REVIEW ARTICLE

The Applications of Machine Learning Algorithms in Multiple Sclerosis: A Systematic Review

Ali Garavand[1], Mahnaz Samadbeik[2], Nasim Aslani[1]

[1] *Department of Health Information Technology, School of Allied Medical Sciences, Lorestan University of Medical Sciences, Khorramabad, Iran*

[2] *Department of Health Information Technology, Social Determinants of Health Research Center, Lorestan University of Medical Sciences, Khorramabad, Iran*

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Abstract- Multiple Sclerosis (MS) is a common chronic disease that affects society, especially young people. In recent years, data sciences have been used extensively to deal with the disease. Machine learning is one of the main data sciences types which has been used to deal with chronic diseases such as MS. This study aimed to identify the applications of machine learning algorithms in MS disease. This study is a systematic review that conducted in 2020. The searches were done in PubMed, Scopus, ISI Web of Sciences, Ovid, Science Direct, Embase, and Proquest scientific databases, by combining related keywords. Data extraction was done by using a data extraction form to follow the trends of this field of study. The results of the study showed that diagnosis of MS was the main application of machine learning in MS (33.3 %); also, assessment (24.24%) and prediction (18.18 %) of the disease were other main applications. The most used data type was medical images such as MRI and CT scans (55.17 %). The most used machine learning algorithm type was Support Vector Machine (SVM) (30 %) as a classification algorithm. The most optimized algorithm for the diagnosis and prediction of MS was KNN. It's suggested to use machine learning algorithms to diagnose, assess, predict lesion classification, treatment, and severity determining of MS disease. Although the most common form of data used for MS is medical images, it is suggested that other types of data are generated to be used in machine learning algorithms. Considering the optimization rate of the algorithms used, it is suggested to pay more attention to the type of data and study objectives in data analysis using machine learning.

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Introduction

Multiple sclerosis (MS) is a disease that attacks the central nervous system (brain, spinal cord, and optic nerves) (1). Environmental and genetic factors contribute to the incidence of this disease. The onset of MS is usually the early to mid-adult years, at 15-50 years of age (2), and its prevalence is about three times higher in women than men (3). The clinical progress of MS may vary greatly, ranging from a benign disease to a rapidly progressing and debilitating one. The prevalence of MS impacts the economy and the loss of the active force in society (4,5). About 5.2 million people worldwide suffer from this disease. It seems that MS prevalence has been continually increasing over the past century.

This increased prevalence has increased the volume of data on MS, in this patients, signs and symptoms, outcomes, and diagnostic and therapeutic measures (6,7). An increased volume of data often complicates the accurate management and exploitation of data. Machine learning is a novel method for the organization, analysis, and exploitation of big data by using different algorithms. It is defined as the process of discovering patterns in generated data. Machine learning is used for three main purposes, including data description, prediction based on previous data, and prescription of measures based on the previous two types (8-12). Machine learning in different classifications assist physicians and other healthcare

Corresponding Author: N. Aslani
Department of Health Information Technology, School of Allied Medical Sciences, Lorestan University of Medical Sciences, Khorramabad, Iran
Tel: +98 9168593457, Fax: +98 2122721150, E-mail address: aslaninasim@yahoo.com

providers in the description, prediction, diagnosis and treatment, and preventive measures based on data elements with different algorithms and methods and is also employed in the process of MS (10-13).

The main type of machine learning method is classification; also clustering and association rule mining are other machine learning methods. The classification algorithms can be used for many purposes in health problems such as prediction, diagnosis, and screening of diseases. There are many classification algorithms used in clinical data analyses such as artificial neural networks (ANN), Random Forests algorithm, k-nearest neighbors (KNN), support vector machine (SVM), decision tree (DT), and Naive Bayes (NB) (14). In the field of MS, there are many studies have been conducted by applying machine learning methods in recent years.

Raeesi *et al*., conducted a study based on machine learning algorithms for MS to identify and examine the clinical symptoms affecting the disease. Based on the results, the most effective factors on MS were clinical symptoms related to vision. Some MS symptoms are transient and are ignored by patients in most cases. In case of awareness of the prevalence of clinical symptoms, this may be a red flag for patients before the critical period of the disease, which can contribute to the more rapid diagnosis, more effective treatment, and relative prevention of disease progress (6). Goldberg *et al*., used the ANN algorithm for the diagnosis of MS lesions in MRI images. The ANN algorithm was used in 45 images from 14 patients with MS. The sensitivity of this algorithm was 87%, and its specificity was 96%. This algorithm can be used as a pre-processing tool for quantitative MS monitoring through MRI imaging (15).

In another study, the diagnosis and evaluation of MS lesion treatment were examined based on brain MRI and reported that despite the examination of MRI images by specialists, the large volume of MRI data is time-consuming, and evaluations are associated with human error. Accordingly, various teams have developed computational methods for examining and classifying brain lesions in MS, methods which had not been classified or compared in the past. Results of this study on the examination and comparison of MS lesion classification showed that unsupervised and supervised techniques such as kNN and Parzen have been employed. Combining knowledge-based with Bayesian approaches enhances the precision of classification. In addition, the use of smart classifications such as Fuzzy Inference Systems, Fuzzy C-Means, Artificial Neural Networks,، and voxels reduces classification errors (16). Xia *et al*., constructed Disease Severity in MS using Electronic health records (EHR) and identified 5495 patients with MS using an algorithm with natural language processing. This study was conducted based on "brain parenchymal fraction" (BPF) and "MS severity score" (MSSS). In this algorithm, sensitivity was 83%, and specificity was 95% (17).

Preliminary reviews showed that no review or meta-analysis had been performed on machine learning for MS. Therefore, the present study aimed to discover the main applications of machine learning methods in MS, most used data types, main machine learning techniques, and optimal algorithms based on the reported indexes such as sensitivity, specificity, precision, and accuracy.

Materials and Methods

Sources of data

This review was done in 2019. The searches were done in PubMed, Scopus, ISI Web of Sciences, Ovid, Science Direct, Embase, and Proquest scientific databases, by using a combination of keywords. Table 1 shows the search strategy.

Study selection

In this study, the searches were done without time limitations (up to October 2019). All steps to selecting the related articles followed based on the PRISMA statement (18,19). The conference papers, as well as articles published in journals in the mentioned databases, were reviewed. The steps of selection and screening were performed by two authors independently, and the third author intervened in case of disagreements.

Inclusion criteria

We include all the original article types about machine learning methods in MS disease, such as using machine learning algorithms to describe, predict, diagnose, and treat MS disease. The selected studies must use the algorithms to analyze the dataset about MS.

Exclusion criteria

In this study, the reports, letters, commentary, books, and e-books were excluded. Duplications, irrelevant articles, and papers with no available full text were also excluded. The articles that used statistical methods were excluded. Also, the studies which used biomedical data in MS were excluded.

Data extraction

The quality of selected articles was assessed by two authors (N.S and A.G), and the disagreements referred to the third author (M.S). Data gathering was done by using a “data extraction form.” The form included: 1- general information (such as author and location), 2- method (such as data mining technique and resource of data), and 3- main findings of the reviewed articles. Data were analyzed using the content analysis method.

Table 1. Search strategy and keywords

Database	Scopus, Pub Med, ISI (Web of Sciences), Ovid, Embase, Science Direct and ProQuest
#1	("Data mining" OR "Association " OR "Clustering " OR "Decision Trees " OR "Linear Regression " OR" Classification " OR "Logistic Regression " OR "Sequence Clustering Algorithm" OR "Time Series Algorithm" OR "Artificial Intelligence" OR "Naive Bayes " OR " Neural Network Algorithm" OR "Apriority Algorithm " OR "K-means" OR "K-medoids" OR " k nearest neighbor algorithm" OR "KNN" OR " Case-based reasoning" OR " Support Vector Machines" OR " Machine Learning")
#2	("MS" OR "Multiple sclerosis" OR (Multiple and Sclerosis) OR (Disseminated and Sclerosis) OR “Disseminated Sclerosis")
#3	#1 AND #2

Results

From the 7621 articles retrieved in the primary search in databases, 29 papers were selected for the study after applying inclusion and exclusion criteria. Figure 1 shows the details of the article selection process of this study.

In table 2, the general information of the selected article, including author, year, country, Data type, algorithm, methods, heath application, and findings, has been shown.

In table 2, the most used data mining Technique was Classification with 82.75% (24 out of 29), and after it, the clustering Techniques 6.89% (2 out of 29) were the more used Technique in the study.

According to table 2, the most algorithm type was Support Vector Machine (SVM) algorithm, 41.37% (12 out of 29) and after it the k-nearest neighbors (KNN), Decision Tree (DT), Bayesian and Random Forests algorithm 13.79% (4 out of 29) were the more used algorithm in the study.

According to table 2, most of the articles were published in the US with 24.13% (7 out of 29).

Other results of the study showed the highest number of articles published in 2017 2018 (n=4). (Figure 2)

Figure 3 shows the geographical distribution of conducted studies all over the world, which limited countries conducted them.

Table 3, with more focus, shows the frequency of methods and algorithms used in the selected articles. Totally, in 7 articles, two or more algorithms were used for MS. SVM (N=12) is the most frequently used algorithm.

Based on Han's classification, the data used in data mining are divided into the database, data warehouse, transaction database, text, image, audio, multimedia data, etc. Based on Table 4, the highest number of data used in data mining performed for MS was image data (55.17%) (n=16). Table 4 presents the frequency of data types used for this purpose.

Figure 4 shows DM applications for MS. Most medical application of DM for MS was in diagnostic (33.33%). Then, the assessment was the most frequent scope that DM used (24.24%). Totally, in 4 articles, two applications were used for MS.

The results showed that clustering algorithms are used for the segmentation of images and clustering of identified symptoms in MS patients, while most machine learning applications such as disease prediction, assessment, and diagnosis are performed using classification algorithms.

Other results of the study showed that the main performance indicators of the algorithms in studies that reported the performance of algorithms were sensitivity, specificity, accuracy, ROC, AUC, and precision. Figure 5 shows the mean performance indicators of machine learning algorithms in MS.

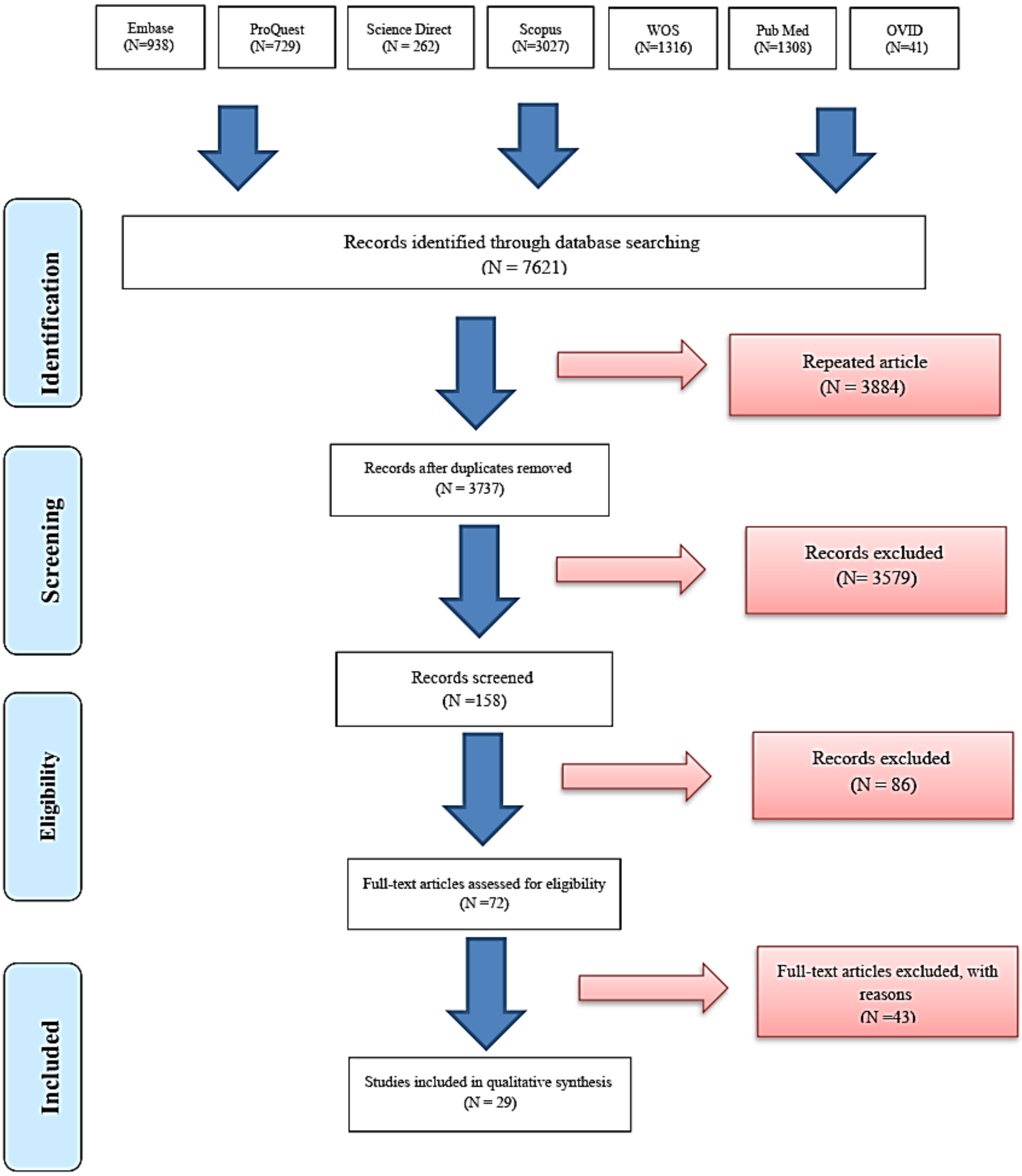

Figure 1. Flow diagram of the article selection process

Table 2. Selected articles main features

NO	Authors	Year/ Country	Data type	Algorithm (Knowledge base)	Method/ Technique	Health Application	Result and Best Performance of Model
1	Zhao & *et al.*, (19)	2017 USA	demographic, clinical, and MRI data	Classification : SVM Logistic regression	Machine learning	Predicting	Clinical observation: sensitivity to 62% and specificity to 65% MRI data: Sensitivity (to 71%) and specificity (to 68%.)
2	Zhao Y *et al.*, (20)	2019 USA	radiologic and demographic data together with bi-annual clinical visits	Classification: SVM, DT, LR, and Random Forests	Machine learning	Predicting (Predict a “worsening” or “non-worsening)	Worsening: 82% accuracy. The performance of SVM, DT, LR, and RF is 76%, 78%, 78%, and 79%, respectively. non-worsening : 61% accuracy. The performance of SVM, DT, LR, and RF are 60%, 64%, 61%, and 61%, respectively.

Cont table 2.

3	Zhao *et al*., (21)	2014 USA	dataset of MS patients	Classification : SVM	Machine learning	Predicting	AN approach is able to prediction performance
4	Zhang *et al*., (22)	2016 China USA	Imaging data (brain images)	Classifiers: DT, KNN, SVM	Machine learning	Multiple sclerosis detection	KNN performed the best among all three classifiers. DT achieves a sensitivity of 96.75%, a specificity of 98.30%, a precision of 97.76%, and an accuracy of 97.62%. kNN achieves a sensitivity of 96.15%, a specificity of 99.32%, a precision of 99.09%, and an accuracy of 97.94%. The SVM achieves a sensitivity of 97.34%, a specificity of 97.73%, a precision of 97.05%, and an accuracy of 97.56%
5	Zhao *et al*., (23)	2015 USA	clinics/physicians data	Bayesian non-parametric mixture models	machine learning (Semi-supervised)	Predicting (predict disease progression)	predict disease progression
6	Yamamoto *et al*., (24)	2010 Japan	Imaging data	Classification: Support Vector Machines (SVM)	Machine learning	Detection of multiple sclerosis lesions	the sensitivity of the algorithm was 81.5%
7	Yahia *et al*., (25)	2018 Tunisia	3D Brain web database, MRI sequences, and noise	Classification: Support Vector Machines (SVM)	Machine learning	Assess multiple sclerosis lesions	Testing of the classification is done in the same conditions of work by means of the multiclass classifier SVM.
8	Xia, Z & *et al*., (17)	2013 USA	EHR Data	Classification EHR algorithm	natural language processing	Deriving MS Severity	The EHR algorithm that identifies MS patients has an area under the curve of 0.958, 83% sensitivity, 92% positive predictive value, and 89% negative predictive value when a 95% specificity threshold is used
9	Weygandt *et al*., (26)	2011 Germany	Imaging data (MRI)	Classification: linear Support Vector Machines	Machine learning	determine the diagnostic accuracy in MS patients	The posterior parietal WM area was (96% accuracy). Cerebellar regions NAGM areas (84% accuracy). A posterior brain region NAWM area (91% accuracy).
10	Weiss *et al*., (27)	2013 Germany UK	Clinical Image Data	Classification	dictionary learning (unsupervised approach)	Diagnostic assessment	show its general applicability to the problem of lesion segmentation by evaluating our approach on synthetic and clinical image data and comparing it to state-of-the-art methods.
11	Raeisi *et al*., (6)	2017 Iran	Dataset of MS patients	Classification: decision tree(DT)	Machine learning	The goal of this research is recognition of effective clinical symptoms on MS and Considering levels of effectiveness of age, sex, and education levels	70% of MS patients with high graduate are in the relapsing-remitting category, and 62.5% of MS patients are 20-40 years old.
12	Wang *et al*., (28)	2018 China	Imaging data	Convolutional neural network(CNN)	artificial intelligence and deep learning method	Early diagnosis and treatment	sensitivity of 98.77, specificity of 98.76, and an accuracy of 98.77
13	Torabi *et al*., (29)	2017 Iran	EEG signals	Classification : SVM and KNN T-test criterion	Machine learning	Diagnosis of multiple sclerosis	maximum classification performances were 93.08 and 79.79%, respectively, which were reached by using an optimal set of features
14	Theocharakis *et al*., (30)	2009 Greece	MRI	Neural network classifier	Pattern recognition	Discrimination of multiple sclerosis (MS) from cerebral microangiopathy (2)	According to the findings of the present study, statistically, significant differences exist in the values of the textural features between CM and MS: MS regions were darker, of higher contrast, less homogeneous, and rougher as compared to CM

Cont table 2.

15	Tardif *et al*., (31)	2010 Canada	The magnetic resonance data set	k-means classifier	Machine learning	Diagnosis	This method is used to a high-resolution quantitative magnetic resonance data set of the fixed post mortem multiple sclerosis brain.
16	Tadayon *et al*., (32)	2016 Iran	1.diffusion tensor MR (DT-MR) 2. conventional magnetic resonance (c-MR)	fuzzy K-nearest neighbor (F-KNN) classifier	Machine learning	classification of MS lesion	Application of the C-MR with the DT-MR images makes possible the classification of MS lesion subtypes with high sensitivity and allows the ability to evaluate MS disease in the treatment process.
17	Tacchella *et al*., (33)	2018 Italy	Clinical record	Classification: Random Forest models	Machine learning	predicted the course of the disease	A significant improvement of predictive ability was obtained when predictions were combined with a weight that depends on the consistency of human (or algorithm) forecasts on a given clinical record.
18	Shahrbanian *et al*., (34)	2015 Canada	symptoms, including fatigue, pain, sleep disturbance, depression, anxiety, irritability, cognitive impairment, spasticity, and poor balance	Hierarchical and K-means cluster	Machine learning	1- to identify, among women and men with MS, 2- to compare the contribution of generated symptom clusters to MS consequences	All symptom clusters showed a significant effect in predicting the overall variability of perceived health status.
19	Saccà *et al*., (35)	2019 Italy	Functional-MRI sequence	Classification: Random Forest, SVM, Naïve-Bayes, K-NN and Artificial Neural Network	Machine learning	Support early diagnosis of Multiple Sclerosis	In this classification, SVM and Random Forest showed the same 5-fold cross-validation accuracies (85.7%) using only this network.
20	Kontschieder *et al*., (36)	2014 Netherlands	Depth video	Classification: SVM	Machine learning	Adding quantitative evidence of disease progression	Achieve average was excess of the 80% mark.
21	Khotanlou & Afrasiabi (16)	2011 Iran	Brain imaging	Clustering : algorithm(FCM, FPCM, PFCM, and SCPFCM algorithms)	Machine learning	segmentation of brain MS lesions	
22	Jog *et al*., (37)	2015 USA	Magnetic resonance imaging (MRI)	Classification: Decision trees (DT)	Machine learning	Diagnosing and tracking the progression of MS	The evaluated algorithm on MS Lesion Segmentation showed improved results in comparison to state-of-the-art methods.
23	Zimring *et al.*, (15)	1998 Israel	Brain magnetic resonance (MR)	Classification**:** Artificial neural networks (ANN)	Machine learning	Lesion detection	In this algorithm, sensitivity (was 0.87)and specificity (0.96.)
24	Elliott *et al*., (38)	2010 Canada	MRI	Classification: Bayesian	Machine learning	Disease progression and for assessing treatment effects	The new method is shown longitudinal MRI with high precision and sensitivity to lesion activity.
25	Chitnis *et al*., (39)	2014 Canada	MRI Data	Classification: support vector machines (SVMs)	Deep Learning	Prediction of Disease Progression	In this study, they develop a 3D CNN with parallel convolutional layers for predicting progression in MS patients using MRI and assessment of disability.
26	Chase *et al*., (40)	2017 USA	Electronic health record (EHR)	Naïve Bayes classification.	Statistical	Early recognition	Classification of patients known to have MS using notes of the MS-enriched cohort entered after the initial ICD9 [MS] code yielded a ROC AUC, sensitivity, and specificity of 0.90 [0.87-0.93], 0.75[0.66-0.82], and 0.91 [0.87-0.93], respectively.

Cont table 2.

27	Bendfeldt *et al*., (41)	2018 international	1. MRI data 2. Clinical and 3.demographic data	Classification: support vector machines (SVMs)	Statistical	Prediction of conversion	The highest prediction accuracies of 70.4% were reached with a combination of demographic/clinical features and lesion-specific geometric.
28	Kurbalija *et al*., (42)	2007 Serbia	Data gained from conversation with the patient Data gained from medical checkup data from previous diagnoses	Classification: Case-Based Reasoning (CBR)	Artificial intelligence	Multiple Sclerosis Diagnoses	This system can help the experts to compare several criteria in diagnoses of MS disease.
29	Schwartz and Carolyn (43)	2011 NARCOMS (USA, Canada, Netherlands)	The sample was from the NARCOMS database.	Regression	Statisticl techniques	Response shift in patients with multiple sclerosis	Small reaction change effect sizes were detected by all of the methods. Re-calibration reaction change was detected by Structural Equalization Modeling.

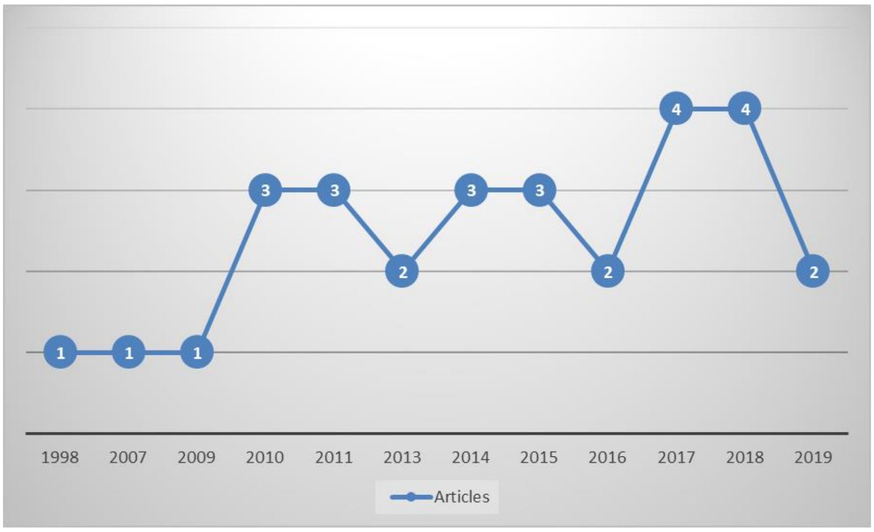

Figure 2. Distribution of articles published over the years

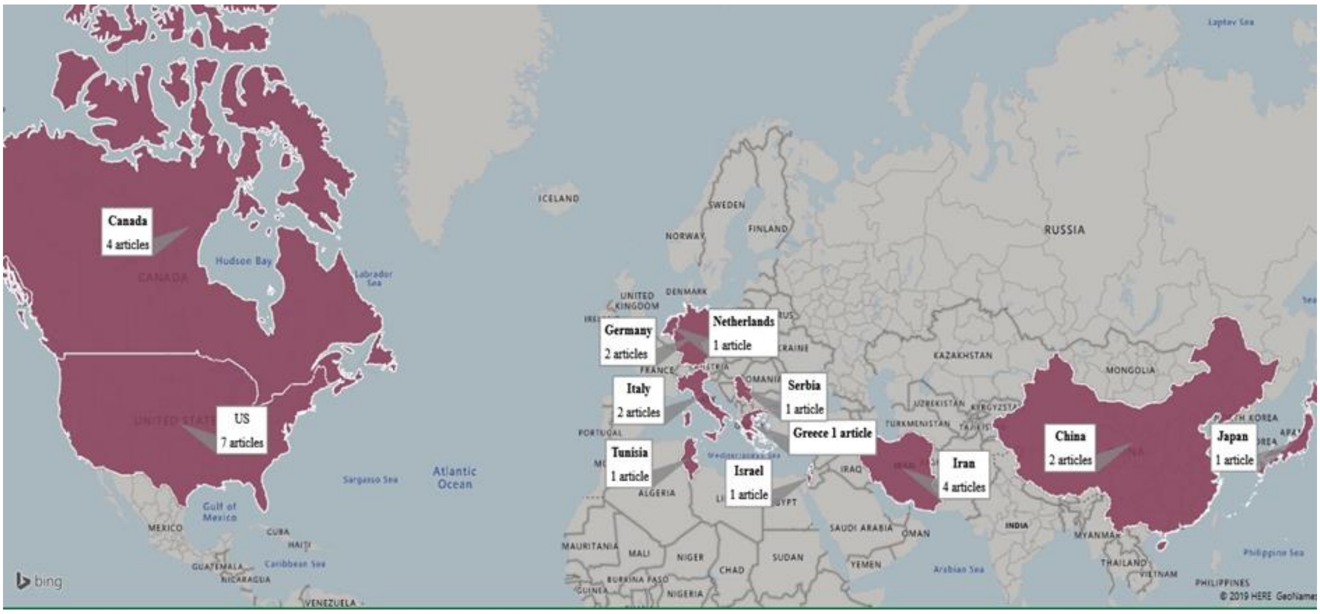

Figure 3. Publication based on place

Table 3. The frequency of algorithm used

Method	Algorithm	No.	%	
Classification	SVM	12	30	85
	DT algorithms	8	20	
	KNN	4	10	
	Bayesian	4	10	
	ANN & CNN	4	10	
	LR	2	5	
Clustering	k-means & k-medoids	2	5	15
	FCM	1	2.5	
	FPCM	1	2.5	
	PFCM	1	2.5	
	SCPFCM	1	2.5	

Table 4. Frequency of data types used for MS data mining

Data type	Frequency	Percent%
Text (Demographic data)	2	6.89
Image data (MRI, CT Scan, ...)	16	55.17
Noise data	1	3.44
Data set (EHR, HIS, ...)	5	17.27
Multimedia (EEG, EDSS, Clinical data, Depth video)	8	27.58
Total	32	100%

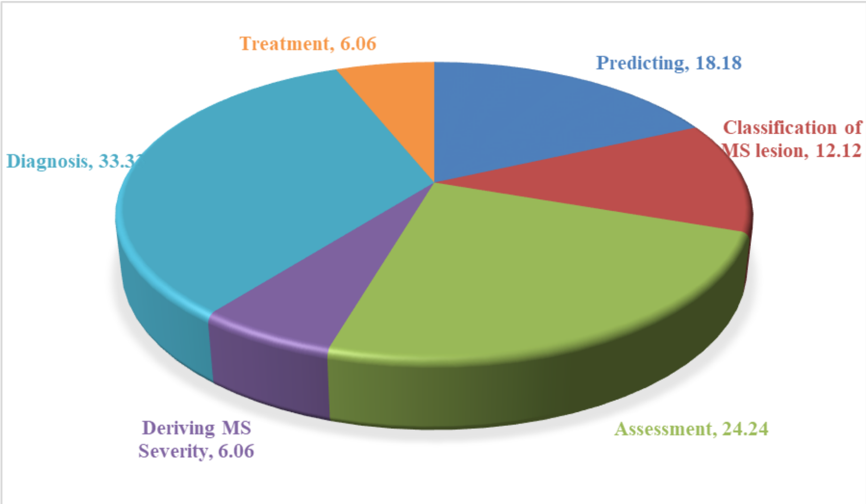

Figure 4. The frequency of DM applications of health aspects for MS

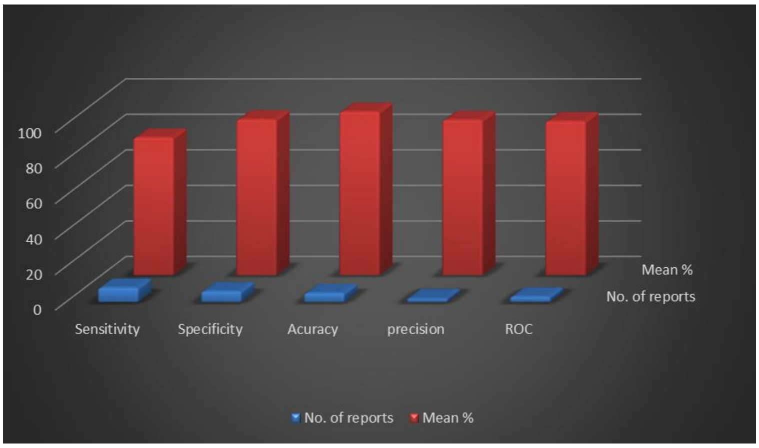

Figure 5. Main performance indicator means for the machine learning algorithms in MS disease

Discussion

As a great practical domain, machine learning includes techniques adopted from other domains, including statistics, pattern recognition, natural language processing, and visualization. The machine learning method automatically identifies complex patterns and makes a smart decision that is performed after training and learning using a set of samples (4). The results of the study showed that, in general, the machine learning algorithms used in MS disease for different purposes have acceptable performance in terms of performance indicators such as sensitivity, specificity, accuracy, precision, and ROC. Chitnis *et al*., predicted the clinical course of MS using machine learning. They attempted to develop a model for MS prediction using machine learning and SVM. Results showed the accuracy of disease course prediction was enhanced using this model (39). Saccà *et al*., evaluated the performance of machine learning algorithms for the rapid prediction of MS. They expressed that the accuracy of MS prediction reaches 85.7% using this method (35). Based on the results, statistical methods were the second most frequently used method in different data mining on MS. Since the machine learning method is the most commonly used method in data mining on MS, it is recommended that physicians and researchers pay more attention to and employ it in their studies. Of course, based on the conditions, other methods can also be employed for machine learning.

Some machine learning methods include characterization and discrimination, association and frequent pattern, classification and regression, and clustering. Using each method, various patterns can be mined (4). The findings revealed that the most commonly used algorithm for data mining on patients with MS belonged to the classification method, with SVM being the most frequently used algorithm. Classification is the process of finding a model in which concepts are described or identified. The model results from the analysis of a training set of data (4). Kontschieder *et al*., examined the quantitative progress of MS via classification of depth videos using the SVM algorithm. The results indicated that the use of SVM enhances the precision and validity of this method (36). Weygandt et al. identified the pattern of MS based on MRI by using a linear SVM algorithm in order to classify lesions. Results indicated the efficiency of this method in detecting the MS pattern (26). Bayesian, DT, RF, and KNN are the other frequently used algorithms for this purpose. Since SVM is the most used in the diagnosis and prediction of MS, it is suggested that researchers adopt it for enhancing the precision and accuracy of diagnoses and predictions required for data mining on patients with MS.

Arguably, machine learning programs can be used wherever there are data. Data mining in the healthcare domain is utilized for description, prediction, diagnosis, and treatment (4). Data mining algorithms were mostly used for the diagnosis of MS. Meanwhile, diagnosis based on lesions using MRI was the most frequent. Wang *et al*., utilized data mining algorithms for the diagnosis and treatment of MS. Results indicated that the use of data mining algorithms with a high percentage of sensitivity and specificity assists rapid diagnosis and treatment (20). Kurbalija *et al*., reported that the use of the CBR algorithm assists the diagnosis of MS (42). Based on the results, the second most frequent application of data mining for MS was the assessment of diagnosis and treatment. With regard to the effective application of data mining in the diagnosis of MS, it is recommended that doctors and decision-makers employ data mining algorithms for the accurate and precise diagnosis of MS.

Machine learning as a general technology can work on any type of data. The basic forms of data for machine learning include application programs, databases, data warehouses, transactional data, text data, image data, audio, multimedia, and other forms (4). From among these, image data had the largest share, and from among image data, brain MRI images had the largest portion. Elliott et al. used MRI imaging data for the classification of MS based on brain lesions (38). Goldberg-Zimring *et al*., employed MRI images in order to predict the diagnosis of MS (15). Multimedia files are the second most frequently used data type in data mining on MS. With regard to the expansive usage of MRI for the diagnosis and prediction of MS, it is recommended that more studies focus on data mining and the discovery of patterns from MRI images in the MS process.

The use of optimal algorithms with the highest level of efficiency selection of an accurate and precise set of data and using suitable machine learning methods based on data type and objectives can enhance the accuracy and precision of machine learning, thereby affecting the process of treating patients with MS. It seems that image data have a more wide application in the diagnosis and treatment of MS. Therefore, it is suggested that this type of data be more accurately and precisely collected. Due to the nature and needs of stakeholders concerning the analysis of MS disease data, such as diagnosis and evaluation of the disease, the use of classification algorithms has been most used among machine learning methods. The type of data was effective in selecting machine learning methods and algorithms, and according to the results of the study, the most important algorithms used to analyze MS data were SVM DT, especially Random Forests, CNN, Bayesian.

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