magnitude (μV)	115.86±61.99	127.02±55.03	92.14±44.41	62.96±17.09
	Time to peak (% stance phase)	30.06±2.3	30.26±3.3	32.40±2.7	33.83±2.9
GM	Peak Magnitude (μV)	396.83±57.39	265.98±22.66	203.32±20.31	131.94±27.86
	Time to peak (% stance phase)	38.50±4.8	38.61±3.6	45.51±4.3	58.24±5.1

Figure 6 shows the muscle activity for VL, TA, and GM muscles concerning the % stance phase during gait. Table 4 is showing the mean peak amplitude and time (% stance phase) to get the activation peak. We have observed the activity peak delay and lowered peak amplitude during gait for different DSPN severity groups for VL and GM muscles. From figure 6 (top), we can observe the activation peak delay in TA muscle for absent, mild, and severe groups whereas the moderate group has an earlier activation peak, which helps us to conclude that the changes in muscle activation do not progress in the same manner from mild to severe stages for TA. On the contrary, VL and GM muscles show delayed activation peak with the progress of severity level as illustrated in figure 6 (middle, bottom). From this observation, we can conclude that for VL, and GM muscles' EMG can be used to identify the severity level of the DSPN patients.

TABLE 5. Performance analysis of ANFIS based DSPN severity classifiers using EMG features during gait dynamics (MODEL 1: trained with peak magnitude model 2: trained with peak magnitude and time to peak occurrence for TA, VL, and GM muscles).

	Model 1	Model 2
Accuracy (%)	96.13±1.70	80.54±3.91
Sensitivity (%)	98.36±1.90	82.23±5.49
Specificity (%)	98.75±1.47	94.49±2.46
Precision (%)	96.11±2.04	80.02±3.41
Recall (%)	94.98±2.80	80.46±4.56
F1 Score (%)	98.16±2.15	68.46±4.93
Classification Rate (%)	96.13±1.70	80.54±3.91
Fold Error (%)	0.44±0.03	0.19±0.04
NPP (%)	98.95±1.22	89.22±2.95
PPV (%)	93.47±4.80	90.80±3.74

Table 5 is showing the performance of the two trained model in classifying DSPN patients based on the

EMG parameters. Accuracy, sensitivity, and specificity of model 1 and model 2 are 96.13±1.70%, 98.36±1.90%, 98.75±1.47%, and 80.54±3.91, 82.23±5.49, 94.49±2.46, respectively.

V. DISCUSSION

Diabetic neuropathy (DN) has received the attention of researchers as one of the major complications for DM patients [37] and DSPN is the most common distal and symmetrical form of diabetic neuropathy. Even though a vast range of diagnostic tools (Symptom scores, quantitative sensory testing, and electrophysiology) have been introduced by researchers over the year for DSPN; screening and stratification of DSPN are still required for manual grading or decision making by the health care professionals which are always subjective and depends on the expertise of the personnel. Hence to successfully mitigate the prevalence of DSPN, a new detection model is required to characterize and intelligently identify DSPN severity with higher accuracy and robustness but non-invasive. Moreover, it must be acceptable by the clinicians. Early detection and better classification tools for DSPN can allow better management of painful diabetic neuropathy as well as foot ulceration, amputation, and other diabetic complications.

Nowadays the use of Artificial Intelligent (AI) in health care systems are getting more popular because of its flexibility, ability to learn, cost-effectiveness, and it helps the healthcare system to provide better patient's satisfaction, reduce workload from the health professionals, and increase the quality of life of the patients. Because of these advantages, researchers are focusing on smart and intelligent systems for the diagnosis and stratification of different diseases. Machine learning algorithms are being used in different biomedical systems for the diagnosis and classification of different diseases and health issues [30]–[33]. Researches are also been conducted to introduce automated systems using artificial intelligence in diagnosing DSPN. Focus is given on clinical diagnosis methods like automated detection of CCM images using machine learning methods [17]–[19] for early and reliable detection of DSPN. However, the initial identification of DSPN is based on the clinical symptoms and signs, and different diagnostic scoring methods such as QST, neuropathy disability score, Michigan neuropathy screening method, vibration sensing with a 128 Hz tuning fork, and monofilament test are used for assessing pain, touch, vibration, and temperature sensation loss due to DSPN [6]. As there is no fixed global scoring method for DSPN severity identification the screening methods to identify and grade the severity levels of the DSPN differ in different countries of the world. Variations in screening methods, scoring, and subjective identification are the reasons to introduce an intelligent system for accurate and reliable diagnosis and severity classification for DSPN. Therefore, this research aims to propose a DSPN severity classifier using the ANFIS algorithm to enhance the diagnosis facility for DSPN patients by early, accurate and reproducible screening and stratification of DSPN.

In the literature, the Fuzzy Inference System (FIS) and support vector machine (SVM) algorithms have been introduced for detecting and classifying the severity of DSPN [20]–[23]. DSPN onset is insidious and progresses differently for every patient which makes it exhibits non-linear characteristics. Researchers using the fuzzy system for classification of the severity of DSPN have to design non-linear characteristics of DSPN through the IF-THEN rules which leave a chance of human error and reliant on expert knowledge, thus its accuracy is questionable. On the other hand, Kazemi *et al.* [23] have identified different levels of DPN severity by using multicategory SVM (MSVM) and considered the neuropathy disability score (NDS) as the input of their MSVM classifier. However, the accuracy of their system was only 76%.

Therefore, for accurate and reliable severity classification of DSPN, this study aims to develop an intelligent ANFIS based classifier to classify the severity level of the DSPN patients into 4 classes- absent, mild, moderate, and severe. ANFIS is an artificial neural network based on Takagi–Sugeno fuzzy inference system (FIS) which has the potential to capture the benefits of both systems in a single framework [24]. Its inference system corresponds to a set of fuzzy IF-THEN rules that have the learning capability to approximate nonlinear functions. ANFIS can work with non-linear structures and have a fast learning capacity. As we aim for a cost-effective and simple DSPN severity classifier, we need data from a screening method, which is simple, inexpensive, accurate, non-invasive, and does not require expensive instruments or tools. Besides increasing patient's awareness and urgency about the seriousness of DSPN, simple diagnosis tools like a 128-Hz tuning fork, monofilament test and temperature sensation test, reflexes of ankle test are required to be provided to the primary healthcare professionals [38]. So, we have selected Michigan Neuropathy Screening Instrumentation (MNSI) [28] as input to train our DSPN severity classifier using the ANFIS algorithm. MNSI is a simple and inexpensive screening method that did not require any special expertise and is a very simple clinical examination that can be done in any regular healthcare center. Among the MNSI variables, we have ranked the importance of these variables in identifying DSPN using the XGBoost feature ranking method. So, for our input, we have taken into consideration the following three parameters from MNSI based on their importance index in feature ranking: vibratory perception, tactile sensitivity, and history questionnaire. The feature ranking methods helps to enhance the performance of the ANFIS classifier and reduce the costs of doing a number of the clinical tests for DSPN diagnosis. It will help the health professionals to screen DSPN in a faster way using a minimal number of tests.

To train an intelligent system, the data fed to it plays a very crucial role. The accuracy of the system will depend on how well the data showcases the objectives close to the human-like experience. As DSPN exhibits non-linear characteristics, we need a large training dataset for training the ANFIS algorithm. We have used the database from the EDIC,

which is a long-term observational follow-up of the Diabetes Control and Complications Trial (DCCT) cohort [35] with 1,375 of the surviving DCCT subjects since 1994. MNSI was used to assess DSPN in the EDIC studies annually [28], [35]. We have used 8-years' MNSI data from the EDIC study to train the ANFIS model. As the ANFIS model was trained with a real dataset, it can accurately learn the non-linear characteristics of DSPN and has a very small training error which is 0.235. -Furthermore, all the input parameters selected here are semi-quantitative or non-quantitative tests and are simple and easily available in all the healthcare facilities. As we have used a large dataset with a wide range of demographic variables from the EDIC trials with different severity of DSPN, it has also been observed that the patients had different diabetic duration which made this dataset more realistic in observing different classes of DSPN severity.

The performance of the proposed ANFIS model has been compared with different conventional ML algorithm-based classifiers such as ensemble classifier, SVM, KNN, naïve Bayes, and DAC. The comparative study showed that ANFIS exhibits better sensitivity, specificity, and accuracy compare then different ML classifiers. For this study, deep learning algorithms have not been considered as they are more suitable for extracting high-level, complex features [39]. Introducing deep algorithms classification problems where regular clinical scorings like MNSI have been used as inputs can introduce higher computational costs due to the complex nature of the algorithms which can hinder the idea of a cost-effective diagnosis system for DSPN patients [40].

DCCT/EDIC studies were designed to observe the effects on the development and progression of the early vascular and neurologic complications of type 1 insulin-dependent diabetes mellitus [35]. In this study, we have determined the severity level of the EDIC study subjects from the first, eighth, and nineteenth years to observe the progression of DSPN severity with time. From EDIC year 1 to 8, the number of patients with non-neuropathic patients decreased by 20%, which means with time, new EDIC patients have developed DSPN. Initially, there were no severe DSPN patients in year 1, which increased to 6 in year 8 and 39 in year 19th. Also, in year 1 to 19, 59% of patients were neuropathic. From this observation, we can conclude that, with time, all diabetic patients have higher risks to have DSPN and early detection is very crucial for diabetic patients to provide medication to prevent the consequences of severe DSPN.

In our study, we have investigated the changes in activity in lower limb muscles during gait in DSPN patients with different degrees of neuropathy in order to extract EMG features that exhibit a change in muscle activities with the progression of DSPN severity. Three lower limb muscle signals during the gait cycle were investigated. We have observed the peak magnitude and the time to reach the muscle activation peak for each muscle during gait in different DSPN severity groups. This study observes changes in muscle activity due to DSPN; although, it does not follow a specific order for all the lower limb muscles that have been also reported in different studies [22], [28], [30], [33]. We have found that both VL and GM muscles show an increase in delayed peak activation and decrease in peak magnitude with the progress in severity degree whereas TA muscle does not follow this pattern. So, the peak amplitude and activation peak delay for VL and GM muscles can potentially be used as an important feature to identify the degree of DSPN in patients.

Based on the above finding, we have prepared a dataset consists peak magnitude and time to get the activation peak during gait from these three lower limb muscles and used it to train the ANFIS classifier to identify DSPN severity from the EMG parameters. Here two different model was trained using ANFIS algorithm. We can observe that model 1 which was trained using only the peak magnitudes of three muscles during gait from different severe groups performs better than model 2 where both peak magnitude and time (% stance phase) to get the peak were considered as inputs. We can observe that using the muscle peak magnitude, we can classify the DSPN severity. ANFIS algorithm showed significantly better performance using MNSI and EMG parameters for stratification of DSPN.

According to the International Diabetic Federation [1] in 2019 1 one, in 11 people have diabetes and 10% of the global health expenditure which is USD 760 million is spent on diabetics. 50% of the diabetes patient will suffer from DSPN- one of the most common and costly complications. According to Aljunid *et al.* [41], the health expenditure for diabetic patients increases with severity. The diagnostics tools available for DSPN are expensive, time-consuming, required specialized personnel and some of them are invasive and painful. Hence to successfully mitigate the prevalence of DSPN, our DSPN severity classifier using ANFIS can intelligently identify DSPN severity in real-time which will allow early detection and treatment of diabetic neuropathy as well as a timely intervention to prevent foot ulceration, amputation, and other diabetic complications. This system has benefits to overcome the limitation of conventional methods that often leads to a late diagnosis and heavily relied on offline analysis of the healthcare experts.

This DSPN severity classifier can work as a stand-alone system and can be implemented on any host computer in a health-care system. It will help in saving a lot in annual healthcare expenditure and improve the quality of life among diabetes patients. Also, in the future, we can add a prediction system in our DSPN classifier which will be able to predict patients future conditions based on their previous records and will help the health professionals to enhance the healthcare of diabetic patients in relations to identifying the high-risk individuals to improve their risk factors.

VI. CONCLUSION

Due to unclear and subjective screening processes and uncertainties in symptom measurements, diagnosing DSPN is complicated. Many research and different diagnostic methods have been introduced, yet no specific baseline is available and conflicting diagnosing criteria are available in a different part

of the world. Therefore, researchers are trying to implement intelligent systems for diagnosing DSPN. In this research, an ANFIS model was proposed which is a simple yet most used screening method for DSPN. This can be done in a regular healthcare center without specialized personals and equipment. The ANFIS model showed better performance in comparison to different ML models. Due to its learning capabilities to approximate the nonlinearity of DSPN, it can provide a better human-like experience for classifying the severity of DSPN. Using the designed model, we have classified the severity level of the patients from the EDIC clinical trials and observed that, with time, how DSPN's severity increases among patients and could successfully identify those patients who need immediate medication. After severity classification, the patient's EMG signals from three different lower limb muscles (TA, VL, and GM) were analyzed to find the muscles that accurately show a delay in activation peak with the progression of DSPN severity from absent to severe condition. VL and GM muscles showed decreased peak magnitude and delayed activation peak with the progression of severity level. Extracted EMG features were used in the proposed DSPN classifier and it exhibits promising performance in DSPN severity stratification. Our proposed DSPN severity classifier was able to perform better with both MNSI data and EMG variables. So, this system has the capability to act as a stand-alone system and help the health professionals for decision making in DSPN identification and stratification.

ETHICAL STATEMENT

No ethical statement to be declared

AUTHORS CONTRIBUTION

Conceptualization, F. H. & M.B.I.R. methodology, F. H. & M.B.I.R. software, F. H. & M.E.H.C. validation, F.H. formal analysis, F. H.; investigation, M.B.I.R.& M.E.H.C.; resources, F.H., M.B.I.R.; data curation, F.H..; writing—original draft preparation, F.H.; writing—review and editing, M.E.H.C. visualization, F.H.H. S.H.M.A, N.A..; supervision, M.B.I.R., M.E.H.C.; project administration, M.B.I.R, S.H.M.A & N.A; funding acquisition, M.B.I.R, M.E.H.C., F.H.H., S.H.M.A & N.A,

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