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Factors associated with the number of months of delaying in multiple sclerosis diagnosis: Comparison of count regression models

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Keywords
Multiple Sclerosis; Delayed Diagnosis; Disability; Iran

Abstract

Background: It may take a long time to diagnose multiple sclerosis (MS) since the emergence of primary symptoms. This study aimed to use count regression models to compare their fit and to identify factors affecting delay in the diagnosis of MS.

Methods: Data were collected from the Nationwide MS Registry of Iran (NMSRI) for Mazandaran Province, Iran, using census sampling until April 2022. The four models of Poisson regression, negative binomial (NB) regression, zero-inflated Poisson (ZIP) regression, and zero-inflated negative binomial (ZINB) regression were used in this study.

Results: In this study on 2894 patients, 74.0% were women, and 8.5% had a family history of MS. The mean ± standard deviation (SD) of the patients' age was 34.96 ± 9.41 years, and the mean delay in diagnosis was 12.32 ± 33.26 months, with a median of 0 (Q1-Q3: 0-9). The NB regression model showed the best performance, and factors, including a history of hospitalization and the year of symptom onset, had significant effects on a delayed diagnosis. Besides, the Expanded Disability Status Scale (EDSS) score was significantly different before and after 2017; it was also associated with sex, type of MS, and history of hospitalization.

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Conclusion: The mean diagnostic delay and the mean age of MS diagnosis are critical in Mazandaran Province. Patients with MS develop the disease at an early age and are diagnosed with a long delay. The time of symptom onset is a significant factor in the diagnosis of MS, and in recent years, there have been improvements in the diagnostic process.

Introduction

Multiple sclerosis (MS), the most common neurological disease in young adults, is an autoimmune disorder, which affects the central nervous system (CNS) and leads to severe physical and cognitive disabilities and neurological problems in young adults.[1,2] The MS symptoms are generally unpredictable and unclear and vary considerably between patients and throughout the course of the disease. Since MS can affect any area of the CNS, it can cause neurological symptoms.[3,4] The most common clinical symptoms of MS include fatigue, tremor, bladder and bowel dysfunctions, cognitive and emotional disorders (e.g., learning disabilities and depression), dizziness, and sexual problems.[5-7] Although there are different diagnostic methods for MS, McDonald's criteria have been used as the primary index for the diagnosis of MS since 2017.[6,8]

According to previous studies, the prevalence of MS has an increasing trend and varies in different populations and countries.[9-11] In 2018, researchers reported the prevalence of MS in Mazandaran Province, Iran, to be 72.5 per 100000 people. The prevalence rates were 37.1 and 108.5 per 100000 in men and women, respectively, with a mean ± standard deviation (SD) of age of 38.5 ± 10.1 years.[12] Besides, the standardized incidence rate of MS increased from 3.28 in 2008 to 4.17 per 100000 in 2018.[13] Due to the complexity of the diagnostic process, it may take a long time from the onset of primary symptoms until the diagnosis of MS.[14] Therefore, immediate treatment is crucial for these patients, and delayed diagnosis may affect the severity and progression of the disease.[8-15]

Researchers have reported different delays in diagnosis. In this regard, Ghiasian et al., in a study in Hamadan, Iran, found that the mean delay from the onset of symptoms until a physician visit was 3.25 months, and the gap between the physician visit and MS diagnosis was 14.98 months. Therefore, delay from the onset of symptoms until diagnosis was 18.01 months.[16] In another study in Shiraz, Iran, Mobasheri et al. reported an average delay of seven months in MS diagnosis.[17] On the other hand, in Spain, the median time from the onset of symptoms until MS diagnosis was 24.9 months.[18]

Researchers have proposed several reasons for a delayed MS diagnosis, including a lack of facilities for diagnosis of this disease or differences in the prevalence of MS due to latitude differences. So far, various factors that can affect a delayed MS diagnosis have been introduced in the literature.[5,19] Studies commonly use linear regression models to identify factors affecting delay in diagnosis. However, the present study used count regression models because of the numerical and non-normally distributed response variable. Overall, a delayed MS diagnosis has many physical and psychological consequences for the patients. Various studies have introduced different variables affecting delay in the diagnosis of this disease. Therefore, the present study aimed to compare different models to select the one with the best fit and to identify factors affecting delay in the diagnosis of MS patients in Mazandaran Province.

Materials and Methods

The population of this retrospective cohort study included patients with MS, diagnosed based on clinical examinations in Mazandaran Province, a northern province in Iran with a population of more than 3000000 people. A neurologist examined and diagnosed the patients, and the magnetic resonance imaging (MRI) results confirmed the diagnosis based on the 2017 McDonald criteria. Data were extracted from the Nationwide MS Registry of Iran (NMSRI),[20] which records the information of all diagnosed patients in hospitals, medical centers, private offices, and MS societies in different cities of this province. Shahin et al. confirmed the validity and reliability of NMSRI.[21]

The data of all patients with MS were collected by census sampling until the end of April 2022. The inclusion criterion was a diagnosis of MS, and the exclusion criteria were incomplete records and living in other provinces. After data cleansing, the data of 2894 patients entered the analysis process. The variables recorded in this database included the demographic information (e.g., age, sex, place of residence, and family history) and clinical data [date of symptom onset, date of diagnosis, type of disease, admission unit including hospital, Vice-Chancellor of Treatment Affairs (university), MS societies, and physician office, history of hospitalization due to MS, and the primary Expanded Disability Status Scale (EDSS) score]. In

this study, the number of months of delaying in diagnosis (from the onset of symptoms until diagnosis) was considered as the response variable.

Statistical methods: Poisson regression is applied to investigate the relationship between independent variables and a count dependent variable. The primary assumption of Poisson regression models is the equality of mean values and variance in the response variable.[22,23] Note that when variance is larger than the mean value, it is known as overdispersion, and rather than Poisson regression, the negative binomial (NB) regression is used to identify factors affecting the count response variable.[23] On the other hand, zero-inflated Poisson (ZIP) regression is applied when there is excess zero values for the response variable.[24] Finally, Similar to the ZIP regression, Zero-inflated negative binomial (ZINB) regression can be used when there is an excess zero value for the response variable.[24]

To determine factors affecting delay in MS diagnosis, researchers first examined the normal distribution of this variable using Shapiro-Wilk and Kolmogorov-Smirnov diagrams and normality tests. The results demonstrated a considerable deviation from the normal distribution. Moreover, Kruskal-Wallis test was used to compare the median delay in MS diagnosis and EDSS score between the subgroups. Considering the use of a discrete quantitative scale and the counting nature of the response variable, Poisson and NB regressions were used to model the independent variables on the response variable. Zero-inflated models were also used to investigate the possibility of excessive zeros for the response variable. Finally, the performance of the four models, including Poisson, NB, ZIP, and ZINB regressions, was compared using the Akaike information criterion (AIC) and mean squared error (MSE) indices (with smaller values indicating the better fit of the model). After selecting the best model, the researchers identified factors affecting the duration of delay in diagnosis in the model. They performed statistical analysis in R software (version 4.1.1) at a significance level of 0.05.

Results

In this study, the mean ± SD of the patients' age was 34.96 ± 9.41 years (median: 34), ranging from 6 to 97 years. Upon diagnosis, the mean ± SD of age of the patients was 27.73 ± 8.37 years, and the median age was 27 [interquartile range (IQR): 22-34] years. Among 2894 patients, 74% were women, and 8.5% had a family history of MS. The majority of the patients (50.3%) were diagnosed by MS societies, and the most common type of disease was relapsing-remitting MS (RRMS) (72%). Besides, 66.1% of the patients had a history of hospitalization. Table 1 presents the descriptive information related to all variables.

Table 1. Descriptive information and median delay (month) in multiple sclerosis (MS) diagnosis based on the demographic and clinical data of the patients

Variables	n (%)	Mean ± SD	Median (IQR)	P*
Sex				
Men	753 (26.0)	13.6 ± 33.2	0 (0-12)	0.748
Women	2141 (74.0)	11.9 ± 33.3	0 (0-8)	
Family history				
No	2648 (91.5)	12.1 ± 33.1	0 (0-9)	0.481
Yes	246 (8.5)	13.4 ± 34.0	0 (0-6.5)	
Place of diagnosis				
Hospital	273 (9.4)	16.8 ± 41.6	0 (0-10.5)	0.010
University**	17 (0.6)	27.9 ± 59.0	4 (0-5)	
MS societies	1456 (50.3)	15.0 ± 23.1	1 (0-24)	
Physician office	1148 (39.7)	11.3 ± 31.2	0 (0-7)	
MS type				
RR	990 (72.0)	9.4 ± 27.4	0 (0-5)	0.087
SP	259 (18.8)	-	-	
PR	20 (1.5)	18.6 ± 40.5	1 (0-12)	
PP	106 (7.7)	18.8 ± 42.3	0 (0-12.7)	
Hospitalization				
No	469 (33.9)	13.2 ± 32.0	0 (0-12)	0.004
Yes	915 (66.1)	12.1 ± 32.2	0 (0-5)	

*P-value based on Kruskal-Wallis test, **Vice-Chancellor of Treatment Affairs
IQR: Interquartile range; SD: Standard deviation; MS: Multiple sclerosis; RR: Relapsing remitting; SP: Secondary progressive; PR: Progressive relapsing; PP: Primary progressive

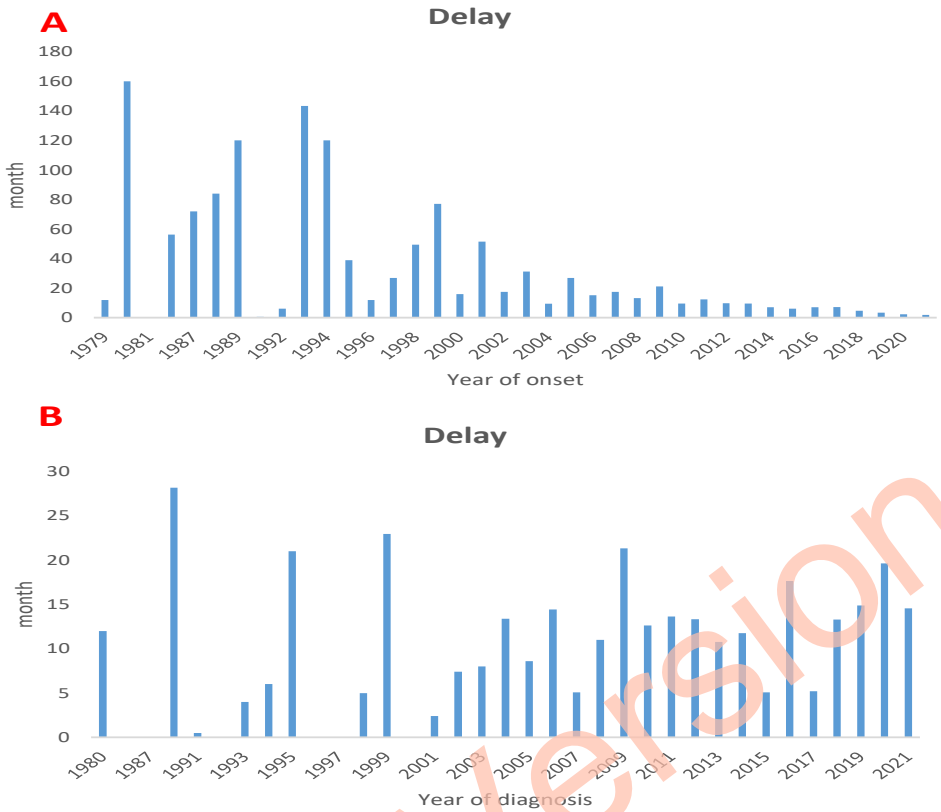

Figure 1. A) Bar chart for year of onset and mean time of diagnostic delay (month); B) Bar chart for year of diagnosis and mean time of diagnostic delay (month)

The mean ± SD of delay in MS diagnosis was 12.32 ± 33.26 months, and the median delay was 0 (IQR: 0-9). The minimum and maximum delay was 0 and 312 months, respectively. Table 1 presents the median and mean values of delay (month) in MS diagnosis in the subgroups. There was a significant association between the median delay in diagnosis and the admission unit and history of hospitalization due to MS. Therefore, patients without a history of hospitalization had a longer delay in MS diagnosis.

Figure 1 shows the relationship between year of onset and mean time of diagnostic delay (month) (A), and the relationship between year of diagnosis and mean time of diagnostic delay (month) (B). Based on year of onset, the mean time of diagnostic delay (month) was maximum in the year 1981 (Figure 1, A). In addition, year of diagnosis 1987 had maximum of diagnosis delay (month) (Figure 1, B).

Figure 2 presents the delay in MS diagnosis. This histogram is right-skewed, suggesting that many patients had a slightly delayed diagnosis. The results of Shapiro-Wilk test, Kolmogorov-Smirnov test, and the diagrams demonstrate deviations from a normal distribution

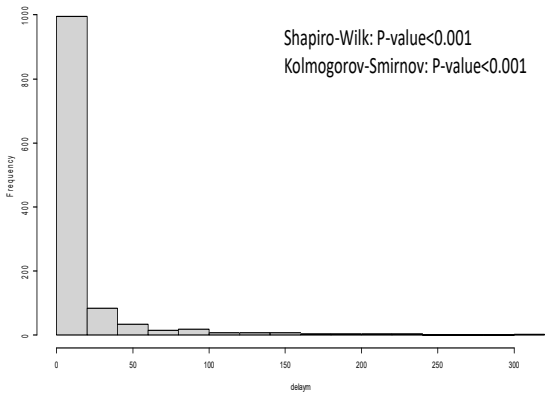

Figure 2. Histogram of delay (month) in multiple sclerosis (MS) diagnosis

This study used Poisson, NB, ZIP, and ZINB regression models to select the best model for identifying factors affecting delay in MS diagnosis. Table 2 presents the performance of the models. According to the AIC and MSE indices, the NB regression model showed the best performance.

Table 3 presents the results of NB regression model for identifying factors influencing delay in MS diagnosis. According to this model, a history of hospitalization and the year of symptom onset were significantly correlated with delay in MS diagnosis. The number of months of delaying in patients with a history of hospitalization was 45% less than others. With an increase of one calendar year in delayed diagnosis, the risk of delay decreased by 15%; it should be noted that in recent years, patients with MS are diagnosed earlier.

Table 2. Comparison of model performance regarding factors affecting delay in multiple sclerosis (MS) diagnosis

Index	Poisson	NB	ZIP	ZINB
AIC	25919	4177	15500	8228
MSE	36.76	0.55	3.82	0.99

NB: Negative binomial; ZIP: Zero-inflated Poisson; ZINB: Zero-inflated negative binomial; AIC: Akaike information criterion; MSE: Mean squared error

Considering the significant effect of the year of symptom onset on the delayed diagnosis of MS, the EDSS score was calculated in these years. This score was estimated for individuals who had the MS symptoms for at least two years. In this study, the mean ± SD of EDSS score was 2.36 ± 2.31 for all patients (1093 patients with MS for at least two years). In 326 (29.8%) patients, the onset of symptoms was reported after 2017 (the time of using the McDonald criteria). Table 4 presents the descriptive EDSS scores before and after 2017.

The median and mean EDSS scores were higher before 2017, and there was a significant difference between the two groups. Table 4 presents the results of comparison of EDSS scores between the subgroups. Sex, type of MS, and history of hospitalization were significantly associated with the EDSS score. The EDSS scores were higher in men, patients with secondary progressive MS (SPMS), and patients with a history of hospitalization compared to others. The correlation coefficient for the relationship between delay in MS diagnosis and the EDSS score was 0.18 [95% confidence interval (CI): 0.13-0.23], and their relationship was significant (P < 0.001).

Discussion

Considering the numerical nature of the response variable and its deviation from a normal distribution despite a sufficient sample size, the performance of four count regression models was compared in this study to select the best model for identifying factors affecting delay (months) in MS diagnosis. Based on the AIC and MSE indices, the NB regression model showed the best performance. Besides, the greater variance in delay in MS diagnosis (33.26) relative to the mean value (12.32) confirms the effective application of NB regression models.

The mean delay (months) in MS diagnosis was shorter in the present study compared to studies conducted by Ghiasian et al.[16] (18.23 months) and Thormann et al.[20] (47.5 months) and longer than the study by Aires et al.[19] (9 months). The mean age and median age at MS diagnosis were 27.73 and 27 years, respectively, which is almost equal to the mean value estimated by Mobasheri et al.[17] (29.1 years) and lower than that reported by Aires et al. (36 years). These findings show that the prevalence of MS is high in young adults in Mazandaran Province.

The results of the univariate analysis revealed a significant association between delay in MS diagnosis and the admission unit and history of hospitalization. In other words, patients admitted to the university had the longest delay in MS diagnosis.

Table 3. Factors affecting delay in multiple sclerosis (MS) diagnosis based on negative binomial (NB) regression models

Variables		b	SE	P	Exp(b)	95% CI Exp(b)
Sex	Women	-0.110	0.22	0.611	0.90	0.58-1.38
Age	-	-0.001	0.01	0.816	1.00	0.98-1.02
Family history	Yes	-0.100	0.24	0.674	0.90	0.57-1.45
Place of diagnosis	Hospital	ref				
	University	-2.150	1.93	0.264	8.58	0.20-> 30
	MS societies	-1.950	2.99	0.513	0.14	0.00-> 30
	Physician office	0.010	0.35	0.992	1.01	0.51-2.01
MS type	RR	ref				
	PR	-0.270	0.66	0.681	0.76	0.21-2.78
	PP	0.510	0.31	0.110	1.67	0.91-3.06
Hospitalization	Yes	-0.590	0.19	0.002	0.55	0.38-0.80
Year of onset	-	-0.160	0.02	< 0.001	0.85	0.82-0.89

RR: Relapsing remitting; PR: Progressive relapsing; PP: Primary progressive; MS: Multiple sclerosis; CI: Confidence interval

Table 4. Comparison of Expanded Disability Status Scale (EDSS) scores between the subgroups

Variables		n (%) (n = 1093)	Mean ± SD	Median (IQR)	P*
Year of onset	< 2017	759 (70.0)	2.80 ± 2.42	2.0 (1-5)	< 0.001
	≥ 2017	326 (30.0)	1.30 ± 1.61	1.0 (0-2)	
Sex	Men	282 (25.8)	2.89 ± 2.38	2.5 (1-5)	< 0.001
	Women	811 (74.2)	2.17 ± 2.26	1.0 (0-3.5)	
Family history	No	908 (83.1)	2.37 ± 2.33	1.5 (0-4)	0.852
	Yes	185 (16.9)	2.29 ± 2.21	2.0 (0-3.5)	
Place of diagnosis	Hospital	112 (10.3)	2.62 ± 2.15	2.0 (1-4.5)	0.292
	University	9 (0.8)	2.00 ± 2.30	1.5 (0-4)	
	MS societies	10 (0.9)	3.00 ± 2.31	3.0 (0-3)	
	Physician office	961 (88.0)	2.33 ± 2.33	1.5 (0-4)	
Type of MS	RR	740 (68.4)	1.10 ± 1.28	1.0 (0-2)	< 0.001
	SP	235 (21.7)	5.52 ± 1.25	5.5 (5-6.2)	
	PR	19 (1.8)	5.34 ± 2.13	6.0 (4.2-7)	
	PP	88 (8.1)	3.73 ± 1.78	3.5 (3-5)	
Hospitalization	No	355 (32.5)	1.93 ± 2.22	1.0 (0-3.5)	< 0.001
	Yes	736 (67.5)	2.55 ± 2.32	2.0 (0-4.5)	

*P-value based on Kruskal-Wallis test

MS: Multiple sclerosis; RR: Relapsing remitting; SP: Secondary progressive; PR: Progressive relapsing; PP: Primary progressive; IQR: Interquartile range; SD: Standard deviation

One of the possible reasons for the longer delay in diagnosis at the university was their inattention to the initial symptoms of the disease, aggravation of their condition, and referral of critically ill patients to hospitals. Moreover, patients without a history of hospitalization had a longer delay in MS diagnosis. In the NB regression model, the history of hospitalization was significantly correlated with delay in diagnosis. According to the initial descriptive data, the average delay in MS diagnosis was shorter in patients with a history of hospitalization compared to others. One of the reasons for this finding may be the patients' referral to hospitals due to the onset of their symptoms and their early diagnosis.

Additionally, the year of symptom onset was significantly associated with a delayed diagnosis. With a one calendar-year increase in MS diagnosis, the average delay in diagnosis decreased. In other words, patients who have recently developed MS were identified earlier by healthcare providers; it seems that delay in MS has decreased over time. Possible reasons for this finding can be the availability of facilities and medical advances, changes in diagnostic criteria, patients' greater sensitivity to the symptoms and personal health, and increased knowledge of MS in recent years. Other studies have also found that the year of diagnosis is one of the factors affecting delay in MS diagnosis.[25-29]

Besides the mentioned factors, the effects of age, sex, diagnosis unit, and type of disease on delay in MS diagnosis were investigated in this study. However, no significant relationship was found between these factors and delay in MS diagnosis. Furthermore, in this study, family history had no significant relationship with a delayed MS diagnosis, although other studies have reported a significant relationship between these two variables.[8] Based on the present findings, the primary EDSS score was higher in patients before 2017, and there was a significant difference before and after this year. These findings suggest that the EDSS scores have decreased due to changes in the diagnostic criteria. One possible reason for this finding is the faster identification of patients since 2017 based on the McDonald criteria, resulting in a reduction in disabilities.[29] Expectedly, the MS type was significantly associated with the EDSS score. Moreover, progressive MS had worse outcomes. In line with a study by Kingwell et al.,[28] the present study found a significant positive relationship between delay in MS diagnosis and the EDSS score. Besides, the EDSS scores were higher in men and patients with a history of hospitalization.

Similar to other studies, the present study is subject to some limitations. First, this was a retrospective study, and the patient or the patient's companion provided some of the information; therefore, there might be some report or recall bias. Another limitation of this study was delayed MS diagnosis depending on the waiting list of MRI and the lack of diagnostic facilities in the patient's city of residence.

Conclusion

A comparison of the results of the present study with previous research revealed that the average delay in MS diagnosis and the average age at the time of diagnosis were critical in Mazandaran Province. Patients develop MS at a young age and are diagnosed with a longer delay. Nevertheless, the significant relationship between the onset of MS symptoms and the time of diagnosis demonstrates an improvement in MS diagnosis in recent years.

Conflict of Interests

The authors declare no conflict of interest in this study.

Acknowledgments

This study was extracted from a research project, approved by Mazandaran University of Medical Sciences, Sari, Iran, with the ethics code of IR.MAZUMS.REC.1398.6026. We would like to express our gratitude to the university, the officials of NMSRI, and MS societies in Mazandaran Province.

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