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RESEARCH

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A machine learning approach to determine the risk factors for fall in multiple sclerosis

Su Özgür[1,2], Meryem Koçaslan Toran[3,7], İsmail Toygar[4*], Gizem Yağmur Yalçın[5] and Mefkure Eraksoy[6]

Abstract

Background Falls in multiple sclerosis can result in numerous problems, including injuries and functional loss. Therefore, determining the factors contributing to falls in people with Multiple Sclerosis (PwMS) is crucial. This study aims to investigate the contributing factors to falls in multiple sclerosis using a machine learning approach.

Methods This cross-sectional study was conducted with 253 PwMS admitted to the outpatient clinic of a university hospital between February and August 2023. A sociodemographic data collection form, Fall Efficacy Scale (FES-I), Berg Balance Scale (BBS), Fatigue Severity Scale (FSS), Expanded Disability Status Scale (EDSS), Multiple Sclerosis Impact Scale (MSIS-29), and Timed 25 Foot Walk Test (T25-FW) were used for data collection. Gradient-boosting algorithms were employed to predict the important variables for falls in PwMS. The XGBoost algorithm emerged as the best performed model in this study.

Results Most of the participants (70.0%) were female, with a mean age of 40.44 ± 10.88 years. Among the participants, 40.7% reported a fall history in the last year. The area under the curve value of the model was 0.713. Risk factors of falls in PwMS included MSIS-29 (0.424), EDSS (0.406), marital status (0.297), education level (0.240), disease duration (0.185), age (0.130), family type (0.119), smoking (0.031), income level (0.031), and regular exercise habit (0.026).

Conclusions In this study, smoking and regular exercise were the modifiable factors contributing to falls in PwMS. We recommend that clinicians facilitate the modification of these factors in PwMS. Age and disease duration were non-modifiable factors. These should be considered as risk increasing factors and used to identify PwMS at risk. Interventions aimed at reducing MSIS-29 and EDSS scores will help to prevent falls in PwMS. Education of individuals to increase knowledge and awareness is recommended. Financial support policies for those with low income will help to reduce the risk of falls.

Keywords Multiple sclerosis, Machine learning, Fall, Risk factors,Risk prediction

*Correspondence:
İsmail Toygar
ismail.toygar1@gmail.com
[1] Department of Biostatistics and Medical Informatics, Ege University Faculty of Medicine, Izmir, Türkiye
[2] Ege University Faculty of Medicine, EgeSAM-Translational Pulmonary Research Center, Bornova, İzmir, Türkiye
[3] Bahçeşehir University, Institution of Postgraduate Education, Istanbul, Türkiye
[4] Muğla Sıtkı Koçman University, Fethiye Faculty of Health Sciences, Fethiye, Muğla, Türkiye
[5] Istanbul University-Cerrahpasa, Institute of Graduate Studies, Istanbul, Türkiye
[6] Department of Neurology, Istanbul University Faculty of Medicine, Istanbul, Türkiye
[7] Üsküdar University Faculty of Health Sciences, Istanbul, Türkiye

Background

Multiple sclerosis (MS) is a chronic, autoimmune disorder in which an people's physical and cognitive abilities progressively deteriorate [1]. Number of the people with Multiple Sclerosis (PwMS) was 2.8 million in 2020 [2]. Multiple Sclerosis is a disease that leads to many problems in peoples including weakness, fatigue, vision problems, cognitive problems, balance, and movement disorders. Gait and balance are two of the most important symptoms of MS. Gait and balance problems affect people's mobility and daily life activities. They also decrease the quality of life in PwMS [3]. Three out of four PwMS report reduced mobility due to impaired walking at some point during their lifetime [4]. Balance, gait, and movement problems are the most common reasons for falls in PwMS [5, 6]. Abou et al. (2023) reported that falls is a common problem in PwMS [7]. In another study by Nilsagard et al. (2015), it was reported that 56% of people with progressive MS fell three months [8].

Fall-related injuries in PwMS are ranged from mild sprains to serious fractures. In addition, PwMS due to these injuries are at the risk of hospitalizations, job losses, increased care costs, and even death [9, 10]. In a study comparing healthy individuals and PwMS in the United Kingdom, it was reported that PwMS were three times more likely to experience a hip fracture [11]. In a study of middle-aged and elderly PwMS, 17% of the PwMS experienced severe head trauma and injuries due to fall-related fractures [12]. In a study utilizing the Danish National Health Register, the risk of femur/hip fractures in PwMS was significantly high compared to control groups (HR: 1.9) [13].

To predict and prevent falls in PwMS, it is important to define the risk factors of falls. The most important risk factor for falls in PwMS is balance and gait problems. It is also stated that fatigue, cognitive impairment, spasticity, and visual impairment increase the risk of falling for PwMS [14]. In a systematic review and meta-analysis study of the risk factors for falls in PwMS, it was reported that the risk factors of falls are respectively; having a progressive MS type, cognitive status, and balance disorders [3].

In recent years, there has been a notable surge in machine learning (ML) applications focusing on neurological diseases. ML algorithms represent data science approaches to constructing predictive models capable of capturing intricate patterns and understanding relationships within data, all with minimal human interference [15, 16].

Various measurement tools are used to determine symptom severity and functional status of PwMS. Among these tools, the Fall Efficacy Scale (FES-I), Berg Balance Scale (BBS), Fatigue Severity Scale (FSS), Expanded Disability Status Scale (EDSS), Multiple Sclerosis Impact Scale (MSIS-29), and Timed 25 Foot Walk test (T25-FW) are the tools that commonly used in the researches and clinical practice [17, 18]. Also, subjective findings reported by the PwMS are used in the assessment of symptom severity and functional status [19]. However, the studies investigating MSIS-29 scores as a risk factor for falls in PwMS are limited.

The MSIS-29 is designed as an MS-specific HRQoL tool. It is self-administered and self-reported by people with MS and provides a measure of HRQoL outcomes relevant to these patients that are sometimes overlooked by clinicians. The scale consists of two subscales measuring physical (20 items) and psychological (nine items) impact. The MSIS-29 has been reported to have better measurement properties than the SF-36 and the FAMS in terms of physical and psychological health [19–21].

The existing literature suggests that fatigue, depression, physical function and fear of falling may need particular attention in order to reduce the rate of falls and injurious falls in people with MS. Looking at the sub-dimensions and items of the MSIS-29 scale, the physical dimension of the disease includes items such as sleep problems, depression, cognitive status and participation in social life, lack of confidence, which may be associated with fear of falling [7, 22, 23].

When the psychological impact of falls and injuries was investigated, people with MS reported that they found falls humiliating, embarrassing and caused them to avoid social situations. They emphasised that falls made them feel even more insecure. Assessment of balance confidence should be encouraged in people whose MSIS-29 assessment shows a decline in social participation [24].

The MSIS-29 predicts the need for an in-depth understanding of the factors that determine both the physical and psychological impact of the disease (such as insomnia, feeling depressed, physical impact of MS on activities of daily living) in people with MS [7, 25–27].

In recent years, limited studies determining specific conditions in MS have seen a notable increase in the literature [16, 17, 28, 29]. The objective of the study was to determine the risk factors of falls in MS by employing machine learning algorithm (XGBoost Algorithm), combining test results, disease-specific scores, including the MSIS-29, and demographic characteristics [30–32].

Methods

Aim of the study

This study aimed to determine the risk factors of falls in MS by employing machine learning algorithm.

Study design

In this cross-sectional study, a machine learning approach was used to determine the important variable as risk factors of falls in PwMS (Fig. 1).

Study settings and sample

The study was conducted in the MS polyclinics of the neurology department of a university hospital in the province of Istanbul, Turkey, between February and August 2023. The study population consisted of patients who were admitted to the hospital during the study period. A convenience sample was used for data collection. The patients who agreed to participate in the study and completed the forms and test were the sample of the study.

Inclusion and exclusion criteria

People who are 18 years of age or older, have a clinical diagnosis of MS, do not have a cognitive impairment, can communicate in Turkish, and are volunteers to take part in the study were included in the study. Individuals who had an attack/relapse in the last month, who have undergone foot, knee, or hip surgery, and who had diseases such as arthritis, low back pain, dementia, and parkinsonism, which are known to cause limitations in walking and balance, apart from MS, were excluded from the study.

Clinical diagnosis of MS, cognitive impairment, attack/relapse, dementia, arthritis and parkinsonism were diagnosed and confirmed by medical specialists. For this study, these characteristics were collected from the participant's electronic records.

A convenience sample was used for the study. A total of 384 PwMS were admitted to the outpatient clinic of the hospital between February and August 2023. Among these PwMS, 131 were excluded from the study because of the following conditions; 45 of them didn't meet the inclusion criteria, 28 of them refused to participate in the study, and 58 of them didn't complete the tests or surveys. Most of the PwMS who didn't complete the surveys or tests reported that their time in the hospital was limited and that they needed to leave. The study was completed with 253 participants.

Data collection

Data were collected by the researcher in the outpatient clinic of a university hospital. For the sociodemographic and disease-related characteristics of the participants, a sociodemographic data collection form was developed by the researchers. Fall Efficacy Scale (FES-I), Berg Balance Scale (BBS), Fatigue Severity Scale (FSS), Expanded Disability Status Scale (EDSS), Multiple Sclerosis Impact Scale (MSIS-29), and Timed 25 Foot Walk test(T25-FW) were used in data collection. All process of data collection, surveys, and tests, was carried out by one researcher to prevent observational bias between researchers. An informed consent form was first presented to the participants and all participants read and signed the informed

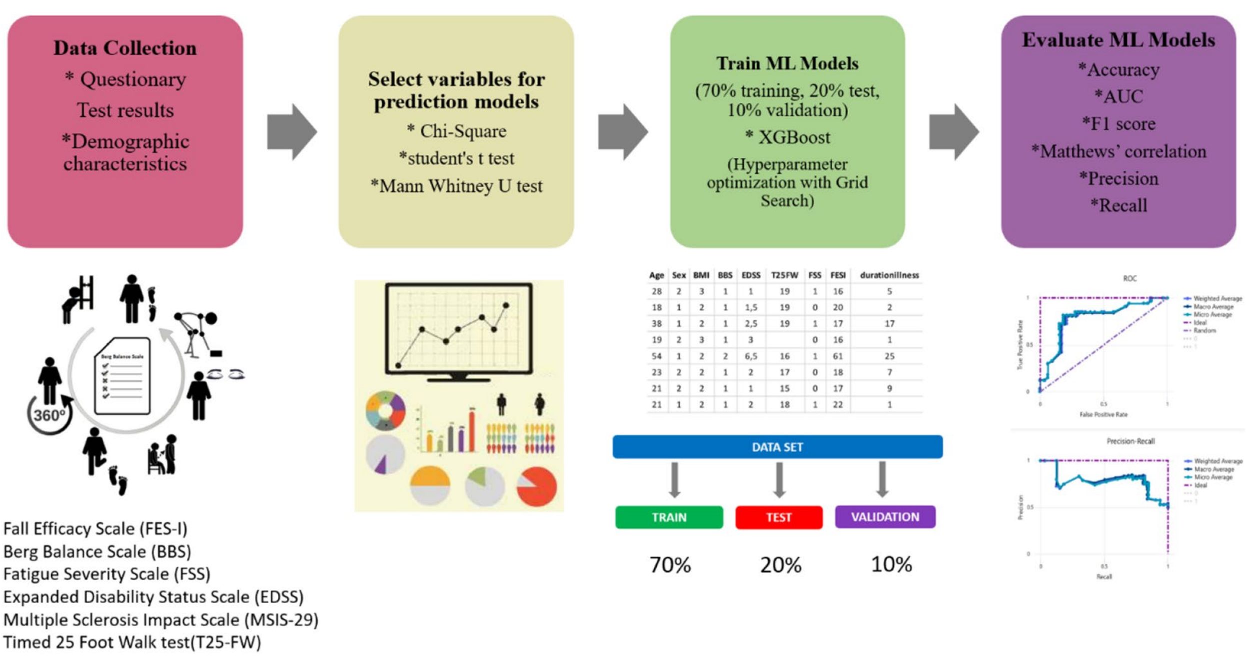


Fig. 1 Study workflow

consent form. Data were then collected in the following order: obtaining socio-demographic and disease-related data from the participants and their electronic medical records, completion of the FES-I and FSS scales, assessment of EDSS scores by a neurologist, assessment with the Berg balance scale, resting for two minutes, and assessment with the T25-FW test. Informed written consent to participate in the study was obtained from all participants who met the inclusion criteria. During the data collection process, certain precautions were taken to ensure the safety of people with MS and the collection of accurate data, and a procedure was followed. Safety instructions regarding the risk of falling and the data collection process were explained in detail to the patients face-to-face in a quiet room, and any additional questions were asked. Then the data collection instruments that would not create a risk of falling (completed in a seated position) were used first. These are the socio-demographic data collection form, the FES-I and FSS forms completed by the patient. Forms such as EDSS, Berg Balance and T25-WF, in which patients were instructed to walk, sit up, etc., were collected in the next step. During the collection of these data, a safe walking area (non-slip floor, lighted, no obstacles) was provided for patient safety. Patients were accompanied by a supervisor (rapid intervention in case of a fall) and patients were allowed to use walking aids (cane, etc.) if necessary. Patients were allowed to rest between interventions as needed. Data collection took between 25 and 30 min for each patient.

Sociodemographic data collection form

The form was developed by the researchers in line with the literature and consists of a total of 27 questions [18, 19]. The form consisted of a total of three main domains consisting of questions about demographic characteristics such as age, gender, educational status, disease-related characteristics such as MS type, disease duration, drug use, and fall-related characteristics, such as the number of falls and the presence of fall history in last year.

In the assessment of falls, the researchers considered participants as fallers if they scored from grade 2 to grade 4 on the Hopkins Falls Grading Scale [33]. Participants who did not fall and near-falls (grade 1) were considered non-fallers.

Expanded Disability Status Scale (EDSS)

The scale was developed by Kurtzke et al. to asses MS-related neurological disability. The EDSS score is calculated by evaluating pyramidal, cerebellar, brainstem, sensory, visual, bowel-bladder, and mental functions. The total score ranges between 0 and 10; higher scores indicate greater disability. Turkish version of the EDSS is used routinely in MS clinics [34, 35]. EDSS scores were determined by the same neurologist for each participant.

Berg Balance Scale (BBS)

The scale was developed by Berg et al. (1989) [36]. The scale consists of 14 items and is an objective measurement tool in the assessments of static balance and fall risk in adults. Each item consists of a five-point ordinal scale ranging from 0 to 4, with 0 indicating the lowest level of function and 4 the highest level of function. It was reported that the scale takes approximately 15–20 min to complete [37]; however, in studies with PwMS, it was reported that the test took approximately 10–15 min to complete [38, 39]. In the current study, the participants completed the BBS taskings in approximately 10–15 min. The Cronbach's alpha value of the scale was reported as 0.96 [36]. The validity and reliability of the scale for Turkish society were assessed by Şahin et al. (2008) [40]. Cronbach's Alpha value for the Turkish version of the scale was reported as 0.98. On this scale, 0–20 points are considered a high fall risk, and a wheelchair is suggested, 21–40 points moderate fall risk and walking with assistance or a tripod is suggested, and 41–56 points low fall risk and independent [40].

Timed 25-Foot Walking Test (T25-FW)

This test evaluates lower extremity functions. In this test, the participants is directed to walk 25 feet as quickly and safely as possible, and the completion time is recorded in seconds. Participants were free to use an assistive device while performing this task. The average of the two trials is taken as the T25FW score. The time limit per attempt is 180 s. T25FW is one of the common test methods used to evaluate walking speed and impairment in PwMS [41]. The researcher used a chronometer to calculate the time. The calculation started with the start command and ended with the 25th foot.

Fall Efficacy Scale (FES-I)

FES-I, which is called the international fall effectiveness scale, was developed by the Prevention of Falls Network Europe (PROFANE) as a modified version of FES [42]. FES-I is a self-report scale that provides information about the level of fear and anxiety about falls during activities of daily living. The questionnaire contains 16 items scored on a 4-point Likert scale. The total score on the scale is ranging from 16 (no worries) to 64 (extremely worried). The validity and reliability study of the Turkish version of FES-I was carried out by Ulus et al. in 2012 and the scale was reported as valid and reliable for Turkish society [43].

Fatigue Severity Scale (FSS)

The scale used to evaluate the severity of fatigue was developed by Krupp et al. (1989) for PwMS [44]. The scale is a widely used scale with high reliability and validity in PwMS. The scale consists of 9 questions investigating the severity of fatigue in the last month. In this scale, each item is scored between 1 (disagree) and 7 (agree). The lowest total score on the scale is 9, and the highest total score is 63. For the assessment of the scale, an average of nine items is used. Individuals with a score of less than 4 are defined as "not tired" and individuals with a score of 4 and above are defined as "tired". The validity and reliability study of the scale for Turkish society was conducted in 2007 by Armutlu et al. and the scale was reported as valid and reliable for Turkish society [45].

The Multiple Sclerosis Impact Scale-29 (MSIS-29)

The Multiple Sclerosis Impact Scale was developed by Hobart et al. in 2001 to evaluate the effects of the disease both physically and psychologically in individuals with MS [46]. The validity and reliability of the Turkish version of the scale were studied by Özden et al. (2022). The scale includes 20 items investigating physical problems related to MS disease and 9 items investigating psychological problems. The total score of the 29 items is arithmetically converted into a score between 0 and 100. High scores indicate high disease impact [47].

Statistical analysis

Sociodemographic and disease-related characteristics of the participants were presented with percentage (%), number (n), mean (M), and standard deviation (SD). To compare the sociodemographic and disease-related characteristics between the fallers and non-fallers, chi-square and independent sample t-tests were used. A comparison of the frequency and mean scores between groups was performed by using IBM SPSS v27.

The machine learning analyses were performed using Ddsv4-series Azure Virtual Machines with a vCPU count of 32 and a memory capacity of 128 GiB. The results and parameters of the best model obtained as a result of the analyses conducted in Azure Automated ML, XGBoost, the best-performed algorithm, have been presented.

The reason for choosing the XGBoost algorithm was its ability to handle complex data structures and effectively capture intricate relationships, including non-linear relationships, within the dataset. We also trained other machine learning algorithms (Random Forest, Support Vector Machine). But their overall accuracy was around 50%. Therefore, they were not reported in this study. Basic information about the algorithms were presented.

Grid sampling

Grid sampling is beneficial for discrete hyperparameters. Employ grid sampling when you have the resources to thoroughly explore the entire search space. It facilitates the early termination of underperforming jobs [48].

XGBoost algorithm

The XGBoost (Extreme Gradient Boosting) algorithm is a powerful and widely used machine learning technique known for its exceptional predictive performance across various domains. Developed by Chen and Guestrin in 2016, XGBoost is an ensemble learning algorithm based on gradient-boosting frameworks. It has gained popularity due to its ability to handle complex data structures, manage missing values, imbalanced data handling, and effectively capture intricate relationships (e.g., non-linear relationships) within data. XGBoost combines the strengths of decision trees and boosting techniques, utilizing a regularized objective function to minimize loss while preventing overfitting. This algorithm has been successfully applied to diverse applications, including classification, regression, and ranking tasks, making it a staple in many data science and machine learning pipelines [49, 50].

In the context of gradient boosting for regression, the fundamental building blocks are regression trees. Each regression tree maps an input data point to one of its leaf nodes, where a continuous score is assigned. XGBoost employs an objective function that undergoes regularization through the inclusion of both L1 (Lasso: Least Absolute Shrinkage and Selection Operator) and L2 (Ridge) terms.

By constraining the model coefficients, L1 regularization reduces the variance of the model and prevents overfitting. Unlike L1, L2 regularization does not perform feature selection; it only reduces the influence of less important features. L2 regularization is useful in situations where all features are expected to contribute to the outcome in some way. It is particularly beneficial in cases of multicollinearity [51].

These regularization terms are integrated into XGBoost's objective function to control the complexity of individual trees, mitigating overfitting and promoting model generalization. The objective function unites a convex loss function, responsible for quantifying the disparity between predicted and target outputs, with a penalty term aimed at addressing model complexity, specifically the functions represented by the regression trees [52] (Fig. 2).

The training process in XGBoost unfolds iteratively. It commences with the addition of new trees that predict the residuals or errors of previous trees. Subsequently,

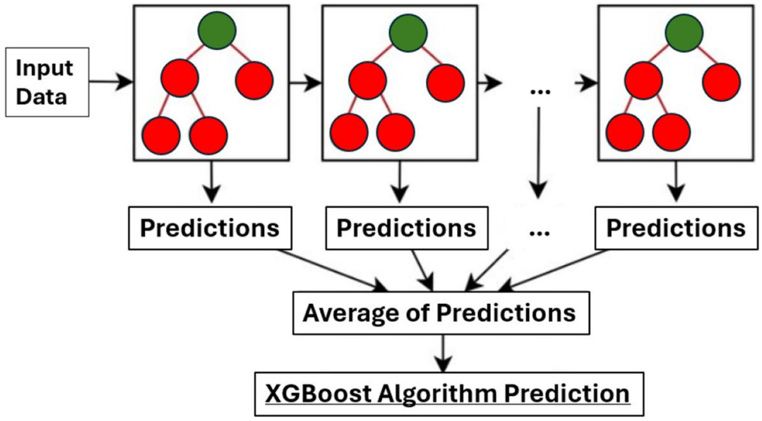


Fig. 2 Flow chart of XGBoost Algorithm

these new trees are harmoniously integrated with the existing ensemble of trees to make the final prediction. The term 'gradient boosting' is aptly attributed to XGBoost as it harnesses a gradient descent algorithm to minimize the loss when introducing these new models [52, 53].

Random forest

The Random Forest is a supervised learning algorithm extensively capable of performing both regression and classification tasks. It functions by constructing multiple decision trees during training and provides the mode of the classes for classification tasks or the mean prediction for regression tasks based on the individual tree outputs. It is easier to tune hyperparameters when performing model optimization compared to other algorithms. Random Forest often achieves higher accuracy than individual decision trees by combining the predictions of multiple trees. This approximation also provides robustness to overfitting. It can handle missing values effectively by estimating them during the training process. Since each tree is created independently, it can be calculated in parallel, which reduces computation time. On the contrary, it can be slow due to the approach of creating a large number of decision trees in large datasets. Due to the number of trees, the model can be large, increasing memory usage. Although Random Forest reduces overfitting compared to single trees, it can still overfit if the data is very noisy, though this is less likely than with individual decision trees [54].

Support vector machine

Support Vector Machine (SVM) is a supervised learning algorithm widely used for classification and regression tasks. SVM aims to find a decision boundary between two classes (the best hyperplane that separates the data) that enables the prediction of labels from one or more feature vectors. This method provides high accuracy, especially with high-dimensional and non-linear data. SVM is less prone to overfitting and more robust to outliers. However, SVM can be slow and memory-intensive with large datasets, and training time can be significantly long. Selecting the right kernel function and parameters (e.g., the C parameter, and kernel parameters: linear, polynomial, radial basis, and sigmoid) can be challenging and affects model performance. When non-linear kernel functions are used, the model can be hard to interpret. Additionally, SVM performance can degrade with imbalanced datasets [55].

Variable importance

Variable importance in machine learning models refers to the measure of the impact that individual input features (variables) have on the model's predictive performance or the outcome of interest. It quantifies the degree to which each variable contributes to the model's ability to make accurate predictions. Variable importance helps in understanding which features are the most influential in making decisions, allowing practitioners to focus on the most relevant factors and potentially improving model interpretability and generalization.

Variable importance can be assessed through various techniques, such as permutation importance, feature importance scores from algorithms like Random Forest, or by analyzing coefficients in linear regression. These methods assign scores or rankings to each feature based on how much the model's performance deteriorates when that feature is altered or removed [56].

XGBoost algorithm makes predictions using a series of decision trees. Each decision tree divides the data by asking a series of "yes/no" questions and reaches a conclusion. Some of the variables in the dataset are used to form these splits (the same questions do not have to be used in every split). A feature is considered more important if it is used more frequently and at higher levels in the decision trees. XGBoost tracks how often and how effectively each feature is used in these decision trees. Using this information, an "importance score" is assigned to each feature. This way, we can understand which features to focus on to improve the model's performance [53].

Performance metrics

Performance metrics are commonly used in the context of machine learning, statistics, and data analysis to evaluate the performance of classification models, particularly binary classification models (Table 1) [57]. Higher performance metrics indicates better prediction.

AUC/ROC

The AUC-ROC metric evaluates a model's capacity to distinguish between positive and negative classes. The ROC curve visually represents the model's performance at various classification thresholds, with a higher value indicating better class discrimination.

Accuracy

Accuracy is a straightforward metric that calculates the ratio of correct predictions to the total number of predictions. This metric is widely employed in machine learning applications in the field of medicine. However, it can be misleading, especially when handling imbalanced datasets.

Precision

Precision measures the proportion of true positive predictions out of all positive predictions made by the model. It primarily focuses on minimizing false positive errors and is particularly valuable when the cost of false positives is significant.

Recall

Recall, also known as sensitivity or the true positive rate, quantifies the proportion of true positives out of all actual positive instances. It is particularly valuable in scenarios where it is critical to identify all positive instances.

F1 score

The F1 Score is the harmonic mean of precision and recall, offering a balanced single metric that considers both false positives and false negatives. It is especially beneficial when dealing with class imbalance.

Matthews Correlation Coefficient (MCC)

MCC is a metric that assesses the quality of binary classifications by considering true positives, true negatives, false positives, and false negatives. It offers a balanced measure, even when confronted with imbalanced datasets [57].

While deciding the statistical significance, the researchers used distribution-based models including a t-test and chi-square test [58]. These methods can be affected by sample size [58]. However, distribution-based methods are not the only methods for the assessment of clinical

Table 1 Performance measurements of the models

$$\text{Accuracy} = \frac{(\text{TP} + \text{TN})}{(\text{TP} + \text{TN} + \text{FP} + \text{FN})}$$

$$\text{Precision} = \frac{\text{TP}}{(\text{TP}+\text{FP})} \qquad \text{Recall} = \frac{\text{TP}}{(\text{TP}+\text{FN})}$$

$$\text{F1 score} = 2 \text{ x } \frac{\text{Precision x Recall}}{\text{Precision} + \text{Recall}}$$

$$\text{MCC} = \frac{\text{TN x TP} - \text{FN x FP}}{\sqrt{(\text{TP} + \text{FP})\ (\text{TP} + \text{FN})\ (\text{TN} + \text{FP})\ (\text{TN} + \text{FN})}}$$

Diagnostic test	**Gold standard**	
	Positive	**Negative**
Positive	TP	FP
Negative	FN	TN

TP: True Positive; TN: True Negative;

FN: False Negative; FP: False Positive

MCC Matthews Correlation Coefficient

significance [58]. The researchers conducted an expert panel to discuss the clinical significance using consensus methods [58]. The experts included a neurologist, a nurse and a physiotherapist. The panel listed 18 variables that may affect the falls and can be risk factors of the falls. These variables are included in the machine learning analysis.

Results

In this study, 40.7% of the participants have a fall history in the last year. Participants' sociodemographic and disease-related characteristics are presented in Table 2. There were statistically significant differences between the fallers and non-fallers regarding their marital status, age, disease duration, EDSS, MSIS-29, FES-I, FSS, BBS, and T25FW scores (Table 2).

As a result of the analyses conducted using Azure Automated ML, the XGBoost algorithm achieved the highest performance levels. The optimized parameter values for the model are presented in Table 3.

The variable importance obtained from the XGBoost model is presented in Table 4 and Fig. 3. Accordingly, variables that considered as risk factors of falls were identified as follows: MSIS-29 (0.424), EDSS (0.406), marital status (0.297); education (0.240), disease duration (0.185), age (0.130), family type (0.119), smoking (0.031), income level (0.031) and regular exercise habit (0.026) were determined to contribute to fall.

The metrics of the prediction model are presented in Table 5 and Fig. 4. Accordingly, the AUC/ROC value for fall prediction by the model was 0.713, Accuracy 0.6667, precision 0.7213, recall 0.6190, F1 score 0.6635, and the Matthews correlation coefficient was calculated as 0.3114.

The greater contributor of the fall was MSIS-29 and has some subdomains. To distinguish which domains contributed to a logistic regression was carried out. According to the analysis, both physical and psychological scores are higher in fallers. The contribution of the psychological subscale was statistically significant according to the regression analysis (Fig. 5).

Discussion

Similar to the socio-demographic findings in the current study, in a study of falls in multiple sclerosis, most participants were female and married [59]. In another study by Cameron et al. (2013), 67% of the participants were women and the mean age was 39.8 ± 8.4 years [60]. These characteristics of the participants reflect the other samples in the literature.

In this study, FES-I, BBS and T25FW were not included in the analysis because they could be affected by the fall. The people who were classified as fallers in this study had a history of falls in last year when they were admitted to hospital and the test was done. For this reason, the researchers believed that the FES-I, BBS and T25FW scores could be influenced by fall history. These parameters were not included in the machine learning analysis.

According to the machine learning analysis, the risk factors of the falls in PwMS were MSIS-29 (0.424), EDSS (0.406), marital status (0.297), education level (0.240), disease duration (0.185), age (0.130), family type (0.119), smoking (0.031), income level (0.031) and regular exercise habit (0.026). FSS was not a significant variable according to the XGboost analysis. To our knowledge, this was the first study to show that MSIS-29, marital status, education level, family type, smoking, and income level are the risk factors of falls in PwMS.

In the current study, MSIS-29 had the highest score among the important variables according to the machine learning analysis. MSIS-29 scores were high in fallers compared to the non-fallers. Ross et al. (2016) reported that there was a positive correlation between the BBS, Mini-BESTest, and MSIS-29 scores [38]. This study shows that MSIS-29 has positive correlations with tools that evaluate the participant's balance. However, MSIS-29 investigate the PwMS status in an extended scope. For this reason, we carried out a regression analysis to determine the contribution of the subscales. Psychological subscale's contribution to the fall was statistically significant.

Among the identified risk factors by machine learning analysis, smoking and regular exercise habits were modifiable risk factors, while age, disease duration, marital status, and family type were identified as non-modifiable risk factors. MSIS-29, EDSS, education level, and income level are not suitable for classification as modifiable or non-modifiable risk factors due to their nature. However, there are interventions and policies that can decrease MSIS-29 and EDSS scores [61, 62], increase awareness and knowledge of the disease through patient education [63, 64], and provide financial support for people with MS who have a low income [65].

The role of demographic characteristics such as marital status, education level and income level in predicting the risk of falls in people with MS; marital status may provide protective social support, while higher levels of education facilitate greater awareness and better income levels facilitate access to resources that may reduce the risk of falls. Accordingly, it is important to consider demographic factors in fall prevention strategies in people with MS [66, 67]. In this study, there was a high rate of falls among those who were married. Iezzoni et al. (2009) reported that people who are married were less likely to use powered equipment to prevent falls compared to those who never married [68]. We believe that high fall

Table 2 Sociodemographic and disease-related characteristics of the participants

		Fallers ($n=103$) n (%)	Non-Fallers ($n=150$) n (%)	Total ($n=253$) n (%)	Test Statistics *p*-value	Effect Size
Gender	Female	72 (69.9)	105 (70.0)	177 (70.0)	$\chi^2=0.000$ $p=0.987$	V = 0.001
	Male	31 (30.1)	45 (30.0)	76 (30.0)		
Education Level	Literate	1 (1.0)	2 (1.3)	3 (1.2)	$\chi^2=4.333$ $p=0.363$	V = 0.136
	Primary School	20 (19.4)	18 (12.0)	38 (15.0)		
	Secondary School	9 (8.7)	13 (8.7)	22 (8.7)		
	High School	22 (21.4)	46 (30.7)	68 (26.9)		
	Bachelor's or Higher	51 (49.5)	71 (47.3)	122 (48.2)		
Marital Status	Single	22 (21.4)	60 (40.0)	82 (32.4)	$\chi^2=9.867$ $\boldsymbol{p=0.002}$	V = 0.620
	Married	81 (78.6)	90 (60.0)	171 (67.6)		
Insurance	No insurance	8 (7.8)	14 (9.3)	22 (8.7)	$\chi^2=0.637$ $p=0.731$	V = 0.040
	Has an insurance	95 (92.2)	136 (90.7)	231 (91.3)		
Working Status	Working	40 (38.8)	66 (44.0)	106 (41.9)	$\chi^2=0.669$ $p=0.413$	V = 0.042
	Not working	63 (61.2)	84 (56.0)	147 (58.1)		
Income Level	Less than expenses	26 (25.2)	24 (22.7)	60 (23.7)	$\chi^2=1.697$ $p=0.428$	V = 0.075
	Equal to the expanses	53 (51.5)	89 (59.3)	142 (56.1)		
	More than expenses	24 (23.3)	27 (18.0)	51 (20.2)		
Family Structure	Living alone	7 (6.8)	18 (12.0)	25 (9.9)	$\chi^2=1.933$ $p=0.380$	V = 0.086
	Nuclear family	87 (84.5)	121 (80.7)	208 (82.2)		
	Extended family	9 (8.7)	11 (7.3)	20 (7.9)		
Smoking Status	Yes	31 (30.1)	42 (28.0)	73 (28.9)	$\chi^2=0.131$ $p=0.718$	V = 0.008
	No	72 (69.9)	108 (72.0)	180 (71.1)		
Alcohol Consumption	Yes	15 (14.6)	23 (15.3)	38 (15.0)	$\chi^2=0.028$ $p=0.866$	V = 0.002
	No	88 (85.4)	127 (84.7)	215 (85.0)		
Regular Exercise	Yes	35 (34.0)	53 (35.3)	88 (34.8)	$\chi^2=0.049$ $p=0.824$	V = 0.003
	No	68 (66.0)	97 (64.7)	165 (64.7)		
Visual Impairment	Yes	64 (62.1)	83 (55.3)	147 (58.1)	$\chi^2=1.161$ $p=0.281$	V = 0.073
	No	39 (37.9)	67 (44.7)	106 (41.9)		
Auditory impairment	Yes	9 (8.7)	9 (6.0)	18 (7.1)	$\chi2=0.693$ $p=0.405$	V = 0.044
	No	94 (91.3)	141 (94.0)	235 (92.9)		
MS Type	PPMS	5 (4.9)	4 (2.7)	9 (3.6)	$\chi2=5.601$ $p=0.061$	V = 0.249
	RRMS	93 (90.3)	145 (96.7)	238 (94.0)		
	SPMS	5 (4.9)	1 (0.7)	6 (2.4)		
Disease-modifying agent use	Yes	100 (97.1)	143 (95.3)	243 (96.0)	$\chi2=0.495$ $p=0.482$	V = 0.031
	No	3 (2.9)	7 (4.7)	10 (4.0)		
Comorbidity	Yes	33 (32.0)	35 (23.3)	68 (26.9)	$\chi2=2.355$ $p=0.125$	V = 0.148
	No	70 (68.0)	115 (76.7)	185 (73.1)		
		Fallers ($n=103$) Mean ± SD	**Non-Fallers ($n=150$) Mean ± SD**	**Total ($n=253$) Mean ± SD**	**Test Statistics *p*-value**	**Effect Size**
Age (years)		43.39 ± 9.92	38.42 ± 11.09	40.44 ± 10.88	t = 3.653 $\boldsymbol{p<0.001}$	g = 0.477
Disease Duration (years)		12.09 ± 7.54	10.15 ± 7.21	10.94 ± 7.39	t = 2.058 $\boldsymbol{p=0.041}$	g = 0.264
EDSS		3.23 ± 1.60	2.04 ± 1.11	2.53 ± 1.45	t = 7.004 $\boldsymbol{p<0.001}$	g = 0.894
MSIS-29		74.53 ± 25.67	56.11 ± 24.43	63.61 ± 26.49	t = 5.771 $\boldsymbol{p<0.001}$	g = 0.739
FES-I		32.88 ± 11.16	23.71 ± 9.17	27.45 ± 10.98	t = 7.146 $\boldsymbol{p<0.001}$	g = 0.915
FSS		5.01 ± 1.43	3.97 ± 1.93	4.39 ± 1.82	t = 4.662 $\boldsymbol{p<0.001}$	g = 0.596
BBS		46.14 ± 7.40	49.13 ± 5.98	47.91 ± 6.74	t = -3.545 $\boldsymbol{p<0.001}$	g = 0.453
T25FW		24.19 ± 12.43	18.44 ± 4.84	20.77 ± 10.42	t = 4.452 $\boldsymbol{p<0.001}$	g = 0.657

Table 2 (continued)

χ2 Chi-square test, *t* independent sample t-test, *SD* Standard deviation, *g* Hedge's g, *V* Cramer's V, *PPMS* Primary Progressive Multiple Sclerosis, *RRMS* Relapsing–remitting Multiple Sclerosis, *SPMS* Secondary progressive multiple sclerosis, *EDSS* Expanded Disability Status Scale, *MSIS-29* Multiple Sclerosis Impact Scale, *FES-I* Falls Efficacy Scale International, *FSS* Fatigue Severity Scale, *BBS* Berg Balance Scale, *T25FW* Timed 25-Foot Walk

Table 3 Optimized parameter of the best model – XGBoost Algorithm

Parameters	Values	Definition
Class name	XGBoostClassifier	Extreme Gradient Boosting
Booster	gbtree	Specifies which booster to use: gbtree (tree-based models), gblinear (linear models), or dart (Dropouts meet Multiple Additive Regression Trees)
Eta (Learning rate)	0.5	Controls the learning rate, i.e., the step size shrinkage used to prevent overfitting
Gamma (Minimum Loss Reduction)	10	Specifies the minimum loss reduction required to make a further partition on a leaf node of the tree. It is used to control overfitting
Max Bin	63	Defines the maximum number of bins that feature values will be bucketed into in histograms. This parameter is used with the histogram-based algorithm
Max Depth	6	Specifies the maximum depth of a tree. Increasing this value will make the model more complex and more likely to overfit
Max Leaves	255	Specifies the maximum number of leaves in each tree. It is an alternative to max_depth
Reg Alpha (L1 regularization)	0.104	L1 regularization term on weights. It can be used to add bias against large weights
Reg Lambda (L2 regularization)	1.146	L2 regularization term on weights. It is used to handle the overfitting problem
Subsample	0.7	Denotes the fraction of observations to be randomly sampled for each tree. It helps prevent overfitting

Table 4 Variable Importance of the Model

Variable	Importance
MSIS29	0.424
EDSS	0.406
Marital status	0.297
Education	0.240
Disease duration	0.185
Age	0.130
Family type	0.119
Smoking	0.031
Income level	0.031
Regular exercise habit	0.026

EDSS Expanded Disability Status Scale, *MSIS-29* Multiple Sclerosis Impact Scale

prevalence in married PwMS may be related to the less support equipment used in these individuals. However, in this study, the use of powered equipment was not investigated. Further studies are needed to investigate this relationship [5].

Fallers were older and had longer disease duration compared to the non-fallers in the present study. Piryonesi, Rostampour, and Piryonesi (2021) reported that participants' age and disease duration are two leading factors associated with falls [29]. Sosnoff et al. (2011) reported that fallers were older in their study [69]. Similarly, it was reported that the risk of falling is increasing with age [70]. Late ages are commonly linked with fragility, a high number of comorbidities, and decreased functional and psychological capacities [71]. This increases the risk of falls at late ages. Another reason is the association between age and disease duration. MS is a disease that typically has a mean age of onset of 20–30 years [72]. For this reason, there is a relationship between the participants' age and disease duration. Disease duration was reported as an important factor associated with an increased risk of falls in PwMS [5]. It was reported by Tajali et al. (2017) that the disease duration of the fallers was higher than non-fallers [19]. Givon et al. (2009) also reported that there was a positive correlation between disease duration and gait impairment [73]. We believe that there are two possible reasons for these relationships; (1) functional and gait impairment as the disease progresses and (2) a decrease in the functional capacity with aging.

In the present study, the EDSS scores of the fallers were high compared to the non-fallers. Similarly, Moen et al. (2011) reported that EDSS was associated with falls in PwMS [74]. Gunn et al. (2014) reported that the people with higher EDSS scores had a higher number of actual falls [75]. Similarly, Prosperini et al. (2011) reported that fallers had higher scores compared to the non-fallers in their study [76]. EDSS is the method of quantifying the disability of PwMS. For this reason, our results, also results of the studies reported in the literature, showed that frequency of the falls increases as the EDSS score (disability of the individuals) increases.

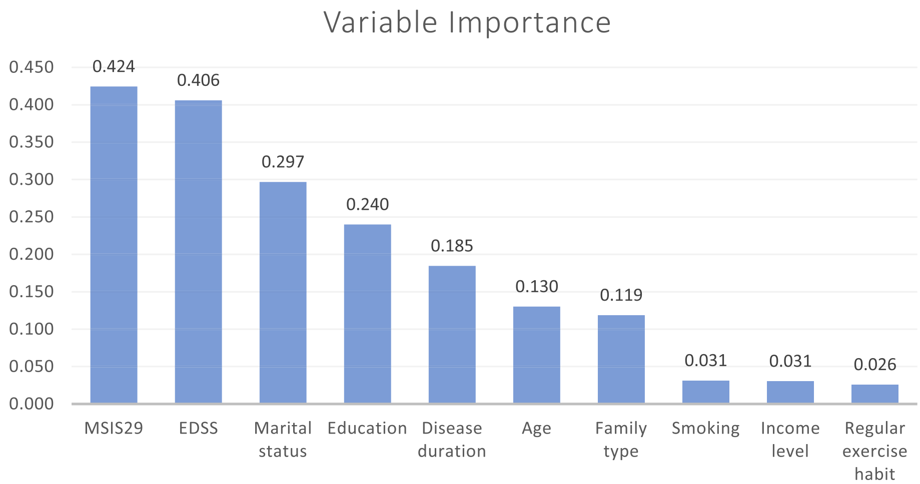


Fig. 3 Variable Importance in Machine Learning Analysis

Table 5 Performance of the model

Metrics	Scores
AUC/ROC	0.713
Accuracy	0.667
Precision	0.721
Recall	0.619
F1 score	0.663
Matthews Correlation Coefficient	0.311

AUC/ROC Area Under Curve / Receiver Operating Characteristic Under Curve

FES-I was the tool used to assess participants' concerns about falls in this study. FES-I scores were higher in fallers compared to non-fallers. There is a two-sided interaction between the fear of falling and falls in PwMS. Fear of falling affects gait and fall experience affects fear of falling [77, 78]. Similar to our findings, Khalil et al. (2017) reported that FES-I scores were higher in fallers compared to non-fallers [78]. However, in this study, the falls were evaluated retrospectively. For this reason, we were not able to diminish the side of this interaction. A protective study is suggested to investigate the side of the interaction between the fear of falling and falls in PwMS.

In the current study, FSS scores were higher in fallers compared to non-fallers. Rice et al. (2017) also reported that FSS scores were higher in fallers [79]. Vister et al. (2017) reported that the duration of the functions such as sitting was higher in those with higher FSS scores [80].

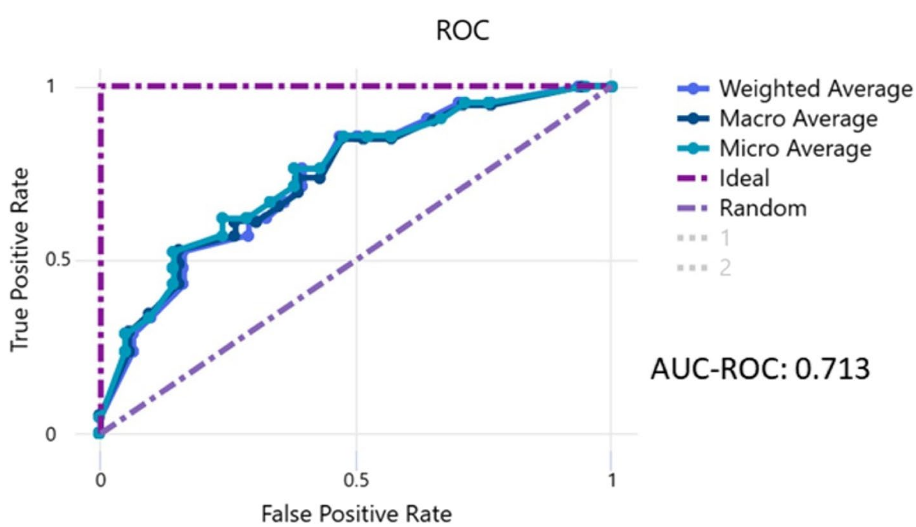
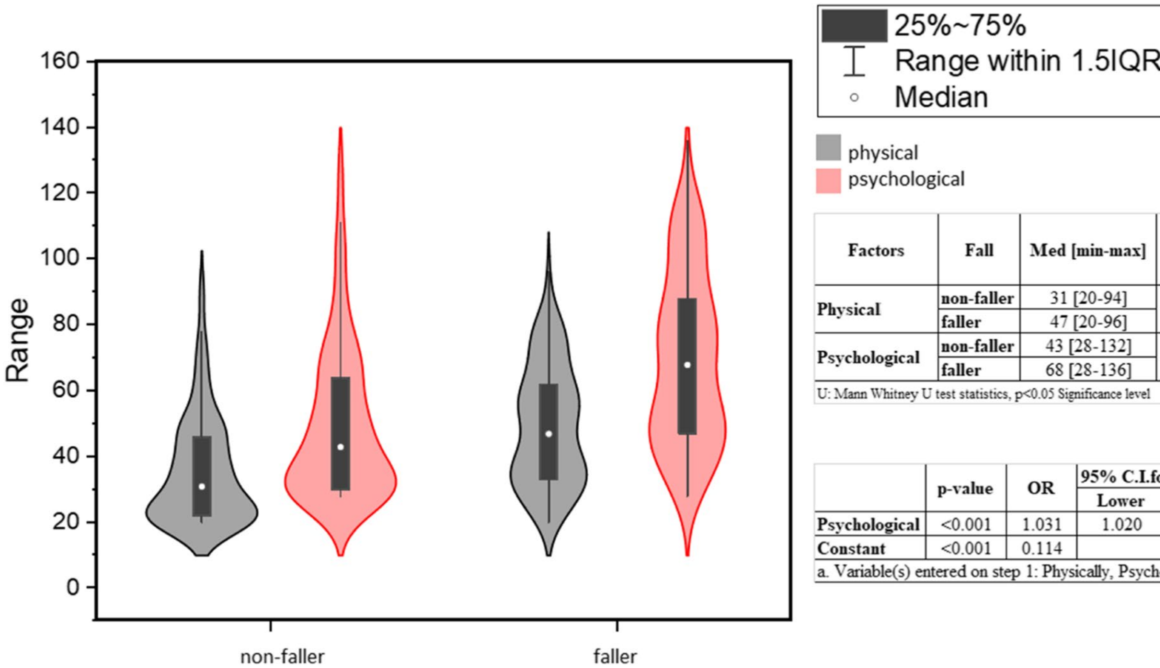


Fig. 4 AUC ROC for the prediction model



Factors	Fall	Med [min-max]	Test statistics; p-value
Physical	non-faller	31 [20-94]	U=4167.5
	faller	47 [20-96]	p<0.001
Psychological	non-faller	43 [28-132]	U=4130.5
	faller	68 [28-136]	p<0.001

U: Mann Whitney U test statistics, p<0.05 Significance level

	p-value	OR	95% C.I.for EXP(B)	
			Lower	Upper
Psychological	<0.001	1.031	1.020	1.043
Constant	<0.001	0.114		

a. Variable(s) entered on step 1: Physically, Psychological

Fig. 5 Regression estimates on the MSIS-29 subscales on falls

Our findings reflect the literature in this view. BBS was another scale used in this scale. Nilsagard et al. (2009) reported that BBS is one of the predictors of accidental falling in multiple sclerosis [81]. Similarly, Dibble et al. (2013) reported that among the two balance scales and one clinical balance assessment, BBS has the highest AUS point estimator with 0.71 [82]. However, contrary to other studies, Neuls et al. (2011) reported that BBS is not useful by itself in predicting falls in older adults with MS [83]. Even though our findings on the relationship between BBS and falls are similar to most of the studies in the literature, some studies reported findings contrary to ours.

In this study, T25FW duration was longer in fallers. Tajali et al. (2017) reported that T25FW is one of the significant predictors of falls in PwMS [19]. Similarly, Kolb et al. (2016) reported that PwMS reported a fall that took a longer duration to complete T25FW [84]. Stough et al. (2010) also reported that T25FW duration was significantly slower in fallers [85]. Sandroff et al. (2015) reported that T25FW durations are a useful assessment in discrimination between high and low fall risk [86].

In the current study, AUC/ROC, which is one of the performance metrics of machine learning, was 0.713. AUC ranged between 0.5 and 1, 0.5 means no apparent distributional difference between the parameters while 1 means perfect discrimination [87]. Although the cut-off score for AUC is controversial, Unal (2017) reported that AUC greater than 0.7 is considered high [87].

Sun et al. found that the RF classifier, based on sway metrics, exhibited high accuracy (> 86%) in distinguishing controls from individuals with MS. Sway sample entropy emerged as the most influential feature for classifying low-risk MS individuals from healthy controls. However, for all other comparisons, mediolateral sway amplitude proved to be the most robust predictor for fall risk groupings. The diagnostic performances of the RF algorithm ranged from 73.5% to 95.6%. In our study, we focused solely on individuals diagnosed with MS, aiming to predict the high-fall-risk group identified by domain experts. As a result, we achieved an accuracy level of approximately 70% [28].

In recent years, MS prediction using genetic data has gained prominence in the literature, achieving accuracy values exceeding 0.75. In our study, with a focus on determining the risk factors of fall, we obtained high AUC and accuracy values using tests and demographic data. The results suggest that combining individuals' demographic, clinical, and genetic data can lead to highly accurate predictions [16, 88, 89]. XGboost is a relatively new method, developed in 2016, in machine learning and is well-known for it is advantages compared to other methods [49]. To our knowledge, this is the first study using XGboost to predict falls in multiple sclerosis.

The results of this study presented a multifactorial risk assessment with demographic, physical, cognitive, social and environmental dimensions related to falls in people with MS. These results may help healthcare professionals to better analyse patients and identify risk factors. The findings will encourage multidisciplinary collaboration between specialists in neurology (neurologists, nurses), physiotherapy, psychology, social work and other related fields. A multidisciplinary approach ensures that all of the patient's needs are addressed in a comprehensive way. In addition, the results of this study may guide future studies in larger and different groups of neurological patients, especially those at risk of falls, to obtain broader and more generalisable results. The results of the study may contribute to the development of technological solutions (smart home systems) and environmental regulations (use of assistive devices, home organisation) to reduce the risk of falls. In addition, the results may contribute to the development of clinical guidelines and health policies that include fall prevention strategies.

Limitations

The data on falls were collected retrospectively and the study was conducted in a single centre. For this reason, the generalizability of the study is limited. People with other conditions which may affect the balance were excluded from the study. This is a limitation of the generalizability of the study. FSS, BBS, and T25FW were not included in the analysis because they might be affected by the fall experience. This is another limitation for the study. Balance and falls are complex phenomena and may be influenced by many cognitive, physical, physiological or social factors. Therefore, other potential confounding factors not listed in this manuscript are another limitation of this study.

Conclusion

This study revealed that MSIS-29, EDSS, marital status, education level, disease duration, age, family type, smoking, income level, and regular exercise habits were the risk factors of falls in PwMS. This estimation has 71% accuracy. We recommend further studies in larger samples and different populations. MSIS-29 was the most important variable contributing to the falls in PwMS. The use of machine learning approaches can be a great decision support tool to determine the risk factors of falls.

Regarding the clinical implications of the current study, we recommend practices according to the modifiable and non-modifiable risk factors. Smoking and regular exercise were the modifiable factors contributing to falls in PwMS. We recommend that clinicians facilitate the modification of these factors in PwMS. Age and disease duration were non-modifiable factors. These should be considered as risk increasing factors and used to identify PwMS at risk. Interventions aimed at reducing MSIS-29 and EDSS scores will help to prevent falls in PwMS. Education of individuals to increase knowledge and awareness is recommended. Financial support policies for those with low income will help to reduce the risk of falls.

Clinicians should comprehensively assess the physical and psychological status of patients using MSIS-29 and EDSS scores, which play a critical role in determining fall risk. Individualised physical rehabilitation programmes including balance, coordination and muscle strengthening exercises are recommended for patients with high MSIS-29 and EDSS scores. In addition, the provision of counselling and support groups for psychologically distressed patients may reduce the risk of falls. Family members of married patients should be educated about MS and fall risks and how to help their patients. Educational programmes on MS and fall prevention for patients with low educational levels can increase patient awareness and reduce the risk of falls. Patients with low income levels can be helped to set up economic support programmes that provide facilities for access to health services, assistive devices and environmental modifications. Individualised programmes with regular follow-up and assessment can be planned for patients of advanced age and disease duration. Smoking cessation interventions can be planned for patients who smoke.

In conclusion, we emphasise the importance of an individualised multidisciplinary approach with continuous follow-up and evaluation by clinicians, taking into account the socio-demographic characteristics of patients, to prevent or reduce falls in people with MS.

Supplementary Information

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Supplementary Material 1.

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Authors' contributions

Su Özgür: Conceptualization, Methodology, Formal Analysis, Writing—Original Draft, Investigation Meryem Koçaslan Turan: Conceptualization, Methodology, Data Curation, Writing—Original Draft, Investigation İsmail Toygar: Conceptualization, Methodology, Validation, Formal analysis, Writing—Original Draft, Supervision, Visualization, Writing—Review & Editing, Gizem Yağmur Yalçın: Conceptualization, Methodology, Data Curation, Writing—Original Draft, Investigation Mefkure Eraksoy: Conceptualization, Methodology, Data Curation, Writing—Original Draft, Investigation.

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Availability of data and materials

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Written permission was obtained from the Uskudar University Medical Research Ethical Committee of the relevant university (Protocol: E-29624016–050.99–1669762). Informed consent was read and signed by each participant. All principles of the Helsinki Declaration were followed throughout the study. A document indicating that the study had been reviewed by the ethics committee was obtained prior to the start of the study. Before patients were enrolled in the study on a voluntary basis, the Informed Voluntary Consent Form, which contained clear and understandable information about the purpose, method, duration, possible risks and benefits of the study, was obtained in writing in a face-to-face interview. Until the end of the research, we acted in accordance with the purpose and ethical rules (reporting research results accurately and honestly, including negative results, keeping participants' personal information confidential and using it only for research purposes). In addition, measures were taken to minimise potential harm to patients, particularly the risk of falling, and participants were informed of this risk.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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