Turkish Journal of Neurology

Turk J Neurol 2025;31(4):440-449
Doi: 10.55697/tnd.2025.511

ORIGINAL ARTICLE

Development of restless legs syndrome severity prediction models for people with multiple sclerosis using machine learning

Ergi Kaya[1], Murat Emeç[2], Asiye Tuba Özdoğar[3], Ela Simay Zengin[4], Hilal Karakaş[5], Seda Daştan[5], Cavid Baba[5], Mehmet Hilal Özcanhan[6], Serkan Özakbaş[4]

[1]Department of Neurology, Dokuz Eylül University Faculty of Medicine, İzmir, Türkiye
[2]Department of Informatics, İstanbul University, İstanbul, Türkiye
[3]Department of Physiotherapy, Van Yüzüncü Yıl University Faculty of Medicine, Van, Türkiye
[4]Department of Neurology, İzmir University of Economics, İzmir, Türkiye
[5]Department of Physiotherapy and Rehabilitation, İstanbul Bilgi University, Faculty of Health Sciences, İstanbul, Türkiye
[6]Department of Computer Engineering, Dokuz Eylül University, İzmir, Türkiye

ABSTRACT

Objectives: This study aimed to develop an artificial intelligence-supported restless legs syndrome (RLS) severity prediction model for people with multiple sclerosis using machine learning methods.

Patients and methods: Twenty-three individuals (14 females, 7 males; mean age: 40.6±10.9 years; range, 33 to 44 years) with multiple sclerosis with RLS were included in this observational study between March 2022 and March 2023. The International Restless Legs Syndrome Study Group Rating Scale was used to determine the RLS severity of the participants. The age, sex, body mass index, regular exercise habits, disease duration, Expanded Disability Status Scale (EDSS), estimated maximal aerobic capacity (VO_2max), Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale, Multiple Sclerosis International Quality of Life Questionnaire, Multiple Sclerosis Walking Scale-12 (MSWS-12), and timed 25-foot walk test were determined as predictive variables. A correlation matrix was created. DecisionTree, RandomForest, and XGBoost machine learning methods were used to develop a model for predicting the RLS severity.

Results: According to the obtained correlation matrix, PSQI scores strongly correlated with RLS severity (Pearson r=0.76). Meanwhile, EDSS scores (0.49), MSWS-12 scores (0.45), and disease duration (0.45) showed moderate correlations with RLS. Among the three different meachine learning methods, XGBoost demonstrated the best performance in predicting the severity of RLS, with a mean absolute error of 1.94, mean squared error of 4.58, mean absolute percentage error of 0.0735, and a test accuracy of 92.65%. The results showed that the severity of RLS could be estimated with 92.65% accuracy.

Conclusion: This study showed a strong correlation between PSQI scores and RLS severity and that RLS severity could be predicted using machine learning methods.

Keywords: Machine learning, multiple sclerosis, quality of life, restless legs syndrome, sleep quality.

Sleep disorders affect 74% of people with multiple sclerosis (MS), and are associated with increased fatigue and daytime sleepiness.[1,2] Furthermore, sleep deprivation was linked to oxidative stress bouts that have a toxic effect on oligodendrocytes and, thus, myelin damage.[3] Despite these harmful effects, clinicians may underestimate the conditions related to sleep, or their evaluation and management may be overlooked in routine clinical practice. Restless legs syndrome (RLS) is among the most frequently reported sleep disturbances.[4] The prevalence of

Correspondence: Ergi Kaya, MD. Dokuz Eylül Üniversitesi Tıp Fakültesi, Nöroloji Anabilim Dalı, 35340 İnciraltı, İzmir, Türkiye.
E-mail: ergikaya@gmail.com

Received: July 11, 2025 **Accepted:** November 13, 2025 **Published online:** December 08, 2025
Cite this article as: Kaya E, Emeç M, Özdoğar AT, Zengin ES, Karakaş H, Daştan S, et al. Development of restless legs syndrome severity prediction models for people with multiple sclerosis using machine learning. Turk J Neurol 2025;31(4):440-449. doi: 10.55697/tnd.2025.511.

RLS in people with MS ranges between 13.2% and 65.1% and is 5.6 times higher than in the general population.[5]

Innovative physical activity and correlation measurement methods have recently emerged in the literature. Miniaturized accelerometers and gyroscopes, for example, are widely used to measure human movements and physical performances. Machine learning (ML), another cutting-edge technology, determines the relationships between physiological events and their factors. Machine learning is a branch of computer science that applies expert mathematical algorithms to simulate human learning. Machine learning algorithms are currently widely used in healthcare. Statistical expert algorithms are used in ML to train a learning model to identify correlations among analyzed data, classify results, determine the importance of the features involved in that specific model, and assist in decision-making. By providing sensitive algorithms, ML was successfully used in studies to identify people with MS, predict diagnosis, and monitor disease severity.[6-11]

The present study aimed to use ML methods to investigate the relationship between RLS severity in people with MS and their sleepiness state, demographic, clinical, physical data, and survey parameters.

PATIENTS AND METHODS

This observational study included 23 individuals with MS and RLS (14 females, 7 males; mean age: 40.6±10.9 years; range: 33 to 44 years) who were evaluated at the MS Clinic of Dokuz Eylül University Faculty of Medicine, between March 2022 and March 2023. The Demyelinating Disease Clinic cohort was used to recruit patients. Inclusion required being over the age of 18, having relapsing-remitting MS according to the 2017 McDonald criteria, and meeting the RLS criteria recently established by the International Restless Legs Syndrome Study Group.[4,12] Exclusion criteria included having a disability that would interfere with or prevent performance on physical tests, having orthopedic surgery on the ankle, foot, knee, hip, or spine at any time, having a severe cognitive or psychiatric impairment, having congestive heart failure, coronary artery disease, cerebrovascular disease, chronic obstructive pulmonary disease, polyneuropathy, or hypertension. All participants gave written informed consent. The study protocol was approved by the Dokuz Eylül University Ethics Committee (Date: 30.03.2022, 6965-GOA 2022/12-18). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Before the test, participants were instructed to avoid alcohol, cigarettes, food, and caffeine and not to exercise for 3 h. During the experimentation, patients cycled for 6 min at 50, 75, 100, 125, or 150 watts on a bicycle ergometer, or as close to one of these watts as possible. A pedal speed of 50±5 rpm was maintained throughout the test. The heart rate was measured using a polar heart rate sensor, and the pulse was kept between 120 and 170 beats per minute. The patient's sex, weight, age, and values obtained from submaximal exercise testing (pulse rate, workload) were used to calculate maximal aerobic capacity (VO_2max) using the Astrand-Rhyming nomogram (Figure 1).[13,14]

Basal and clinical characteristics of the participants, including age, sex, body mass index, regular exercise status, disease duration, Expanded Disability Status Scale (EDSS) scores, timed 25-foot walk (T25FW) results, Epworth Sleepiness Scale (ESS), Pittsburgh Sleep Quality Index (PSQI), Multiple Sclerosis International Quality of Life (MusiQoL), and Multiple Sclerosis Walking Scale-12 (MSWS-12) surveys, were determined before the experimentation. Severity of RLS was calculated using the International Restless Legs Syndrome Rating Scale (IRLSRS). The IRLSRS score was used as the dependent variable in the analysis.

Basal and clinical values, physical test scores, survey scores, and experimentation results were entered into ML algorithms. The correlations between IRLSRS, ESS, EDSS, T25FW, PSQI, MusiQoL, and MSWS-12 scores and their potential explanatory factors were numerically validated using statistical and ML approaches.

The EDSS score is a valid and reliable method for determining disability, developed by Kurtzke.[15] It is the most common disability measurement scale in people with MS and relies on the neurological examination and ambulation performance.

The T25FW test was used to assess lower extremity performance and ambulation in people with MS. It is a quantitative and reliable disability measurement method.[16] On the other hand, MSWS-12 was used to determine the impact of MS on walking abilities and measured the participant-reported ambulatory performance. Higher scores indicate worse walking performance in people with MS.[17]

The ESS, a questionnaire consisting of eight questions, was used to evaluate daytime sleepiness in participants.[18] Sleep quality was assessed using the PSQI, a self-reported sleep quality measurement method.[19]

An international study group developed the MusiQoL to measure self-reported quality of life in people with MS. It has twelve sections and a total of 54 questions.[20]

The IRLSRS was developed to consider the severity of the RLS symptoms. It has 10 questions, each scored on a scale from 0 to 4.[21]

Statistical analysis

Statistical analyses were performed using Python (SciPy and statsmodels). The Pearson correlation coefficients and two-sided p-values were calculated to assess pairwise associations between the IRLSRS (dependent variable) and candidate predictors. To control for type 1 error arising from multiple comparisons, both Bonferroni correction (family-wise error rate) and the Benjamini-Hochberg procedure (false discovery rate) were applied. Given m=12 comparisons, the Bonferroni adjusted significance threshold was set at α Bonf=0.05/12=0.00417. We reported unadjusted *p* values together with Bonferroni-adjusted *p* values and false discovery rate (FDR) q values. Associations were considered robust if they remained significant after Bonferroni correction, whereas associations significant only by FDR were interpreted as exploratory and in need of independent replication.

Data preprocessing

The test results were entered into a table as rows, one for each patient. The table was later

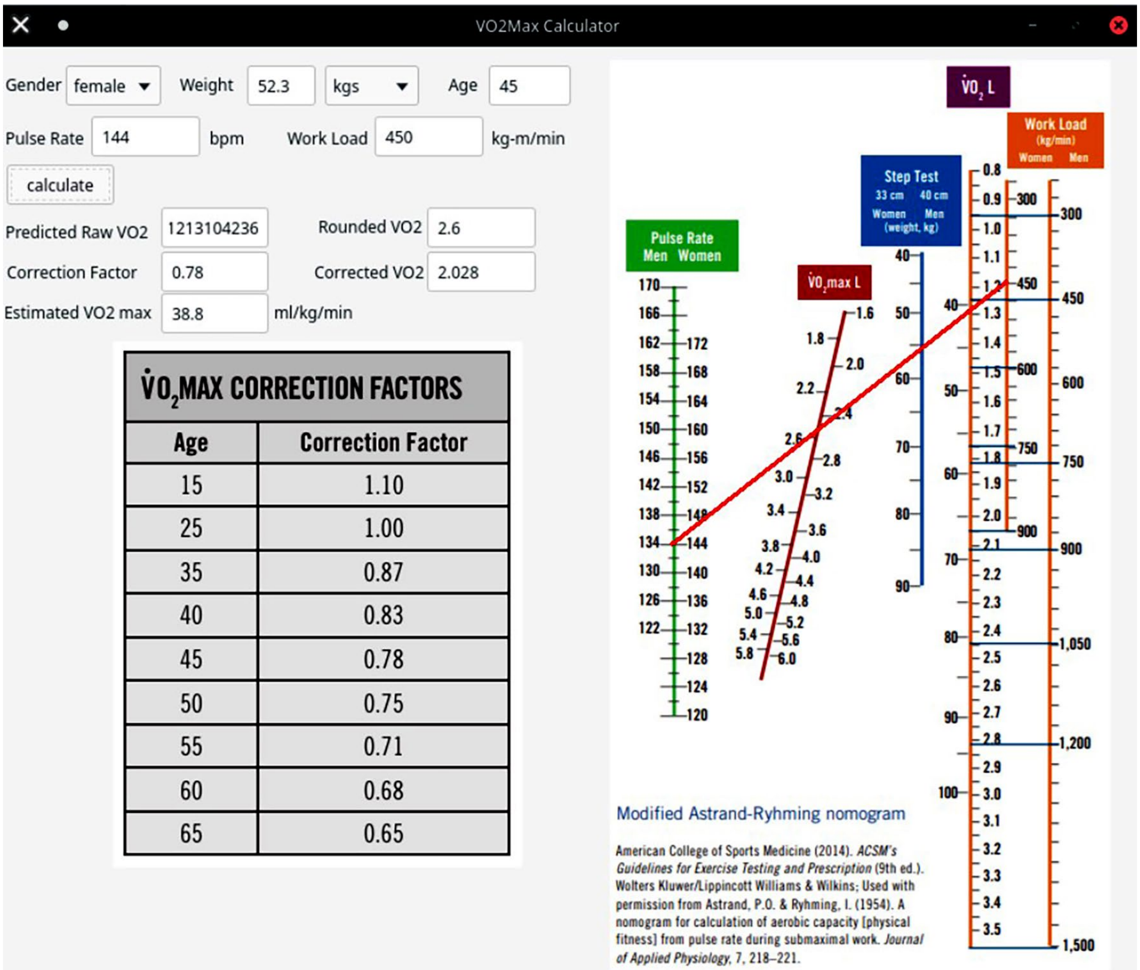

Figure 1. VO_2max calculator application graphical user interface (Astrand-Rhyming nomogram).

stripped of names and sequentially numbered, resulting in an anonymous dataset. The dataset was divided into train and test parts, with 80% used for training and 20% for testing predictions.

The hardware and software used

The analyses were performed on a computer with a Ryzen 5 1500 CPU (six cores, 12 threads), NVidia RTX 2600 GPU, and 32 GB main memory, running the Manjaro Linux operating system with Kernel 5.15.28 Preemptive. Analyses were conducted using Python programming language, the web-based interactive computing platform Jupyter notebook, and Seaborn, Pandas, Numpy, Scikit-learn (sklearn), and XGBoost libraries.

Astrand-rhyming nomogram software

Manually drawing lines on the Astrand-Rhyming nomogram contains an impractical human error. Thus, an electronic version of the nomogram was created to calculate the VO_2max value for each patient. Figure 1 depicts the user interface of the developed software. The VO_2max value was calculated using the multiple linear regression algorithm. The software development used the Python programming language and the Qt graphical user interface development tool. The pseudo-VO_2max values were calculated and tested using randomly generated values for sex, weight, age, and pulse rate. The R-squared (R^2) and mean squared error values of the pseudo-VO_2max were used to assess the tool's accuracy.

Machine learning algorithms

We treated the prediction of IRLSRS as a supervised regression task and evaluated three tree-based regression algorithms: Decision Tree, Random Forest, and XGBoost. The dataset was randomly split into training (80%) and test (20%) sets with a fixed random seed to ensure reproducibility. Hyperparameter tuning was performed on the training set using a grid search with five-fold cross-validation. The final models were refitted on the entire training set using the best hyperparameters selected by cross-validation. Hyperparameters explored included, for example, tree depth, number of estimators, minimum samples per leaf (for Decision Tree/Random Forest), and learning rate, max_depth, and n_estimators (for XGBoost).

Model performance was evaluated on the held-out test set using standard regression metrics: mean absolute error (MAE), mean squared error (MSE), mean absolute percentage error (MAPE) and R^2 (explained variance). To provide an intuitive, clinically interpretable measure, we also reported the proportion of test predictions that fell within a prespecified margin of the observed IRLSRS (reported in the manuscript as "test accuracy"); the margin used was stated in the Results. All reported metric values in Abstract and Results were harmonized to reflect this definition.

Feature importance for tree-based models was obtained from each algorithm's built-in importance measure (mean decrease in impurity for Decision Tree and Random Forest; gain-based importance for XGBoost). Where relevant, conclusions about feature ranking were based on concordant importance across multiple algorithms. For transparency and reproducibility, the final hyperparameter settings, cross-validation details, and the code used for model fitting and evaluation are provided in the Supplementary Materials (or are available from the authors upon request). Analyses were implemented in Python using scikit-learn and XGBoost libraries.

RESULTS

Table 1 displays the participants' baseline and clinical data.

Correlation matrix

A correlation matrix was used to analyze the factors collected and graded during the questionnaires and the assessed scores and estimated VO_2max (Figure 2). The highest correlation values between IRLSRS scores and a possible factor were found in PSQI (r=0.76), EDSS (r=0.49), MusiQoL (r=–0.49), and MSWS-12 (r=0.45) scores, disease duration (r=0.45) and T25FW test results (0.41). The estimated VO_2max had a weak correlation with the ESS scores (r=0.32). No other discernible relationship was detected between the severity of RLS and any of the factors. To account for multiple comparisons (m=12), we applied Bonferroni and Benjamini-Hochberg corrections (Bonferroni alpha=0.05/12=0.00417). After correction, the strongest association between PSQI scores and IRLSRS severity remained highly significant (r=0.76, unadjusted p<0.0001; Bonferroni adjusted p=0.0003; FDR q=0.0003). In contrast, the correlation between EDSS and IRLSRS scores (r=–0.49, unadjusted p=0.0166) and between MSWS 12 and IRLSRS scores (r=0.49, unadjusted p=0.0174) did not survive the conservative Bonferroni correction (Bonferroni adjusted p=0.1992 and 0.2088, respectively). It was

TABLE 1
Basal and clinical characteristics of the study participants

	n	%	Mean±SD	Median	Min-Max
Age (year)			40.6±10.9		
Sex					
Female	14	60.9			
Male	9	39.1			
Regular exercise					
Yes	16	69.6			
No	7	30.4			
Disease duration (year)			9.0±6.52		
Body mass index			25.07±4.16		
Expanded Disability Status Scale			1.85±1.63		
RLS severity score				26.0	19.0-32.0
Estimated VO_2max				41.9	26.30-50.55
T25FW (sec)			5.32±1.76		
MSWS-12			24.91±13.21		
Pittsburgh Sleep Quality Index			9.70±4.02		
Epworth Sleepiness Scale			25.30±8.31		
MusiQoL			62.90±17.56		

SD: Standard deviation; RLS: Restless Legs Syndrome; T25FW: Timed 25 foot walk; MSWS-12: Multiple Sclerosis Walking Scale-12; MusiQoL: Multiple Sclerosis International Quality of Life.

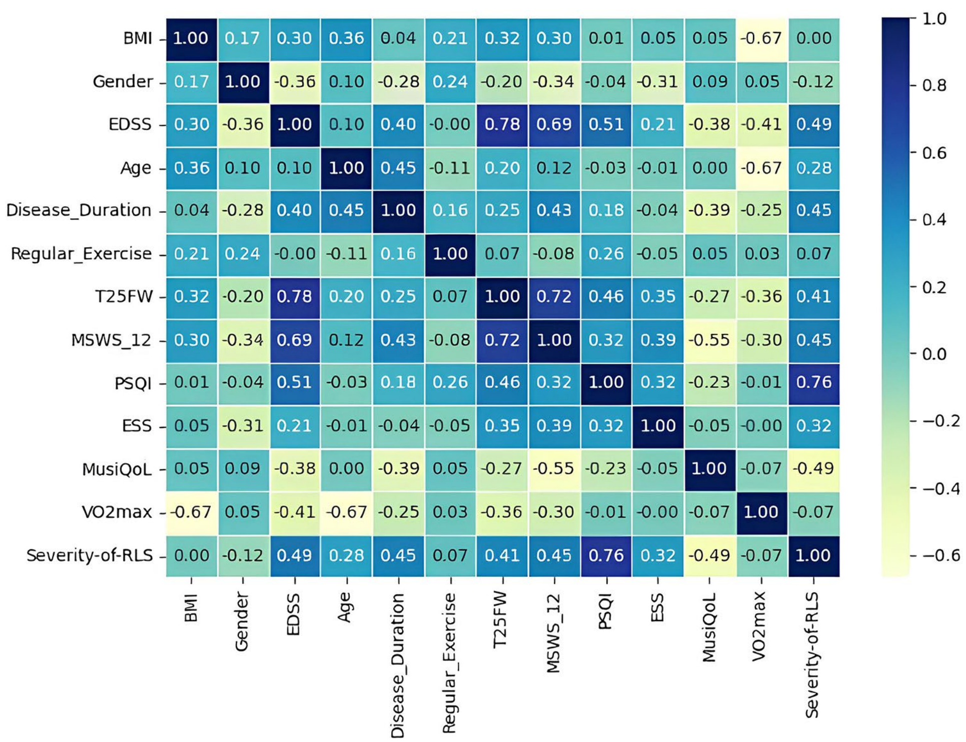

Figure 2. The correlation matrix of the observed factors.

BMI; Body mass index; EDSS: Expanded Disability Status Scale; T25FW: Timed 25 Foot Walk; MSWS-12: Multiple Sclerosis Walking Scale-12; PSQI: Pittsburgh Sleep Quality Index; ESS: Epworth Sleepiness Scale; MusiQoL: Multiple Sclerosis International Quality of Life.

TABLE 2
The first five most important factors for the RLS severity, according to three algorithms

Algorithm	Factor	Importance score
DecisionTree	PSQI	0.572802
	MusiQoL	0.264720
	T25FW	0.038245
	ESS	0.026164
	Sex	0.021400
RandomForest	PSQI	0.42466652039504693
	MusiQoL	0.28901231289572843
	MSWS-12	0.05552458253952133
	ESS	0.04774889892991736
	Age	0.045216751671194065
XGBoost	PSQI	0.55161566
	VO_2max	0.13963656
	ESS	0.13091928
	BMI	0.05600845
	MusiQoL	0.041978948

RLS: Restless legs syndrome; PSQI: Pittsburgh Sleep Quality Index; MusiQoL: Multiple Sclerosis International Quality of Life; T25FW: Timed 25 Foot Walk; ESS: Epworth Sleepiness Scale; MSWS-12: Multiple Sclerosis Walking Scale-12; BMI; Body mass index.

only nominally significant under FDR (q≈0.0696). These adjusted p-values were reported to indicate the associations that were robust to multiple testing. The next session examines the implications of the correlation values.

The most important factors for the RLS severity score

DecisionTree, RandomForest, and XGBoost ML methods were used to determine each feature's importance score in the present analysis. The features were listed from top to bottom, according to their importance values. Afterward, each algorithm's first five most important features were determined. The most important common factors affecting IRLSRS scores are summarized in Table 2. The PSQI score was identified as the most important factor affecting IRLSRS scores across all three algorithm results. The significance of the importance analysis is discussed in the next section.

The performance of ML models in estimating RLS severity was assessed using various evaluation metrics common in ML performance evaluation. The results are summarized in Table 3. The results provide insights into the accuracy and reliability of each model in predicting RLS severity. The performance evaluation helps in deciding the final model.

Among the models, hyperparameter-tuned XGBoost demonstrated the best performance by achieving the lowest errors, MAE (1.944), MSE (45.880), and MAPE (0.0735), along with the highest accuracy (92.65%), indicating that XGBoost was the most effective model for estimating RLS severity based on the selected features. Random Forest also performed well, with a test accuracy of 90.48%, but its error metrics were higher than XGBoost. The Decision Tree model showed the lowest performance, with the highest MAE (3.000), MSE (130.000), and MAPE (0.1183), as well as the lowest test accuracy (88.17%).

Our explorative study showed that the ML results were consistent with classic statistical correlation analysis. In addition, ML analysis revealed the same factors not highly related to our dependent variable (IRLSRS scores), agreeing with the correlation matrix in Figure 2. Machine learning algorithms consistently found associations between RLS severity and sleep quality, sleepiness state, and cardiovascular fitness. Next, the agreement between the real RLS severity values and the predicted RLS severity values was closely examined.

The Bland-Altman plot in Figure 3 illustrates the agreement between the true and predicted RLS severity values. The x-axis represents the mean of the true and predicted values, while the

TABLE 3
Performance metrics of ML models for RLS severity estimation

ML model	MAE	MSE	MAPE	Test accuracy (%)
XGBoost (hyperparameter tuning)	1.944	45.880	0.0735	92.65
Random forest	2.583	96.635	0.0952	90.48
Decision tree	3.000	130.000	0.1183	88.17

ML: Machine learning; RLS: Restless legs syndrome; MAE: Mean absolute error; MSE: Mean squared error; MAPE: Mean absolute percentage error.

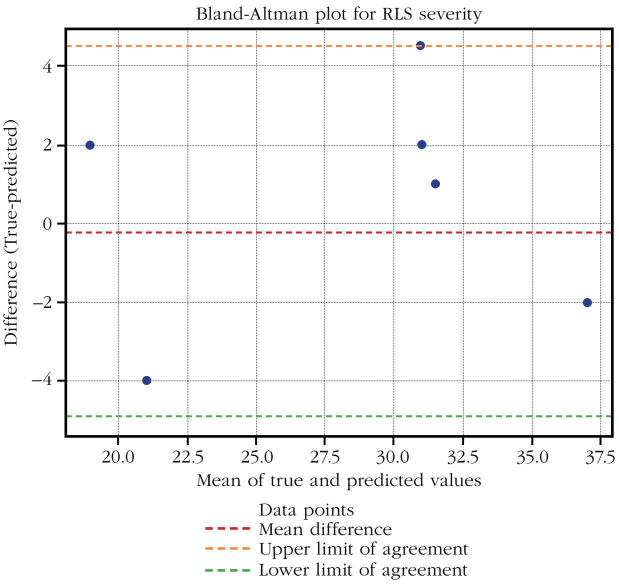

Figure 3. Bland-Altman plot for RLS severity.
RLS: Restless legs syndrome.

y-axis shows the difference between the true and predicted values (True-Predicted). The red dashed line indicates the mean difference, which reflects the average bias between the true and predicted values.

The plot demonstrated that the ML model provided reliable predictions for RLS severity, with only minor deviations observed in a few cases, supporting the model's accuracy and consistency in estimating RLS severity.

DISCUSSION

In this exploratory study, we showed that ML results for correlation analyses were similar to those of classic statistical tests. We explicitly addressed multiple comparison bias by applying Bonferroni and Benjamini-Hochberg corrections. The primary finding (a robust positive association between sleep quality [assessed by PSQI] and RLS severity) remained significant after conservative Bonferroni correction, reinforcing its prominence. Several secondary associations (e.g., EDSS and MSWS 12 scores) were attenuated after Bonferroni adjustment and should therefore be regarded as exploratory; these require confirmation in larger, independent cohorts. In addition, ML revealed factors not associated with our dependent variables in the correlation matrix. Machine learning algorithms were consistent in their results regarding associations between sleep quality, RLS severity, sleepiness state, and cardiovascular fitness.

Restless legs syndrome is highly prevalent in people with MS. Different cohorts established contradictory results regarding the presence of RLS and its relation to age and disease duration in MS.[5] However, RLS severity did not show any correlation with age and disease duration in this patient group.[5,22-24] We found a moderate positive correlation between IRLSRS scores and disease duration (r=0.45). According to the results of the ML analysis, disease duration did not play a significant role in RLS severity. The fact that RLS severity and occurrence of RLS were unrelated to age and disease duration may suggest a special link between RLS and MS. A weak positive correlation between body mass index and IRLSRS score was detected in a study.[25] However, the number of participants was low, and further results that were in line with our research were established.[24,25] The relationship between EDSS scores and RLS severity is complex. Although some studies indicated a weak positive correlation between EDSS scores and RLS severity, the relation was not detected in other studies.[22,24-26] However, RLS severity might be related to lower extremity performance in people with MS.[25,26] Our correlation analysis demonstrated that EDSS scores and T25FW test results had a moderate positive correlation with RLS severity, which was also reflected in patient-reported walking performance. Additionally, in ML analysis, the most important variables predicting RLS severity were T25FW test results and MSWS-12 scores. The severity and localization of central nervous system damage might have played a role in the relationship between RLS severity and physical performance in people with MS. However, the fact that EDSS scores and lower extremity performance results were different suggests that more comprehensive studies are required to shed light on this issue.

Restless legs syndrome in people with MS can decrease the quality of sleep. Various studies demonstrated that sleep quality deteriorates with the severity of RLS symptoms.[25,27,28] Moreover, RLS may also affect cognitive performance by impairing sleep quality.[29] Although daytime sleepiness is more prevalent in people with MS with RLS, studies did not show a relationship between RLS severity and daytime sleepiness.[25,27,28] Quality of life in people with MS is significantly affected by RLS severity, disability, and physical performance.[2,25] In our study, RLS severity had a strong positive correlation with sleep quality, and quality of life had a moderate positive correlation with RLS severity. In ML analysis, the two most important factors in RLS severity were sleep quality and quality of life. Therefore, the diagnosis and effective treatment of RLS in people with MS is important and can enhance their related quality of sleep and life.

A sedentary life and low regular physical exercise might be an important factor in RLS severity.[30] A study suggested a relationship between RLS severity and reduced physical function; however, another study demonstrated no relationship between them.[26,31] It was found that sedentary behavior patterns were positively correlated with RLS severity.[31] On the other hand, physical activity level and fatigue are related to cardiovascular fitness and can be predicted by a sedentary lifestyle or time spent in leisure activities. Maximal aerobic capacity is a tool for measuring cardiovascular wellness, and it is a valid method in people with MS.[32] As a result, VO_2max could be used to investigate the relationship between RLS severity and an active lifestyle or a person's tolerance to physical exercise load.[33] In our study, we found no relationship between regular exercise and the severity of RLS in both ML and correlation analysis. Cardiopulmonary fitness was found to be related to disability and physical performance in people with MS.[34-36] Grey volume loss, particularly insular lesion volume and volume loss, can cause low cardiopulmonary performance in people with MS.[36] Cardiopulmonary fitness level (VO_2max) did not exhibit a relation with physical performance or disability accumulation in our study. However, it showed a weak positive correlation with ESS scores. Our analysis did not identify any casualties, and the results must be interpreted with caution due to the limited number of participants and the level of correlation. However, in XGBoot analysis, VO_2max level was determined as the second most important factor after sleep quality in predicting RLS severity, indicating that cardiopulmonary wellness may be a predictor of RLS severity. The fact that exercise significantly reduces the severity of RLS and increases the quality of sleep in people with MS was established in prior studies.[37,38] Routine exercises and training for high cardiopulmonary fitness may directly cause an alleviation in RLS severity and related worse outcomes.

The use of ML methods in neurology and daily clinical practice is an evolving field. It is used in imaging interpretation, early disease diagnosis, or detection of progression in neurological diseases.[39] A study demonstrated an accurate ML method that could predict RLS diagnosis by considering wearables and smartphone data. This ML method could enhance the early diagnosis of RLS.[40] Our ML model successfully predicted the severity of RLS. The efficient use and development of ML methods for RLS severity in the MS population might be important. Limited time for clinical examination and assessments used in MS may lead to underestimation of RLS severity. Our ML-based prediction model can be an assistive tool in detecting RLS severity. Symptoms of RLS may be confused with neuropathic pain, leg cramps, and other factors.[41] Predicting the severity of RLS can help us understand how much RLS bothers the patient compared to different symptoms and thus indicate which symptoms we need to control. Furthermore, it can be used to assess the efficacy of RLS treatments in MS. Therefore, an ML-based assistive tool that predicts RLS severity may be helpful in daily practice for symptom management in MS. New studies and models with large numbers of participants can enhance the predictive value and generalizability of ML models. Additionally, using wearable or smartphone variables can improve the accuracy of ML-based models.

This study had several limitations. First, the low number of participants was one of the main limitations. The low number of participants may limit the generalizability of the results. The participants had a low mean EDSS score, another obstacle to the generalizability of our results in people with MS. Since we measured cardiopulmonary fitness, people with MS with high disability may have been unable to take part in this study. Studies in populations with higher disability levels can provide more information, particularly about cardiopulmonary wellness and its relationship to RLS or sleep measurements. We did not examine the lesion location, lesion volume, or grey matter volume in the study. As mentioned above, insular lesion volume might be related to cardiopulmonary wellness.[36] Furthermore, RLS itself can disrupt physiological hypothalamic-pituitary-adrenal system functions and autonomic disturbance in the general population.[42] Therefore, a detailed analysis of magnetic resonance imaging metrics in people with MS with RLS can establish the relationship between RLS and cardiopulmonary fitness.

In conclusion, there is a substantial amount of evidence to support the idea that sleep disturbances contribute to the aggravation of chronic health issues or the difficulty in managing current ones. Sleep deprivation and RLS are two medical conditions that can reduce the quality of life in people with MS. Knowing the association between these two conditions may help with managing the day-to-day symptoms of MS, as alleviating the severity of RLS may help with insomnia. However, improved sleep quality may minimize other associated difficulties.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Contributed the idea/concept of the study: A.T.O., M.E., S.D.; Designed the study: A.T.O., M.E., C.B., H.K.; Collected and processed the data: E.S.Z., H.K., S.D., C.B., S.O.; Did the analyses: E.K., A.T.O., M.E., M.H.O.; Did the literature review and wrote the manuscript: E.K.,A.T.O., M.E.; Did the critical review and supervised the study: M.H.O., S.O.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: The authors received no financial support for the research and/or authorship of this article.

REFERENCES

1. Veauthier C, Radbruch H, Gaede G, Pfueller CF, Dörr J, Bellmann-Strobl J, et al. Fatigue in multiple sclerosis is closely related to sleep disorders: A polysomnographic cross-sectional study. Mult Scler 2011;17:613-22. doi: 10.1177/1352458510393772.
2. Cederberg KLJ, Jeng B, Sasaki JE, Braley TJ, Walters AS, Motl RW. Restless legs syndrome and health-related quality of life in adults with multiple sclerosis. J Sleep Res 2020;29:e12880. doi: 10.1111/jsr.12880.
3. Fiorini A, Koudriavtseva T, Bucaj E, Coccia R, Foppoli C, Giorgi A, et al. Involvement of oxidative stress in occurrence of relapses in multiple sclerosis: The spectrum of oxidatively modified serum proteins detected by proteomics and redox proteomics analysis. PLoS One 2013;8:e65184. doi: 10.1371/journal.pone.0065184.
4. Allen RP, Picchietti DL, Garcia-Borreguero D, Ondo WG, Walters AS, Winkelman JW, et al. Restless legs syndrome/Willis-Ekbom disease diagnostic criteria: Updated International Restless Legs Syndrome Study Group (IRLSSG) consensus criteria--history, rationale, description, and significance. Sleep Med 2014;15:860-73. doi: 10.1016/j.sleep.2014.03.025.
5. Ozdogar AT, Kalron A. Restless legs syndrome in people with multiple sclerosis: An updated systematic review and meta-analyses. Mult Scler Relat Disord 2021;56:103275. doi: 10.1016/j.msard.2021.103275.
6. Buçan Kırkbir İ, Kurt B, Boz C, Terzi M. Determination of important predictors for the fifth-year Expanded Disability Status Scale scores of patients with multiple sclerosis using machine learning. Turk J Neurol 2024;30:157-66. doi: 10.55697/tnd.2024.107.
7. Trentzsch K, Schumann P, Śliwiński G, Bartscht P, Haase R, Schriefer D, et al. Using machine learning algorithms for identifying gait parameters suitable to evaluate subtle changes in gait in people with multiple sclerosis. Brain Sci 2021;11:1049. doi: 10.3390/brainsci11081049.
8. Seccia R, Romano S, Salvetti M, Crisanti A, Palagi L, Grassi F. Machine learning use for prognostic purposes in multiple sclerosis. Life (Basel) 2021;11:122. doi: 10.3390/life11020122.
9. Darvishi S, Hamidi O, Poorolajal J. Prediction of Multiple sclerosis disease using machine learning classifiers: A comparative study. J Prev Med Hyg 2021;62:E192-9. doi: 10.15167/2421-4248/jpmh2021.62.1.1651.
10. Brichetto G, Monti Bragadin M, Fiorini S, Battaglia MA, Konrad G, Ponzio M, et al. The hidden information in patient-reported outcomes and clinician-assessed outcomes: Multiple sclerosis as a proof of concept of a machine learning approach. Neurol Sci 2020;41:459-62. doi: 10.1007/s10072-019-04093-x.
11. Kaur R, Chen Z, Motl R, Hernandez ME, Sowers R. Predicting multiple sclerosis from gait dynamics using an instrumented treadmill: A machine learning approach. IEEE Trans Biomed Eng 2021;68:2666-77. doi: 10.1109/TBME.2020.3048142.
12. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, et al. Diagnosis of multiple sclerosis: 2017 Revisions of the McDonald criteria. Lancet Neurol 2018;17:162-73. doi: 10.1016/S1474-4422(17)30470-2.
13. Legge BJ, Banister EW. The Astrand-Ryhming nomogram revisited. J Appl Physiol (1985) 1986;61:1203-9. doi: 10.1152/jappl.1986.61.3.1203.
14. Astrand PO, Ryhmıng I. A nomogram for calculation of aerobic capacity (physical fitness) from pulse rate during sub-maximal work. J Appl Physiol 1954;7:218-21. doi: 10.1152/jappl.1954.7.2.218.
15. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: An Expanded Disability Status Scale (EDSS). Neurology 1983;33:1444-52. doi: 10.1212/wnl.33.11.1444.
16. Motl RW, Cohen JA, Benedict R, Phillips G, LaRocca N, Hudson LD, et al. Validity of the timed 25-foot walk as an ambulatory performance outcome measure for multiple sclerosis. Mult Scler 2017;23:704-10. doi: 10.1177/1352458517690823.
17. Hobart JC, Riazi A, Lamping DL, Fitzpatrick R, Thompson AJ. Measuring the impact of MS on walking ability: The 12-Item MS Walking Scale (MSWS-12). Neurology 2003;60:31-6. doi: 10.1212/wnl.60.1.31.
18. Johns MW. A new method for measuring daytime sleepiness: The Epworth sleepiness scale. Sleep 1991;14:540-5. doi: 10.1093/sleep/14.6.540.
19. Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: A new instrument for psychiatric practice and research. Psychiatry Res 1989;28:193-213. doi: 10.1016/0165-1781(89)90047-4.
20. Simeoni M, Auquier P, Fernandez O, Flachenecker P, Stecchi S, Constantinescu C, et al. Validation of the multiple sclerosis international quality of life questionnaire. Mult Scler 2008;14:219-30. doi: 10.1177/1352458507080733.

21. Walters AS, LeBrocq C, Dhar A, Hening W, Rosen R, Allen RP, et al. Validation of the International Restless Legs Syndrome Study Group rating scale for restless legs syndrome. Sleep Med 2003;4:121-32. doi: 10.1016/s1389-9457(02)00258-7.
22. Güneş T, Emre U, Erdal Y, Yalin OÖ. Restless legs syndrome in multiple sclerosis. Noro Psikiyatr Ars 2019;58:94-8. doi: 10.29399/npa.23429.
23. Fragoso YD, Finkelsztejn A, Gomes S, Kaimen-Maciel DR, Oliveira CL, Lopes J, et al. Restless legs syndrome and multiple sclerosis: A Brazilian multicenter study and meta-analysis of the literature. Arq Neuropsiquiatr 2011;69:180-3. doi: 10.1590/s0004-282x2011000200007.
24. Ozdogar AT, Ertekin O, Kahraman T, Baba C, Ozakbas S. Restless legs syndrome and related factors in people with multiple sclerosis in Turkey. Neurol Res 2022;44:415-22. doi: 10.1080/01616412.2021.2000822.
25. Giannaki CD, Aristotelous P, Stefanakis M, Hadjigeorgiou GM, Manconi M, Leonidou E, et al. Restless legs syndrome in Multiple Sclerosis patients: A contributing factor for fatigue, impaired functional capacity, and diminished health-related quality of life. Neurol Res 2018;40:586-92. doi: 10.1080/01616412.2018.1454719.
26. Cederberg KLJ, Schuetz ML, Mathison B, Motl RW. Restless legs syndrome severity associated with reduced physical function in adults with multiple sclerosis. Gait Posture 2022;97:56-61. doi: 10.1016/j.gaitpost.2022.06.012.
27. Minár M, Petrleničová D, Valkovič P. Restless legs syndrome in multiple sclerosis de-creases health-related quality of life. Act Nerv Super Rediviva 2016;58:580116-8.
28. Monschein T, Schestak C, Schillerwein-Kral C, Leutmezer F, Berger T, Bsteh G, et al. Restless Legs Syndrome in Multiple Sclerosis: Risk factors and effect on sleep quality - a case-control study. Mult Scler Relat Disord 2021;51:102916. doi: 10.1016/j.msard.2021.102916.
29. Cederberg KLJ, Jeng B, Sasaki JE, Motl RW. Restless legs syndrome, sleep quality, and perceived cognitive impairment in adults with multiple sclerosis. Mult Scler Relat Disord 2020;43:102176. doi: 10.1016/j.msard.2020.102176.
30. Phillips B, Young T, Finn L, Asher K, Hening WA, Purvis C. Epidemiology of restless legs symptoms in adults. Arch Intern Med 2000;160:2137-41. doi: 10.1001/archinte.160.14.2137.
31. Cederberg KLJ, Jeng B, Sasaki JE, Braley TJ, Walters AS, Motl RW. Physical activity, sedentary behavior, and restless legs syndrome in persons with multiple sclerosis. J Neurol Sci 2019;407:116531. doi: 10.1016/j.jns.2019.116531.
32. Langeskov-Christensen M, Langeskov-Christensen D, Overgaard K, Møller AB, Dalgas U. Validity and reliability of VO_2-max measurements in persons with multiple sclerosis. J Neurol Sci 2014;342:79-87. doi: 10.1016/j.jns.2014.04.028.
33. Kour Buttar K, Saboo N, Kacker S. A review: Maximal oxygen uptake (VO_2max) and its estimation methods. Int J Phys Educ Sports Health 2019;6:24-32.
34. Schlagheck ML, Bansi J, Langeskov-Christensen M, Zimmer P, Hvid LG. Cardiorespiratory fitness ($\dot{V}O_2peak$) across the adult lifespan in persons with multiple sclerosis and matched healthy controls. J Sci Med Sport 2024;27:10-5. doi: 10.1016/j.jsams.2023.10.009.
35. Heine M, Wens I, Langeskov-Christensen M, Verschuren O, Eijnde BO, Kwakkel G, et al. Cardiopulmonary fitness is related to disease severity in multiple sclerosis. Mult Scler 2016;22:231-8. doi: 10.1177/1352458515581437.
36. Albergoni M, Storelli L, Preziosa P, Rocca MA, Filippi M. The insula modulates the effects of aerobic training on cardiovascular function and ambulation in multiple sclerosis. J Neurol 2023;270:1672-81. doi: 10.1007/s00415-022-11513-0.
37. Cederberg KLJ, Motl RW. Feasibility and efficacy of a physical activity intervention for managing restless legs syndrome in multiple sclerosis: Results of a pilot randomized controlled trial. Mult Scler Relat Disord 2021;50:102836. doi: 10.1016/j.msard.2021.102836.
38. Ozdogar AT, Ertekin O, Kahraman T, Dastan S, Ozakbas S. Effect of exergaming in people with restless legs syndrome with multiple sclerosis: A single-blind randomized controlled trial. Mult Scler Relat Disord 2023;70:104480. doi: 10.1016/j.msard.2022.104480.
39. Smith CM, Weathers AL, Lewis SL. An overview of clinical machine learning applications in neurology. J Neurol Sci 2023;455:122799. doi: 10.1016/j.jns.2023.122799.
40. Jeong J, Jeon Y, Kim H, Yeom JW, Shin YB, Kim S, et al. Machine learning-based prediction of restless legs syndrome using digital phenotypes from wearables and smartphone data. Sci Rep 2025;15:16349. doi: 10.1038/s41598-025-01215-8.
41. Kwatra V, Khan MA, Quadri SA, Cook TS. Differential diagnosis and treatment of restless legs syndrome: A literature review. Cureus 2018;10:e3297. doi: 10.7759/cureus.3297.
42. Schilling C, Schredl M, Strobl P, Deuschle M. Restless legs syndrome: Evidence for nocturnal hypothalamic-pituitary-adrenal system activation. Mov Disord 2010;25:1047-52. doi: 10.1002/mds.23026.