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Article

Machine learning can predict aggressive Multiple Sclerosis using non-invasive initially collected data at the time of diagnosis

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Abstract:

Background: Multiple sclerosis (MS) is a central nervous system (CNS) disorder characterized by inflammation, demyelination, and neurodegeneration. It is the most common cause of non-traumatic neurological disability in young adults. The course of the disease varies between individuals: some patients accumulate minimal disability over their lives, whereas others experience a rapidly disabling course. This latter subset of patients is often referred to as having 'aggressive' MS. Early intervention might protect patients from irreversible damage and disability. The study objective is to assess a variety of machine learning (ML) models for predicting the disease course. *Material &Method:* A retrospective study was conducted on patients from the Neuropsychiatry MS clinic at Alexandria University. Patients were classified as aggressive or mild MS based on their Expanded Disability Status Scale (EDSS) after 5 years from the onset of the disease. Six ML classification models (XGboost, Support vector machine (SVM), Random Forest (RF), Logistic regression, Decision tree (DT), and Naïve Bayes (NB)) were assessed

to predict disability progression till the end of the first year from the onset of the disease using recursive feature elimination (RFE) and the SHAP method was used to interpret predictions. Demographic, health history, and clinical features were used as predictors. *Results:* The XGBoost classification model was the best performing model with an accuracy of 88.5% and F1 score of 88.9%. Top SHAP predictors were duration of stability without treatment, BMI, and a number of relapses within the first year from the onset of treatment. *Conclusion:* Our independently generated data set and results support previous preliminary work that XGBoost can predict multiple sclerosis progression. Our XGBoost implementation could rule out the aggressive course outcome 94.9% of the time by using only non-invasive features that are routinely collected earliest in the patients' contact with the clinic. This suggests a lower practical burden for the clinical implementation of ML progression algorithms. Finally, our results suggest allergic rhinitis may be a risk factor for the aggressive progression of MS.

Keywords: Multiple Sclerosis, Expanded Disability Status Scale, Machine Learning, XGBoost, SHAP method

Introduction

Multiple sclerosis (MS) is an inflammatory disease of the central nervous system. (1)The clinical presentation and phenotype of MS are variable between patients and over the disease course. It can encompass various degrees of severity. Patients exhibit either a benign profile with little disability accrual over time or an 'aggressive' one with frequent, severe relapses, incomplete recovery, and rapidly accumulating and permanent disability. (2)

Several prognostic factors of disability have been described, and many clinical and demographic features associated with long-term disease courses have been proposed. (3, 4) Older age at onset(5, 6)and male sex (5, 7) have been associated with an increased risk of disability progression in the long term. Environmental and modifiable factors, such as smoking and high body mass index, contribute to impairments in walking speed, overall disability, and associated depression. (8)

Poor prognosis also correlates with a high annualized relapse rate, particularly on treatment, and a short interval between disease onset and first relapse. (9, 10) Incomplete recovery from the first relapse or polysymptomatic onset, (5, 7)motor onset and early cerebellar involvement have been associated with a faster increase in disability, while sensory onset and optic neuritis have been described as favorable prognostic factors. (5, 11)

The most popular and widely used instrument that describes the clinical severity and the resulting functional deficits in multiple sclerosis is the Expanded Disability Status Scale (EDSS) of Kurtzke. (12) The EDSS is a clinician-administered assessment scale evaluating the functional systems of the CNS. The EDSS is used to describe disease progression in patients with MS and to assess the effectiveness of therapeutic interventions. It consists of an ordinal rating system

ranging from 0 (normal neurological status) to 10 (death due to MS) in 0.5 increments intervals

(when reaching EDSS 1). The lower scale values of the EDSS measure impairments based on the neurological examination, while the upper range of the scale (> EDSS 6) measures the handicaps of patients with MS. The determination of EDSS 4 – 6 is heavily dependent on aspects of walking ability. (12)

Several preventive disease-modifying therapies (DMTs) are available nowadays, so that, in principle, it is possible to tailor treatments to the specific needs of each patient. Considering that all therapies are preventive in their essence, it would be extremely useful to project prognoses as exact as possible, to avoid undertreatment of patients with aggressive forms of disease or over-treatment of patients with mild forms. (13)

Given the clinical heterogeneity of multiple sclerosis, reliable prognostic predictors would be of great importance. Early identification of subjects with the aggressive disease at onset or with a disease that becomes more aggressive over time is essential to both aid treatment recommendations and various decisions in the clinic. For support to patient counseling, prognosis, and therapy, attention has increasingly been turned to artificial intelligence, exploiting the ability of Machine learning (ML) approaches to extract complex relations among existing data without requiring a priori models linking input and output variables. (14) Recently, ML techniques have also been applied to analyze clinical and radiological data in MS and reliably distinguish patients with MS from healthy subjects. (15) Previously, models based on demographic, follow-up clinical, and radiological MS features were used to predict secondary progression transformation. (16)

This study aims to create a predictive model for the progression of MS based on sociodemographic, environmental, and earliest baseline clinical disease parameters. By developing a machine learning model, it would be plausible to explore which are the most important parameters in the prediction model allowing clinicians to understand the projected disease progression.

Methodology

Study design and variables:

In a retrospective cohort study, 455 patients with relapsing-remitting MS (RRMS) with a duration of disease more than or equal to 5 years were selected from the MS clinic established in 2016 in the Neuropsychiatry Department, University Hospital, Alexandria, Egypt. Cases were diagnosed according to the McDonald's criteria. (17)

Inclusion criteria:

- Patients with a duration of disease more than or equal to five years.
- Patients of RRMS and secondary progressive (SP) types.
- Available clinical assessment data at baseline before starting disease-modifying therapies (DMT).

The cases were classified as aggressive and mild MS based on the scale of EDSS after 5 years of

MS. The patients with confirmed EDSS ≥ 4.0 after 5 years of disease onset are classified as aggressive MS. (18, 19)

Data were extracted from clinical records of the clinic together with undergoing an in-person interview with patients. The variables collected were sociodemographic including gender, education, occupation at the onset of MS, and residence. Health history information included surgical intervention, family history of MS and autoimmune disorders, diet and appetite change during the first year of disease, body mass index (BMI), vitamins, and supplement intake during the first year after the onset of MS, smoking index till the onset of MS, allergies, comorbidities including other autoimmune disorders and obstetric history during the first year of MS. Clinical features included age at onset of disease, initial symptoms including motor, visual, cerebellar affection, urinary incontinence and paresthesia, time lapse from onset to diagnosis, baseline

Expanded Disability Status Scale (EDSS) with all its domains including pyramidal, brain stem, cerebellar, sensory, visual, cerebral, bladder and bowel, and ambulation scale, number of systems affected at baseline assessment, number of relapses during the first year of disease, baseline magnetic resonance imaging (MRI) affected sites and clinical stability without treatment in the first year.

Data preprocessing:

A total of 71 initial features were collected from participants. The number of patients classified as aggressive MS was 277 while those with mild were 178 participants.

To handle this class imbalance, Synthetic Minority Oversampling Technique (SMOTE) was applied to data resulting in 277 cases in each class. It is an oversampling technique where the synthetic samples are generated for the minority class. This algorithm helps to overcome the overfitting problem posed by random oversampling. It focuses on the feature space to generate new instances with the help of interpolation between the positive instances that lie together. (20)

The dataset is then split into train-test sets in a ratio of 0.8 so that the test set represented 20% of the data.

Feature normalization was done for all numeric data as age at onset of MS, Stability without treatment, the years-lapse between onset and diagnosis of disease, smoking index, and BMI. The normalization step was done after splitting to avoid data leakage.

Also, five-fold cross-validation (CV) was applied and the mean accuracy was calculated for the accuracy of each of the five validation models from CV to avoid overfitting. (21)

Classification models:

Six commonly used ML classification models were applied to the data after preprocessing. These classifiers were Decision Tree (DT), Support Vector Machine (SVM), Bernoulli Naïve Bayes (NB), Logistic Regression (LR) (22), Random Forest (RF), and extreme gradient boosting (XG-Boost). The tuning parameters or hyperparameters for optimization of each model were selected using the Grid search method. (23)

The preprocessing and analysis were done using python 3.10.5. (24) The codes used were adjusted from Scikit learn libraries. (25)

Feature selection:

The best-performing model was selected, and a dimensionality reduction was done using recursive feature elimination. It uses a backward selection of the predictors to build a model on the entire set of predictors and compute an importance score for each predictor. The least important predictor(s) are then removed, the model is re-built, and importance scores are computed again. The subset size of features that optimizes the performance criteria is used to select the predictors based on the importance rankings. The optimal subset is then used to train the final model. (26)

Evaluation criteria:

The evaluation was dependent on the accuracy score after doing 5-fold cross-validation to avoid overfitting problems then mean and standard deviation was calculated for the results from five accuracy scores, F1 score, sensitivity, specificity, and area under the curve (AUC). These metrics are calculated based on the following formulas:

Total accuracy= (TP + TN)/ (TP + FP + TN + FN)

Sensitivity= TP / (TP + FN)

Specificity= TN / (TN + FP)

F1 score= TP / (TP + ½ (FP + FN))

Where TP stands for true positive, TN is a true negative, FP is false positive, and FN is a false negative.

Ethical considerations:

The use of the data for research purposes was authorized by the Ethical Committee of Alexandria University Faculty of Medicine in Egypt (Authorization n. 00012098, June 2020). The federal-wide assurance (FWA) number of this EC is 00018699 and it operates according to the International Conference of Harmonization Good Clinical Practice (ICH GCP) and applicable local and institutional regulations and guidelines. Oral informed consent was obtained from all subjects before recruitment to the study.

Results

Table I reveals the performance of the six applied classification models. In comparing the six ML models regarding accuracy score which is the percent of true prediction from the total predictions, the least was for NB. The accuracy of the DT and LR were almost near followed by RF and the highest was for SVM and XGBoost.

As regards the recall rate, LR was the least in the ability to correctly predict those MS patients with an aggressive course (56.3%) while XGBoost was the highest (87.5%).

For the six applied models, the ability to detect true negatives (those with mild course) was higher

than the sensitivity rate.

The overall evaluation metrics were higher in XG-Boost. That's why the XG-Boost was selected as the best-performing model. After feature selection, the overall accuracy increased while the F1 score and specificity remained the same. On the other hand, sensitivity and AUC were decreased. The hyperparameters for the selected model were subsample equals 0.9, learning rate equals 0.1, minimum child weight equals 2, and the number of estimators is 100. These values were chosen based on using the grid search method and all these parameters worked to prevent this model from overfitting.

Table I: Performance of tested machine learning models in the prediction of multiple sclerosis course progression

Classification model		Accuracy score (5-fold cross-validation)	F1 score	Sensitivity (Recall)	Specificity	Area under curve (AUC)
Decision Tree		80.5% ± 3.6%	75.4%	71.8%	89.8%	80.8%
Support Vector Machine 'linear'		87.4% ± 3.9%	71.2%	65.6%	89.8%	77.7%
Bernoulli Naïve Bayes		71.7% ± 5.4%	55.5%	62.5%	66.1%	64.3%
Random forest		85.4% ± 4.1%	77.2%	68.8%	94.9%	81.8%
Logistic regression		82.4% ± 4%	70.4%	56.3%	94.9%	77.1%
Extreme gradient boost (XG Boost)	Before FS** (71)	87.5%± 4.9%	88.9%	87.5%	94.9%	91.2%
	After FS (35)	88.5% ± 3.4%	88.9%	84.4%	94.9%	89.6%

* The best model to be used is XG-Boost classification model

**Feature Selection (FS)

The features which took rank one in the model after RFE were summarized in **Table II**. The features were categorized as follows: sociodemographic characteristics, baseline MS clinical parameters as EDSS, MRI findings, the type of presenting symptoms, stability during the first year, and relapses during the first year from the onset of disease, obstetric history for female patients, and dietary and supplement factors. The numeric features were BMI, smoking index, the number of relapses, surgeries, domains affected, EDSS, duration of stability, duration from onset to diagnosis, duration from last cesarean section to onset, and age at onset of disease. The rest of the selected features were binary in nature.

Table II: The features in XG-Boost after Recursive feature elimination

1. **Personal demographic, and health history variables:**
    - **Body mass index (BMI)***
    - **Nonacademic education**
    - **Smoking index***
    - **Marital status**
    - **Number of surgeries done before the onset of MS**
    - **Family history of autoimmune diseases**
    - **Autoimmune diseases other than MS**
    - **Allergic rhinitis**
2. **Relapses**
    - **Number of relapses during 1st year of the disease**
3. **EDSS:**
    - **Baseline total EDSS score and its subcategories (bowel, pyramidal, cerebellar, visual, sensory and ambulation)**
4. **Baseline MRI affected foci:**
    - **Periventricular**
    - **Juxtacortical**
    - **Infratentorial**
5. **First manifested symptoms:**
    - **Cerebellar symptoms**
    - **Motor symptoms**
    - **paranesthesia**
6. **Clinical factors:**
    - **Duration of stability without treatment in 1st year after the onset of MS**
    - **Age at onset of disease**
    - **The lapse duration from onset to diagnosis**
    - **The number of domains affected**
7. **Obstetric factors: (among the female subset)**
    - **Irregular menstruation after the onset of MS**
    - **Number of previous cesarean deliveries before the onset of MS (if applicable)**
    - **Duration from last cesarean section to the onset of MS**
    - **Use of mechanical contraception after the onset of disease***
8. **Dietary factors and the start of supplement intake after the onset of MS**
    - **Diet transformation to a healthy pattern ***
    - **Appetite suppression**
    - **Omega 3**
    - **Vitamin D**

* The diet transformation denotes increased vegetables and fruits intake and decreased refined carbohydrates and saturated fat intake.

* Smoking index calculated using the following formula: smoking index = Cigarettes per day × years of tobacco (27)

* BMI = kg/m2 where kg is a person's weight in kilograms and m2 is their height in meters

*Mechanical contraception excluding any hormones as with intrauterine devices, diaphragms, and sterilization

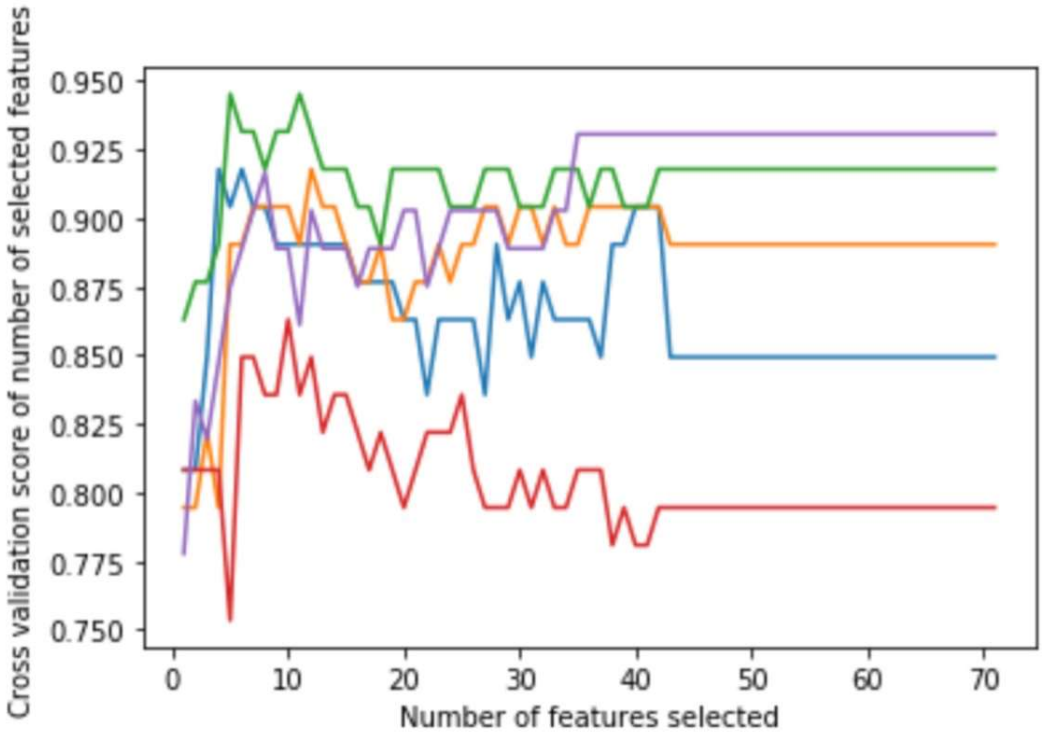

Figure (1): Number of features elected from recursive feature elimination from fivefold cross-validation

The RFE was applied to the XG-Boost model reducing the number of selected features by about 50% from 71 to 35 features. As shown in figure (1), no change in the model performance after exceeding the selected features.

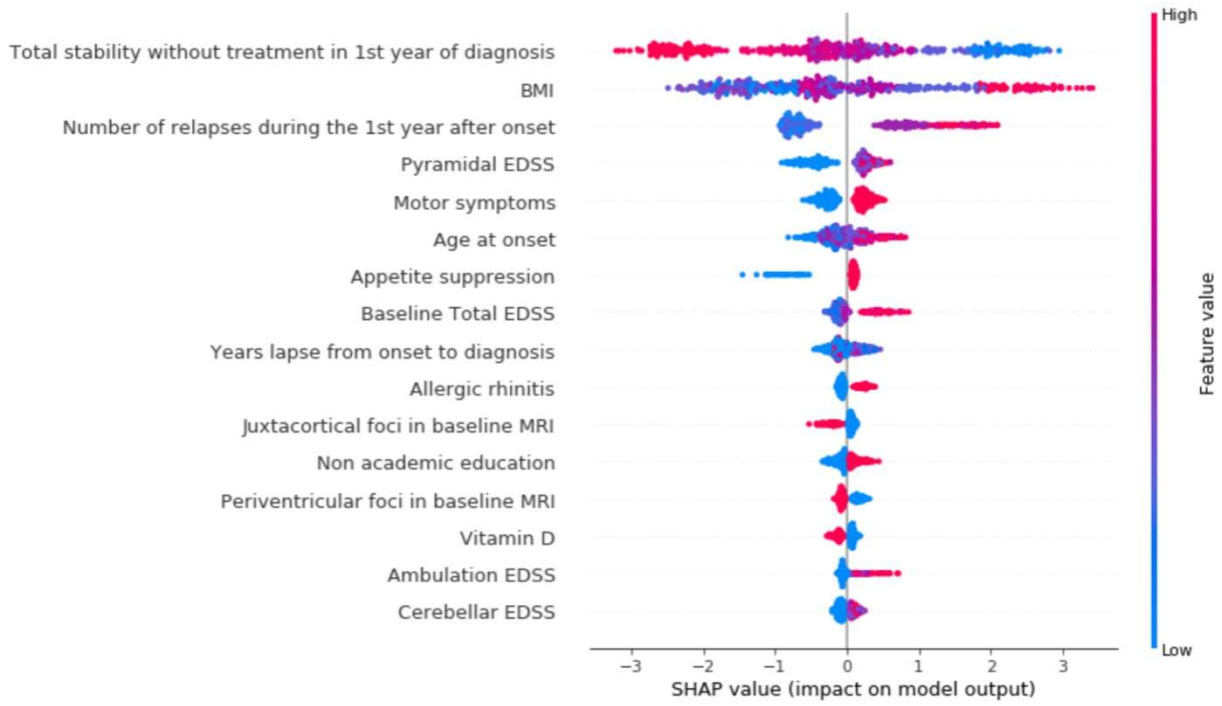

Figure (2): SHAP summary (bee swarm) plot showing factors importance for MS progression prediction

To get an overview of which features are most important for the model, the SHapley Additive explanations (SHAP) values of every feature were plotted, figure (2). SHAP is a method based on cooperative game theory and used to increase the transparency and interpretability of machine learning models. The summary plot sorts the feature by the SHAP value magnitudes in descending order and uses SHAP values to show the distribution of the impacts the first 16 features have on the model output. The color represents the feature value (red means high and blue means low value). A positive SHAP value on the right side of the midline means a positive impact on prediction, leading the model to predict 1 which is the code for the aggressive course and a negative SHAP value on the left of the midline means a negative impact, leading the model to predict 0 which is the code for the mild course. (28)In other words, positive SHAP means the risk while negative means no or low possibility of an aggressive course of MS.

All variables are shown in the order of global feature importance, the first one being the most important and the last being the least important. Effectively, SHAP can show both the global contribution by using the feature importance, and the local feature contribution for each instance of the problem by the scattering of the bee swarm plot. On the bee swarm, the features are ordered by their effect on prediction and show how higher and lower values of the feature will affect the result. (29)

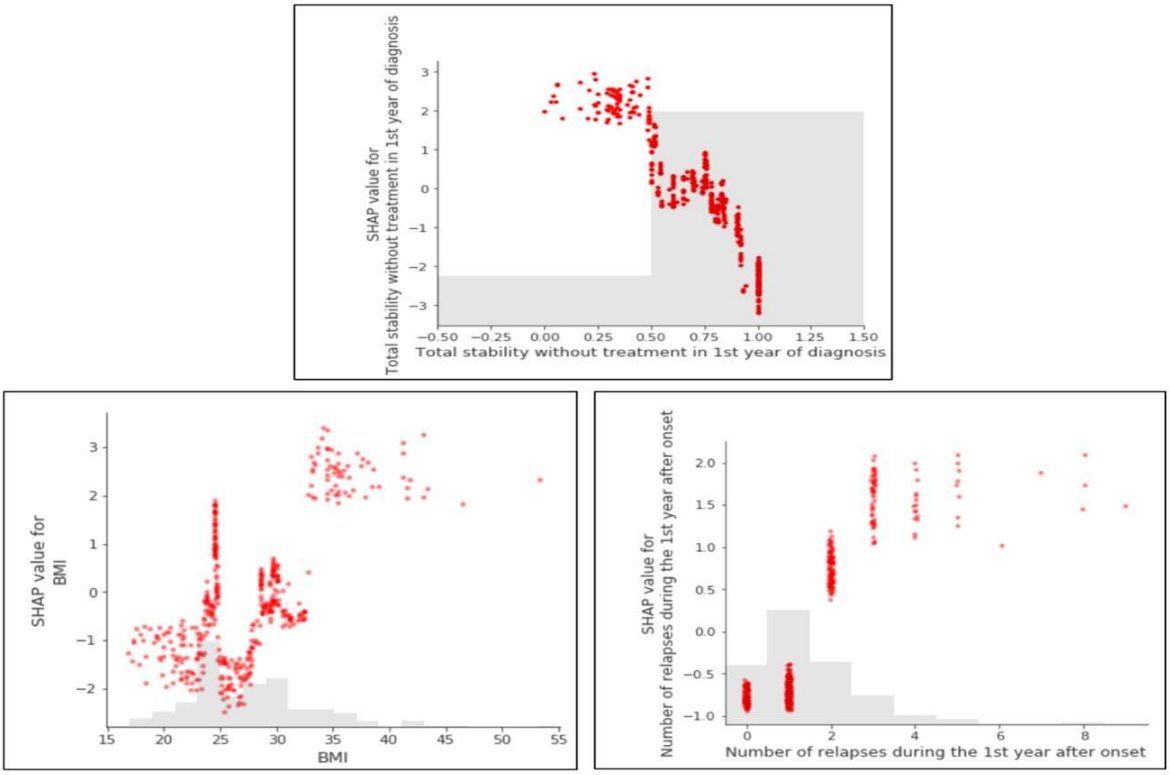

Figure (3): SHAP dependence plot showing the highest three contributing factors for MS progression prediction

As shown in **Figure 2**, the features that have the highest SHAP values are the number of relapses within the first year from the onset of MS, baseline BMI, and total stability without treatment during the first year. SHAP dependence plots were displayed for these features as shown in figure 3. There was an inverse relationship between stability and the SHAP value while there was a direct correlation between BMI and the number of relapses with SHAP values.

Discussion

The present study aimed to use machine learning techniques in the prediction of MS progression based on personal sociodemographic and health data, baseline, and first-year clinical characteristics. Six commonly used ML classification models were tried using all features after hyperparameter tuning using Grid search. Their performance is reported in Table (II). The best-performing model was XGBoost based. This algorithm belongs to the family of homogeneous

ensemble methods, in which the base learners, L1, L2, …, Ln, are created using a single machine learning algorithm exploiting the concept of "adaptive boosting. (30) Tree boosting is considered a novel sparsity-aware algorithm for handling sparse data and a theoretically justified weighted quantile sketch for approximate learning. (31) This ability to handle the sparsity of data may explain its superior performance compared to the other applied five models.

The XGBoost model was trained and validated resulting in a predictive model with the ability to correctly predict the course of 88.5% ± 3.4% of MS patients based on 35 features that were all of a non-invasive nature and are routinely collected on the patients' earliest visit to the MS clinic, making model construction both feasible and cost prohibitive. The accuracy and F1 scores of this model increased after RFE while the sensitivity rate and AUC decreased. However, reducing the number of features needed to be collected from patients and ease of use in clinical practice outweigh the decrease in these two metrics. The final model can correctly identify approximately 95% of MS patients that will have a mild disease course. It also has an AUC of nearly 90%, which means a strong ability to distinguish between cases with mild versus aggressive MS courses. This discriminative power will help clinicians set individualized follow-up policies for each patient.

The weighted average between model precision and recall was 0.89 which is presented on the model's F1 score value.

Similarly, another study conducted by Zhao et al. (32) in 2020 included 724 patients from the Comprehensive Longitudinal Investigation in MS at Brigham and Women's Hospital (CLIMB study) and 400 patients from the EPIC dataset, University of California, San Francisco and aimed to create a prediction model and identify the most important predictors for aggressive MS. The aggressiveness is based on an increase in EDSS ≥ 1.5 (worsening) or not (non-worsening) up to 5 years after the baseline visit. The features used were overlapping with the ones used in this study, and they were demographic, longitudinal features such as the attack in the previous 6 months, attack in the previous 2 years, EDSS, pyramidal, cerebellar, brainstem, and bladder functions, walking ability, and total Gadolinium enhancement (GD). In addition, our study included features about the obstetric history and the start of vitamin D and omega 3 intake after the onset of disease. They applied three ML models: SVM, LR, RF, and ensemble models (XGboost, LightGBM) and found that the ensemble mainly XGboost was more robust than the other four models with an overall accuracy of 79%, sensitivity of 50%, and specificity of 87%. The referred study also reported that the most important predictors that were common in the five used models were EDSS score, pyramidal function affection, and ambulatory scale. These predictors were identified using the regression coefficient. (32) The difference from the present study, is that we used only features at baseline clinical assessment and relapses within the first year from onset without including follow-up or radiological features which might give an earlier prediction ability from the initial patients' visit.

Another study conducted in Italy in 2021 aimed to create a model for the prediction of patients with RRMS to transform to secondary progressive MS (SPMS) as a primary outcome. (16) They included 262 RRMS patients followed up for 10 years, we assessed the probability of developing the SP course based on clinical and conventional and non-conventional MRI parameters at

diagnosis and after 2 years. An RF model was applied using age, EDSS at diagnosis, and a number of MRI T lesions and relapses during the first year. Results were validated on the testing set and showed an accuracy of 74%, a specificity of 67%, and a sensitivity of 92%. This differs from the present study in its aim which is secondary progression rather than aggressiveness.

SHAP Model Interpretation

Interpreting our XGBoost model results with SHAP revealed an increased number of relapses during the first year of disease increased the SHAP value in the prediction of aggressiveness. This supports both the conclusion of a clinical study reporting that a high number of relapses during the first 2 years is considered a bad prognostic factor (10) and another study that showed that having more than two relapses in the duration of 12 months is a predictor of aggressiveness. (33)
Our study also showed that increasing EDSS at baseline will increase the SHAP value for the aggressiveness prediction. Malpas et al (34) documented that baseline EDSS more than or equals 3 is a red flag for the severity of MS. In the present study, the high pyramidal EDSS in the first year was associated with a positive SHAP value. This is consistent with another study reporting that pyramidal symptoms within the first year were associated with an aggressive course in RRMS. (35)

Additionally, we showed that initial affection for the cerebellar and motor function is considered a predictor of disease course. This is consistent with what was reported in many studies that the presence of cerebellar, motor, and sphincteric malfunctioning are potential parameters associated with a more aggressive disease course. (7, 11, 36-39)
Similar to other studies, we showed that increased BMI is associated with an increase in SHAP value denoting an increased risk of aggressiveness. A 5-year study investigating the effects of obesity on the progression of MS found that BMI ≥30 can be a predictor for at least a one-point increase in EDSS among patients with mild disability (EDSS ≤4). (40) The results of Stampanoni et al (41) and Manouchehrinia et al(42) also conform with our results in showing that high BMI was associated with an increased risk of conversion to secondary progressive MS. The association found between obesity and the progression of the disease can be attributed to the link of high BMI to a high level of pro-inflammatory cytokines, such as leptin and interleukin6 (IL6) as well as a reduced level of anti-inflammatory cytokine (interleukin 13) in cerebrospinal fluid (CSF).

Increased pro-inflammatory cytokines in CSF accelerate disease reactivation and neurodegeneration in MS. Another justification might be that obesity interferes with vitamin D metabolism. These changes are associated with MS progression. (43)
Finally, our SHAP summary plot also showed that increased age at the onset of MS increased the prediction of aggressiveness in agreement with Menon et al (44) who stated that older age of onset is considered to be a red flag for the highly active MS. This might be because healthcare providers are more familiar with the disease in younger adults. (45) This unfamiliarity with the disease beginning in old age raises the possibility of delayed diagnosis and control by appropriate treatment regimens.

To our knowledge, our results are the first to show that having allergic rhinitis is considered a predictor of aggressive MS. This is consistent with Krishna et al (46) who reported that patients with allergic rhinitis are at higher risk of developing autoimmune diseases including MS. This association might be due to a gene called BACH2 that may play a central role in the development

of diverse allergic and autoimmune diseases. This Bach2 gene was found to be a critical regulator of the immune system's reactivity. (47) Further studies are required to see the effect of allergic rhinitis on the course of MS.

Regarding imaging, our study showed that juxtacortical or periventricular foci on baseline MRI are considered good prognostic factors. Other studies showed that infratentorial(48, 49) or spinal (48, 50, 51) MRI lesions are predictors of aggressive MS.

Regarding dietary patterns, it was shown that diet modification and change in appetite are important features in the creation of our XGBoost prediction model. Suliga et al (52) concluded that an unhealthy diet is connected with the presence of some metabolic risk factors in patients with MS. The authors of many previous studies have confirmed that the occurrence of comorbidities, including metabolic diseases, may cause a delayed diagnosis and greatly affect the course of MS, degree of disability, and the quality of life in patients with MS.(53, 54).

The start of Vitamin D intake after the onset of MS showed a negative SHAP value in the prediction of aggressiveness. This is consistent with a study that vitamin D intake is associated with decreased hazard of relapse occurrence. (55) Other studies showed that low levels of vitamin D are associated with progression in the course of MS. (56, 57)

Conclusion

Compared to previously published predictive models, the resulting XGBoost model from this study had higher values in accuracy score of 88.5% ± 3.4% with an ability of about 90% to distinguish different classes (AUC) based on personal sociodemographic and health data, and initial and first-year clinical characteristics. An added value is that features used are noninvasive data that are routinely collected earliest in the patients' contact with the clinic.

The model can be used in the clinic to give the clinician at least the ability to rule out those patients that will enter into an aggressive course with a high specificity of 95% and about 90% ability to distinguish the patients with mild from aggressive MS. Such insight can help clinical decision-making in prioritizing various treatment regimens and setting follow-up schemes and procedures according to categories of aggressiveness.

From the Shapley values, the top three predictors for MS aggressiveness were a shorter duration of stability without treatment, higher BMI, and an increased number of relapses within the first year from the onset of disease. Additionally, our study showed that allergic rhinitis may be a risk factor for the aggressive course while having periventricular or juxtacortical foci in baseline MRI are protective.

Limitations

The baseline characteristic of MS patients used in the model as EDSS, and MRI findings depend on the time that the patient will come to the clinic during the disease course. It is also affected by the lapse between onset and diagnosis of MS.

The relatively small sample size and the whole data set derived from just one clinic might have affected the performance of ML classifiers in the prediction of MS aggressiveness.

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Competing interests

No competing interests exist.

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Authorship

All authors state that this manuscript has been read and approved by all the authors, the requirements for authorship as stated earlier in this document have been met and each author believes that the manuscript represents honest work.

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