Multiple Sclerosis Severity Estimation and Progression Prediction Based on Machine Learning Techniques

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Abstract— **The aim of the study is to address the Multiple Sclerosis (MS*)* severity estimation problem based on EDSS score and the prediction of the disease's progression with the application of Machine Learning (ML) approaches. Several ML techniques are implemented. The data are provided by the Neurology Clinic of the University Hospital of Ioannina and were collected in the framework of the ProMiSi project. The features recorded are grouped into: general demographic information, MS clinical related data, results of special tests, treatment, and comorbidities. The records from 30 patients are utilized and are recorded in three time points. The ML methods provided quite high results with 94.87% accuracy for the MS severity estimation and 83.33% for the disease's progression prediction.**

I. Introduction

Multiple Sclerosis (MS) is a chronic inflammatory disease, which affects the Central Nervous System (CNS) [1] and often causes severe physical or cognitive impairment as well as neurological problems in young patients [2]. MS is an autoimmune disease: the immune system attacks healthy tissues just as it can attack a virus or bacterium. The primary cause for MS is the inflammation of the white and gray matter tissues in the CNS due to the infiltration of focal immune cells and their cytokines [2]. An accurate diagnosis of MS is based on a complete medical history and neurological examination using imaging techniques such as Magnetic Resonance Imaging (MRI) that detect tissue damage in the CNS [2]. Also, an eye examination and evaluation of Babinski's reflexes may be helpful. The Trial Capability Test [3], which includes visual, auditory brain radiation, and somatosensory-induced features, provides information on demyelination of the optic nerve and CNS. Furthermore, the cerebrospinal fluid (CSF) analysis for myelin basal protein and immunoglobulin (IgG) assays and blood sample analysis for vitamin deficiency are part of the MS diagnosis [4].

Although it is not possible to predict with certainty how an individual's disease will develop, four types or phenotypes of MS were defined by the International Advisory Committee on Clinical Trials of MS in 1996 [5]. The reason for this was "the need for clarity and consistency in defining patient groups for studies, to enhance homogeneity in clinical trials, and to clarify communication between clinicians and people with MS" [6]. In 2014, the types of MS were updated and the disease depending on its course was divided into four main types: Relapsing-Remitting MS – RRMS, Clinically Isolated Syndrome – CIS, Primary Progressive MS – PPMS and Secondary Progressive MS – SPMS [6]. Moreover, the Expanded Disability Status Scale (EDSS) is a way of measuring the influence of MS. It was proposed by Kurtzke in 1983 [7] and was used to decide which patients can participate in clinical drug trials or who can receive disease modifying therapies (DMTs). The EDSS provides an overall score on a scale of 0 to 10.0. The first levels 1.0-4.5 refer to people with a high degree of mobility, the next levels 5.0-9.5 refer to the loss of mobility, and level 10.0 refers to death due to MS.

Early diagnosis of MS is crucial because it gives the opportunity to apply appropriate treatment immediately. Computer-aided diagnosis systems (CADs) based on artificial intelligence (AI) methods have been proposed in recent years for the accurate diagnosis of MS. In the field of AI, the automated diagnosis of MS is performed using conventional ML, and deep learning techniques (DL).

According to the literature, several studies aim to classify patients suffering from MS based on the type, by using ML techniques. In 2013, Taschler *et al.* [8] analyzed a dataset that consisted of demographics, EDSS score, Paced Auditory Serial Addition Test score (PASAT) and MRI information. By applying the SVM algorithm to the entire dataset, they achieved 56.0% accuracy, while using only the demographic data and scores, they achieved 39.8%. In 2017, Ion-Margineanu *et al.* [9] attempted to classify MS patients based on the type of MS by using demographics, MRI information and metabolic data. The application of the SVM algorithm in clinical data and MRI information achieved 71.00-72.00% accuracy for CIS *vs*. RRMS and CIS *vs*. RRMS + SPMS, respectively. The RRMS *vs*. PPMS classification achieved high results (maximum F1 score 85%) using clinical and metabolic data, while the RRMS *vs*. SPMS received slightly higher results (maximum F1 score 87%) using all available data. Similarly, Karaca *et al.* [10] in 2015, aimed to distinguish the type of MS (RRMS, SPMS, PPMS) by using data from patients with diagnosed MS and data from healthy subjects. The first dataset included only MRI data, while the second included both MRI and EDSS score, aiming to demonstrate the

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importance of the EDSS score for the diagnosis of MS type. For the first dataset, Radial Basis Function approach managed to diagnose the type of MS with 98.90% accuracy while for the second it achieved 99.90% accuracy.

In addition, several studies were conducted to detect a possible worsening of MS according to the EDSS score. Rodriguez *et al.* [11] in 2012, predicted the development of MS in recently diagnosed patients. They analyzed 80 mononucleotide polymorphisms, five variables from clinical data and a variable representing whether the patient has reached EDSS = 6 or not. Zhao *et al.* in their studies in 2017 [12] and 2020 [13] investigated the possible worsening of MS after 5 years according to the EDSS. Patients who would experience worsening of the disease were those who showed an increase in EDSS> = 1.5. The features they used consisted of basic demographic information, clinical data and MRI information. In their study, Law *et al.* [14] categorized participants based on whether they had a confirmed disability progression or not. Individuals were classified as having a confirmed progression of disability only if there was an increase in EDSS after 6 months> = 1 if the initial EDSS was <= 5.5 or an increase> = 0.5 if the initial EDSS was> = 6. The features they utilized were: key clinical prognostic indicators, demographic and MRI information. Similarly, Pruenza *et al.* [15] in 2019 predicted the progression of disability of a patient with MS after one and after two years. The evolution of the disability was defined as follows: increase> = 1.5 in EDSS if the previous EDSS was 0, increase> = 1 in EDSS if the previous EDSS was> = 1 and <= 5.5 and increase> = 0.5 in EDSS if the previous EDSS was> = 6. The dataset they utilized, consisted mainly of demographic information, clinical features, MRI information and therapy treatment.

All previous works that aim to classify patients are based on the MS type. Such an approach, although very helpful for an automated diagnosis system, does not depict the patient's actual disability due to MS. Our study provides an automated severity estimation approach to classify patients based on the EDSS score. The severity of the patients' condition is classified as mild with EDSS<=3.5 (minimal effect on daily activities), moderate (moderate effect on daily activities) with EDSS ranging from 4.0 to 5.0 and severe (severe effect on daily activities) with EDSS>=5.5 [16]. Such an approach could be very useful to reach an accurate diagnosis in cases when unspecialized clinicians or nurses perform the tests and collect all the appropriate clinical data and. Additionally, it can be useful in cases when patients suffer from co-morbidities and can offer the clinicians a further aid in the classification of MS. Furthermore, we aim to detect possible EDSS change in a 6-months period. The patient's progression is estimated as stable (no change at the EDSS), worsening (the EDSS increases) or improving (the EDSS decreases).

II. Materials and methods

A. The dataset

The data were provided from the Neurology Clinic of the University Hospital of Ioannina and were collected in the framework of ProMiSi project [17]. The ProMiSi project combines MRI and other types of information (e.g. clinical, demographic etc.), to evaluate the severity and predict the progress in MS patients. The data for the 30 patients that participated in the study, were collected over three time points: at the baseline visit, at the 1st follow-up after 6 months, and at the 2nd follow-up after 12 months (the clinical study was approved by the board of the University Hospital of Ioannina, approval code: 8/8-3-2019). For the baseline visit, we collected data from all 30 patients, from the 1st follow-up from 28 patients and from the 2nd follow-up from 21 patients.

The features recorded for each patient can be categorized into the following categories (TABLE I): general demographic information, MS clinical related data, results of special tests, treatment, comorbidities. As general demographic information we consider the age and sex of the patient, whereas as MS clinical related data we consider the type of MS, the EDSS score, the disease duration (time since the first diagnosis), and whether the patient had relapses since the last examination. The tests that the patients had to perform were the Timed 25-Foot_Walk (T25FW) [18], [19], the 9-Hole Peg Test (9-HPT) [20], the Multiple Sclerosis International quality of life (MusiQol) [21], the MS Walking Scale (MSWS-12) [22], the Beck Depression Inventory (BDI-II) [23], the Modified Fatigue Impact Scale (MFIS) [24], and the MSIS-29 [25], [26]. Treatment is divided into 1st, 2nd and 3rd line DMTs, regarding the severity of the disease, and is determined by the clinician [27].

TABLE I. RECORDED FEATURES

Category	Features
General demographic information	age, sex
MS clinical related data	type of MS, EDSS score, disease duration, relapses
Tests' results	T25FW, 9-HPT, MusiQol, MSWS-12, BDI-II, MFIS, MSIS-29
Treatment	1st, 2nd and 3rd line DMTs
Comorbidities	comorbidities

B. The proposed methodology

The proposed methodology consists of three main stages: preprocessing, feature selection and classification. Pre-processing included the detection and correction of typographical errors. In addition, the problem of unbalanced class distribution is addressed. Data sampling is one of the most frequently preferred approaches for dealing with an unbalanced dataset. There are generally two types of methods for this: undersampling, and oversampling. In our case, an oversampling technique was selected, where a random order of the majority class was followed, so that all classes have the same number of cases.

Selecting the best features is a fundamental problem in many different areas. For some problems, all attributes may be important, but for some classification problems, only a small subset of attributes is usually relevant. When feature selection is applied, an optimal feature set is selected, by removing unnecessary, irrelevant or noisy data. The feature selection process improves the data mining algorithm, the data quality and increases the understanding of mining results [28]. In this study, filter model method was selected, which distinguishes feature selection process from classifier learning, so that the bias of a learning algorithm does not interact with the bias of a feature selection algorithm. It is based on metrics of the training data such as distance, consistency, dependency, information and correlation [29]. In data processing, we used a feature selection method based on the correlation that

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evaluates the predictive power of each feature separately and the degree of redundancy between them, preferring sets of features that are strongly correlated with the class but with low intercorrelation [30]. The Bestfirst search method was applied to the dataset. This method starts the search from an empty set of features and moves to the search area in both directions taking into account all possible additions and deletions of a feature and making local changes to the current feature subset [29].

For the data analysis, the following classification techniques were applied: Decision Trees, Random Forests (RF), Rotation Forests (ROT), Naive Bayes, K-nearest neighbors (KNN), Support Vector Machines (SVM), Logistic Model Trees (LMT), Bayes Networks and Boosting techniques. Ten-fold cross validation was applied for the evaluation of classifiers. Ten-fold cross validation is a statistical method to evaluate and compare learning algorithms by dividing data into two parts: one is used to learn or train a model and the other is used to validate the model [31]. The results are expressed in terms of common evaluation measures, i.e. Accuracy, and True Positive (TP) rate.

III. Results

A. *MS Severity Estimation*

For the MS severity estimation, the records from the patients in all three time points i.e. 79 patients' records (30 at baseline visit, 28 at 1st follow-up and 21 at 2nd follow-up) were utilized. The records were classified based on the severity as presented in TABLE II.

TABLE II. EDSS Severity Classification

Class	Severity	EDSS	No of records
Low	Mild	0-3.5	51
Medium	Moderate	4.0-5.0	18
High	Severe	5.5-10.00	10

The Random Forest classifier achieved the highest results, in terms of accuracy (94.87%), TP rate for low class (90.40%), medium (94.20%) and high (100.00%). The optimal features that were retained after the feature selection procedure were: gender, age, MSWS-12, the physical impact from MFIS29, and treatment.

B. Progression of MS

For the estimation of the progression of MS, 48 records were utilized i.e. (27 patient's records from baseline visit and 21 from the 1st follow-up). The Random Forest classifier achieved the highest results, in terms of accuracy (83.33%), TP rate for worsening (87.50%), TP rate for improvement (93.80%) and TP rate for remaining at a stable condition (68.8%), using the optimal set of features: comorbidities, treatment, gender, age, the physical impact from MFIS29, relapses and disease duration.

IV. Discussion

Data-driven approaches to classify patients suffering from MS have shown great progress and may prove valuable in the healthcare models especially in costly diseases such as MS. The present study has made a considerable contribution towards the development of such an approach utilizing a multivariate dataset consisting of general demographic information, MS clinical related data, results of special tests, treatment, comorbidities, with the use of various ML techniques. The results for the MS severity estimation based on EDSS score were quite high in terms of accuracy 94.87%, as well as in terms of TP rate for all three classes, confirming the classification power of ML approaches. Relevant approaches in the literature provide a method for classifying patients with MS according the MS type and based on several feature types with an accuracy ranging from 56-99.9% (TABLE III).

Moreover, in our study we predicted the progression of MS in a 6 months period achieving also high results, in terms of accuracy (83.33%), TP rate for worsening (87.50%), TP rate for improvement (93.80%) and TP rate for remaining at a stable condition (68.8%), without including MRI data as most relevant studies do (TABLE IV). In both cases, only the optical feature set was selected.

TABLE III. State of the Art for MS Severity Estimation

MS Severity Estimation		
Study	*Dataset*	*Evaluation measures*
Present Study	78 records 51 with EDSS 0-3.5 18 with EDSS 4.0-5.0 10 with EDSS 5.5-10.0	Accuracy 94.87% TP rate for Low Class 90.40%, TP rate for Medium Class 94.20% TP rate for High Class 100.00%
	General demographic information, MS clinical related data, results of special tests, treatment, comorbidities.	
Tascher *et al.* Diagnosis of MS type	223 patients	Accuracy 56.00%
	Demographics, MRI information, EDSS score, PASAT score	
Ion-Margineanu *et al.*	87 patients 69 with MS 18 controls	F1 score 87% for RRMS vs. SPMS
Diagnosis of MS type	Demographics, MS clinical related data (i.e., patient age, disease duration), EDSS, MRI information: lesion loads (based on T1 and FLAIR), metabolic features (N-acetyl-aspartate (NAA), Choline (Cho), and Creatine (Cre) concentrations)	
Karaca *et al.* Diagnosis of MS type	139 patients, 19 controls	Accuracy 99.9%
	MRI information, EDSS, results of special tests	

TABLE IV. State of the Art for MS Progression

Progression of MS		
Study	*Dataset*	*Evaluation measures*
Present study	48 records 27 patient's records from baseline visit 21 from the 1st follow-up	Accuracy 83.33% TP rate for worsening 87.50%, TP rate for improvement 93.80%, TP rate for remaining at a stable condition 68.8%
	General demographic information, MS clinical related data, results of special tests, treatment, comorbidities.	
Rodriguez *et al.* [11]	605 patients	Accuracy 85.00%
	DNA: 80 single nucleotide polymorphisms, Clinical info: date of birth, gender, type of MS, age at onset, disease duration, and EDSS>6	
Zhao *et al.* [12]	1693 patients from CLIMB study [32]	Accuracy 75.00% Sensitivity 74.00% Specificity 76.00%
	Demographic information, clinical and MRI data	
Zhao *et al.* [13]	724 patients from the CLIMB study [32] 400 patients from the EPIC dataset [33]	AUC 83.00%

	MRI data, EDSS, clinical related data, family history, age	
Law *et al.* [14]	485 patients	AUC 61.80%
	EDSS, T25FW, 9-HPT, PASAT, demographic variables (duration of the disease, age and sex), MRI information	
Pruenza *et al.* [15]	521 patients	AUC 80.00%
	Sex, age, clinical related data (first symptom data, date of diagnosis, date of last visit, EDSS score, relapses, MRI data, treatment	

V. Conclusion

In the current study, we present a method to estimate the severity of MS based on EDSS score and predict the progression of the disease in a 6-months period by implementing various ML techniques on a multisource dataset. The RF classifier achieved the highest results in terms of accuracy (94.87%) for the classification of MS patients based on the EDSS score. For the progression of MS the RF classifier achieved also high results (accuracy 83.33%). In both cases, the models are built utilizing only the optimal feature set that was selected through feature selection, minimizing the need for costly diagnostic tests. That gives the opportunity to clinicians to reach an accurate MS severity estimation and predict the possible worsening in a patient's condition in a 6-months period, without performing an MRI. This renders our study quite innovative since we managed to achieve high results without including MRI information.

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