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# Association of helicobacter pylori with multiple sclerosis: Protective or risk factor?

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**Keywords**
Multiple Sclerosis; Helicobacter Pylori; Clinically Isolated Syndrome; Secondary Progressive Multiple Sclerosis; Iran

**Abstract**

**Background:** Multiple sclerosis (MS) is a common autoimmune inflammatory disease in the central nervous system (CNS) without exact pathology. Environmental factors such as infections have a causal or protective role in MS. Helicobacter pylori (HP) is one of the infections in digestive diseases and previous studies reported controversial findings of this infection role in MS. So, we conducted this study to assess the frequency of HP infection in patients with MS in comparison to the healthy population.

**Methods:** This cross-sectional study was undertaken between 2015 and 2019. 191 participants including 58 patients with clinically isolated syndrome (CIS), 57 patients with relapsing-remitting MS (RRMS), 39 patients with secondary progressive MS (SPMS), and 39 age- and sex-matched healthy controls (HCs) were tested for the presence of HP immunoglobulin G (IgG) and IgM antibodies (Abs) in their serum sample.

**Results:** The frequency of HP IgG seropositivity in patients with SPMS was significantly higher than patients with CIS [Odds ratio (OR): 6.333, 95% confidence interval (CI): 2.522-15.906, $P < 0.001$], patients with RRMS (OR: 4.583, 95% CI: 1.842-11.407, $P = 0.001$), and HCs (OR: 8.485, 95% CI: 3.058-23.540, $P < 0.001$). We did not find a significant difference among other study groups regarding IgG seropositivity. No significant difference among groups regarding HP IgM seropositivity was evident. On univariate model, Expanded Disability Status Scale (EDSS) score (OR: 1.038, 95% CI: 1.038-1.460, $P = 0.017$) and SPMS (OR: 4.583, 95% CI: 1.842-11.407, $P = 0.001$) were predictor for HP IgG seropositivity. On multivariate model, only SPMS had higher risk for HP IgG seropositivity compared to RRMS (OR: 5.554, 95% CI: 1.327-23.253, $P = 0.019$). We did not find a significant association between clinical and demographic variables with HP IgM seropositivity.

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**Conclusion:** Based on our findings, progressive MS and HP infection may have association. Further longitudinal studies with large sample size are needed to determine the role of HP infection in MS.

## Introduction

Multiple sclerosis (MS) is a chronic inflammatory immune-mediated disease in the central nervous system (CNS).[1] The first clinical event that is compatible with MS is clinically isolated syndrome (CIS). The disease follows relapsing or progression course leading to severe disability and is highly associated with mortality and morbidity.[2,3] The exact pathology of MS is still unclear; however, a combination of environmental and genetic factors has important role in pathology of MS.[4,5] A growing body of literature has investigated the effect of infectious agents on the pathology of MS.[6]

Helicobacter pylori (HP) is a gram-negative bacteria which colonizes in the human stomach from early childhood. More than half of the global population is infected with HP.[7] HP has high prevalence in developing countries; while the incidence of the HP is reduced in western countries, because of high hygiene status and widespread use of antibiotics.[8] Although most individuals with HP remain asymptomatic, infection with HP has association with gastric diseases such as peptic ulcer, low-grade gastric mucosa-associated lymphoid tissue (MALT) lymphoma, and gastric carcinoma.[9-11] Also, HP can lead to diseases outside the gastrointestinal (GI) tract including cerebrovascular diseases, Alzheimer's disease (AD), Parkinson's disease (PD), and seizure disorders.[12-14] Paradoxically, several studies showed that getting infected with HP in childhood had a protective role in atopic disorders.[15]

Although it is commonly believed that HP infection has protective role against developing of MS, the evidence is mixed. Li et al. showed lower HP frequency in conventional MS (CMS) compared to general Japanese population. Also, they found inverse association between HP seropositivity and severity of disease.[16] On the other hand, Gavalas et al. showed higher proportion of patients with MS with HP infection compared to healthy controls (HCs).[17] Inconsistent with these findings, Long et al. found no substantial difference between MS and Chinese healthy population regarding HP seropositivity. They also found no association between HP infection and demographic and clinical characteristics of patients with MS.[18]

Whilst some research has been carried out on the patients with MS, limited studies have attempted to investigate the association of HP infection with different clinical courses of MS. Interestingly, it has been suggested that HP infection may have association with secondary progressive MS (SPMS).[19,20] Also, a longitudinal study found high proportion of patients with CIS with HP infection and proposed that eradication of HP infection might reduce the risk of conversion from CIS to definite MS.[21]

Due to limited data regarding the rate of HP infection among different clinical courses of MS, we conducted the present study. The main issues addressed in this paper are: a) determining the frequency of HP immunoglobulin G (IgG) and IgM seropositivity in CIS, relapsing-remitting MS (RRMS), SPMS, and HCs, b) comparison of the frequency of IgG and IgM seropositivity among the study groups, and c) explanatory analysis to identify the risk factor of IgG and IgM seropositivity in patients with MS.

## Materials and Methods

***Study population and design:*** This study was conducted in the MS clinic of Kashani Hospital, affiliated to Isfahan University of Medical Sciences, Isfahan, Iran, from May 2018 to October 2019. In the present study, 154 target participants including 58 patients with CIS, 57 patients with RRMS, and 39 patients with SPMS who referred to outpatient MS clinic were enrolled. Inclusion criteria were: diagnosis of MS as carried out and determined by a trained neurologist according to the McDonald criteria[22,23] and signed written informed consent. Exclusion criteria were neurological disorders rather than MS. In addition, 39 healthy subjects, comprising haphazard selection of sexes and ages from general population referred to Kashani Hospital for routine medical tests, were considered as HCs and their demographic information was obtained. The flow diagram of the patient selection in the study is shown in figure 1.

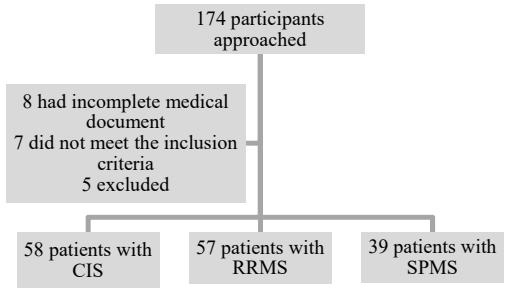


**Figure 1.** The flow diagram of the patient selection in the study

CIS: Clinically isolated syndrome; RRMS: Relapsing-remitting multiple sclerosis; SPMS: Secondary progressive multiple sclerosis

The study protocol was approved by the Regional Bioethics Committee of Isfahan University of Medical Sciences (No. 293006) and written informed consent was obtained from all subjects.

***Demographic and clinical features:*** We recorded demographic information including age, gender, marital status (single/married), employment status (employed/unemployed), and educational levels (Advance/basic). Participants with education lower than diploma were considered as ungraduated. Clinical characteristics including severity of disease, disease duration, and magnetic resonance imaging (MRI) findings were extracted from medical documents. The severity of disease was measured using Expanded Disability Status Scale (EDSS)[24] by single neurologist. All brain MRI scans were performed using GE 1.5-tesla MRI scanner (General Electric, Milwaukee, WI, USA). The slice thickness of the axial scans was 3-5 mm. We assessed the location of brain plaque (supratentorial, infratentorial, and whole of brain).

***Serology:*** The presence of specific IgG and IgM antibodies (Abs) against HP in the test was detected by commercial kit (Euroimmun, Lubeck, Germany), according to the manufacturer's instructions. A measure of 20 RU/ml was set as cut-off value for IgG Ab, such that any reading more than this cut-off point was considered as HP seropositivity. Also, a measure of 40 RU/ml was set as cut-off value for IgM Ab.

All data were presented as mean ± standard deviation (SD) or frequency (%) for continuous and categorical variables, respectively. We performed one-way analysis of variance (ANOVA) and Kruskal-Wallis test with Bonferroni correction and chi-square test to compare demographic and clinical variables among the study groups. The frequencies of HP seropositivity among groups were compared by chi-square test. Logistic regression analysis was performed to predict HP seropositivity versus seronegativity in patients with MS. At first, we performed a univariate logistic regression to determine the association of each variable with HP infection. We reviewed literature to choose potential predictor of HP infection.[16,25] The candidate variables consisted of age, sex (male/female), education level (uneducated/educated), EDSS score, and disease duration. Then, all risk factors which had shown an association in the univariate model were added into the multivariate model. Finally, we used a backward stepwise selection to determine the most important factors associated with outcome in final multivariate model. The order of variable selection was determined by evaluation of the Wald statistic. The level of significance was set at 0.05. All statistical calculations were done using the SPSS software (version 20, IBM Corporation, Armonk, NY, USA).

## Results

***Demographic and clinical information:*** Demographic and clinical information of subjects are presented in table 1. No difference was found among groups regarding education level, marriage status, and employment status. Regarding age of patients, there was a significant difference between SPMS and CIS groups [95% confidence interval (CI): 1.410-12.080, P = 0.007]. We observed a significant difference between RRMS and CIS regarding sex [odds ratio (OR): 4.054, 95% CI: 1.560-10.537, P = 0.004]. Post hoc analysis showed that patients with SPMS had higher EDSS score compared to patients with RRMS (P < 0.001) and those with CIS (P < 0.001). Further analysis showed that patients with RRMS had higher disease duration compared to CIS (P = 0.003). The difference between the SPMS and CIS groups regarding location of brain lesion was significant (P = 0.036). Regarding other variables, no significant difference was found.

***Frequency of HP infection among the study groups:*** The frequency of HP IgG seropositivity was 48.0% in all patients (74/154), with HP IgG seropositivity in 76.9% (30/39) of patients with SPMS, 42.1% of patients with RRMS (24/57), and 34.5% of patients with CIS (20/58). Also, HP IgG seropositivity was presented in 28.2% of HCs (11/39). Figure 2 details the data on HP IgG seropositivity.

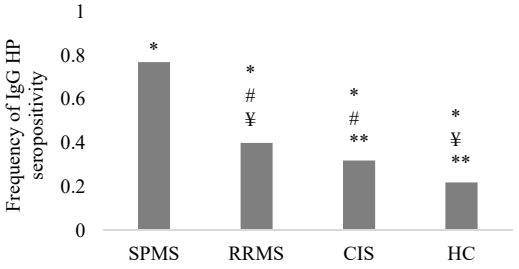


**Figure 2.** Frequency of helicobacter pylori (HP) immunoglobulin (IgG) seropositivity among the study groups

(Rate of HP seropositivity in secondary progressive multiple sclerosis (SPMS) was high compared to relapsing-remitting multiple sclerosis (RRMS), clinically isolated syndrome (CIS), and healthy controls (HCs). There was no difference between frequency of HP seropositivity among RRMS, CIS, and HC.)

*P < 0.001, #P = 0.400, ¥ P = 0.165, **P = 0.516

**Table 1.** Demographic and clinical characteristics in subjects

| Category | | CIS (n = 58) | RRMS (n = 57) | SPMS (n = 39) | Control (n = 39) | Statistics | P |
|---|---|---|---|---|---|---|---|
| Age (year) (mean ± SD) | | 36.07 ± 9.02 | 36.45 ± 7.84 | 39.82 ± 9.96 | 36.84 ± 8.15 | $F_{(3, 145)} = 3.634$ | 0.014 |
| Sex [n (%)] | Female | 37 (63.8) | 50 (87.7) | 30 (76.9) | 30 (76.9) | $\chi^2_{(3)} = 9.107$ | 0.028 |
| | Male | 21 (36.2) | 7 (12.3) | 9 (23.1) | 9 (23.1) | | |
| Education [n (%)] | Advance degree | 46 (79.3) | 42 (73.7) | 28 (71.7) | 34 (82.1) | $\chi^2_{(3)} = 1.660$ | 0.646 |
| | Basic degree | 12 (20.7) | 15 (26.3) | 11 (28.2) | 7 (17.9) | | |
| Marriage status [n (%)] | Married | 39 (67.2) | 35 (61.4) | 28 (71.8) | 26 (66.6) | $\chi^2_{(3)} = 2.899$ | 0.407 |
| | Single | 19 (32.7) | 22 (38.5) | 11 (28.2) | 13 (33.3) | | |
| Employment [n (%)] | Employed | 18 (31.1) | 23 (40.4) | 11 (28.2) | 9 (32.1) | $\chi^2_{(3)} = 4.075$ | 0.253 |
| | Unemployed | 40 (68.9) | 34 (59.6) | 28 (71.7) | 30 (76.9) | | |
| EDSS [median (IQR)] | | 0.0 (0.0-0.25) | 0.0 (0.0-1.5) | 4.0 (3.0-6.0) | N/A | $\chi^2_{(3)} = 39.210$ | < 0.001 |
| Duration of disease [median (IQR)] | | 4.1 (4.3-6.4) | 7.2 (5.1-10.2) | 9.0 (4.7-11.2) | N/A | $\chi^2_{(3)} = 14.124$ | 0.001 |
| Brain plaque [n (%)] | Supratentorial | 25 (43.1) | 14 (24.5) | 7 (17.9) | N/A | $\chi^2_{(4)} = 9.673$ | 0.046 |
| | Infratentorial | 1 (1.7) | - | 1 (2.5) | N/A | | |
| | Whole of brain | 32 (55.1) | 43 (75.4) | 31 (79.4) | N/A | | |
| Disease modifying therapy [n (%)] | INF-β | 18 (31.0) | 23 (40.3) | 13 (33.3) | N/A | $\chi^2_{(6)} = 54.392$ | < 0.001 |
| | GA | 2 (3.0) | 7 (23.3) | 2 (5.1) | N/A | | |
| | Rituximab | - | 3 (5.2) | 17 (43.5) | N/A | | |
| | Others | - | 24 (42.2) | 7 (18.1) | N/A | | |
| | No treatment | 38 (66.0) | - | - | N/A | | |

CIS: Clinically isolated syndrome; RRMS: Relapsing-remitting multiple sclerosis; SPMS: Secondary progressive multiple sclerosis; SD: Standard deviation; EDSS: Extended Disability Status Scale; IQR: Interquartile range; INF-β: Interferon beta; GA: Glatiramer acetate

Compared to HCs, patients with MS had higher HP IgG seropositivity (OR: 2.355, 95% CI: 1.095-5.064, P = 0.026). HP IgG seropositivity was significantly higher in patients with SPMS compared to HCs (OR: 8.485, 95% CI: 3.058-23.540, P < 0.001), patients with RRMS (OR: 4.583, 95% CI: 1.842-11.407, P = 0.001), and patients with CIS (OR: 6.333, 95% CI: 2.522-15.906, P < 0.001). There was no significant difference in HP IgG seropositivity frequency among patients with RRMS compared to HCs (OR: 1.851, 95% CI: 0.773-4.434, P = 0.165) and patients with CIS (OR: 1.382, 95% CI: 0.650-2.939, P = 0.400). The frequency of HP IgG seropositivity did not significantly differ between patients with CIS and HCs (OR: 1.340, 95% CI: 0.554-3.239, P = 0.516). Figure 2 details the data on HP IgG seropositivity.

We found HP IgM seropositivity in 63 (40.9%) patients with MS including 20 (51.3%) patients with SPMS, 19 (33.3%) with RRMS, and 24 (41.3%) with CIS. Also, 20 (51.3%) HCs were HP IgM seropositive. No significant difference between all patients with MS and HCs was observed (OR: 0.658, 95% CI: 0.325-1.331, P = 0.242). As shown in figure 3, patients with SPMS had no significant differences compared to patients with RRMS (OR: 2.105, 95% CI: 0.913-4.853, P = 0.079), patients with CIS (OR: 1.491, 95% CI: 0.659-3.375, P = 0.337), and HCs (OR: 1.000, 95% CI: 0.411-2.430, P > 0.999). Also, patients with RRMS had no significant differences compared to HCs (OR: 0.708, 95% CI: 0.332-1.513, P = 0.373) and patients with CIS (OR: 0.708, 95% CI: 0.332-1.513, P = 0.373). The frequency of HP IgM seropositivity did not significantly differ between CIS and HCs (OR: 0.671, 95% CI: 0.296-1.518, P = 0.337). Totally, no significant difference among study groups was found.

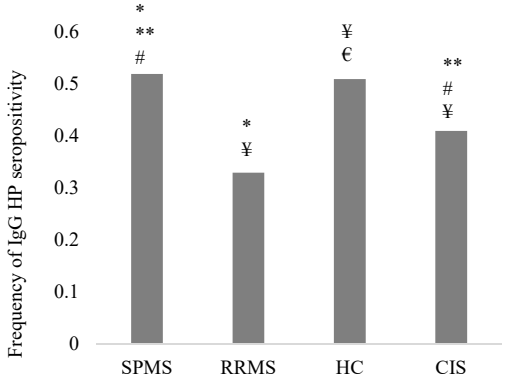


**Figure 3.** Frequency of helicobacter pylori (HP) immunoglobulin M (IgM) seropositivity among the study groups (There was no significant difference among the study groups)

CIS: Clinically isolated syndrome; RRMS: Relapsing-remitting multiple sclerosis; SPMS: Secondary progressive multiple sclerosis; HC: Healthy control

*P = 0.079, **P = 0.337, #P > 0.999, ¥P = 0.373, €P = 0.337

***Association of HP seropositivity with demographic and clinical features:*** On univariate analysis, we found association of HP IgG seropositivity with EDSS score and SPMS. Results showed that one-unit increase in EDSS score could increase 1.231 (95% CI: 1.038-1.460, P = 0.017) times the odds of HP IgG seropositivity. The risk of HP IgG seropositivity among patients with SPMS was higher than patients with RRMS (OR: 4.583, 95% CI: 1.842-11.407, P = 0.001). Only clinical course remained significant in multivariate model. Patients with SPMS (OR: 5.554, 95% CI: 1.327-23.253, P = 0.019) had significantly higher ORs for HP IgG seropositivity compared to patients with RRMS (Table 2).

**Table 2.** Association of immunoglobulin G (IgG) helicobacter pylori (HP) infection with demographic and clinical characteristics of patients with multiple sclerosis (MS)

| Variable | | B | SE | Wald | df | OR | 95% CI | P |
|---|---|---|---|---|---|---|---|---|
| Univariate model | | | | | | | | |
| Age | | 0.018 | 0.021 | 0.778 | 1 | 1.019 | 0.978-1.061 | 0.378 |
| Sex (ref = female) | | 0.174 | 0.377 | 0.212 | 1 | 1.190 | 0.568-2.494 | 0.645 |
| EDSS score | | 0.208 | 0.087 | 5.697 | 1 | 1.231 | 1.038-1.460 | 0.017 |
| Disease duration | | 0.027 | 0.061 | 0.197 | 1 | 1.028 | 0.911-1.159 | 0.657 |
| Couse of disease (ref = RRMS) | CIS | -0.323 | 0.385 | 0.705 | 1 | 0.724 | 0.340-1.539 | 0.401 |
| | SPMS | 1.522 | 0.465 | 10.710 | 1 | 4.583 | 1.842-11.407 | 0.001 |
| Multivariate model | | | | | | | | |
| EDSS score | | -0.005 | 0.146 | 0.001 | 1 | 0.929 | 0.747-1.325 | 0.600 |
| Couse of disease (ref = RRMS) | CIS | -0.195 | 0.434 | 0.230 | 1 | 0.822 | 0.351-1.926 | 0.996 |
| | SPMS | 1.715 | 0.731 | 5.508 | 1 | 5.554 | 1.327-23.253 | 0.019 |

CIS: Clinically isolated syndrome; SPMS: Secondary progressive multiple sclerosis; RRMS: Relapsing-remitting multiple sclerosis; EDSS: Extended Disability Status Scale; SE: Standard error; df: Degree of freedom; OR: Odds ratio; CI: Confidence interval

**Table 3.** Association of immunoglobulin M (IgM) helicobacter pylori (HP) infection with demographic and clinical characteristics of patients with multiple sclerosis (MS)

| Variable | | B | SE | Wald | df | OR | 95% CI | P |
|---|---|---|---|---|---|---|---|---|
| Univariate model | | | | | | | | |
| Age | | 0.001 | 0.018 | 0.003 | 1 | 1.001 | 0.966-1.038 | 0.954 |
| Sex (ref = female) | | -0.705 | 0.361 | 3.813 | 1 | 0.495 | 0.240-1.003 | 0.051 |
| EDSS score | | 0.075 | 0.800 | 0.875 | 1 | 1.078 | 0.921-1.261 | 0.350 |
| Disease duration | | -0.025 | 0.065 | 0.150 | 1 | 0.975 | 0.859-1.107 | 0.698 |
| Couse of disease (ref = RRMS) | CIS | 0.345 | 0.387 | 0.793 | 1 | 1.412 | 0.661-3.016 | 0.373 |
| | SPMS | 0.744 | 0.426 | 3.052 | 1 | 2.105 | 0.913-4.853 | 0.081 |

CIS: Clinically isolated syndrome; SPMS: Secondary progressive multiple sclerosis; RRMS: Relapsing-remitting multiple sclerosis; EDSS: Extended Disability Status Scale; SE: Standard error; df: Degree of freedom; OR: Odds ratio; CI: Confidence interval

We also conducted univariate analysis to evaluate the association of HP-IgM infection with demographic and clinical features. No association was found between HP IgM seropositivity and variables (Table 3).

## Discussion

It is well known that infection agents have important role in the pathogenesis of MS.[26,27] HP is one of the most prevalent infections of the GI system. We found higher rate of HP IgG seropositivity in patients with MS compared to HCs. Our findings showed higher frequency of HP IgG seropositivity in patients with SPMS compared to those with ICS, RRMS, and HCs. There was no significant difference among patients with RRMS, patients with CIS, and HCs regarding HP IgG seropositivity. It seems that the difference between patients with MS and HCs in HP IgG seropositivity is due to high proportion of patients with SPMS with positive HP-IgG. No remarkable difference was observed among patients with MS and HCs regarding HP IgM seropositivity. The same result was found when we compared patients with MS and HCs with respect to clinical course.

Approximately, 70 percent of patients with SPMS had HP IgG seropositivity. In the line with our study, previous investigations showed an association between SPMS and HP IgG seropositivity.[19,20] On univariate model, EDSS score and SPMS had association with HP IgG seropositivity, but in multivariate model, only SPMS had association. It is possible, therefore, that the association of HP infection with EDSS score is related to high EDSS score in SP course. Also, these findings suggest that the association between HP infection and SPMS is related to specific SP course pathogenesis. Efthymiou et al. found that reactivity against particular HP immunodominant antigens such as anti-VacA differed among SPMS, RRMS, and control groups.[19] In their latest study, rate of anti-heat shock protein 60 (HSP60) HP Ab in patients with MS was higher than HCs, especially in SPMS. In this study, HSP60 Ab was presented in all patients with HP seropositivity. Also, correlation between HSP60 Ab and anti-VacA was reported. They found no association between magnitude of HSP60 Ab and EDSS score, number of relapse, and duration of disease.[28] In another study conducted on Egyptian patients with MS, high level of HSP60 Ab in patients with SPMS was observed.[20]

The frequency of HP seropositivity in CIS cases was higher than controls, but this difference was not statistically significant. Greek cohort study hold on patients with CIS grasped an interesting correlation between HP infection and CIS.[21] It found lower risk for conversion from CIS to definite MS in patients who had eradicated HP infection. Pro-inflammatory cytokines level, such as interleukin (IL)-2 and IL-12, in patients with CIS with HP-positive lab label, is detected more. However, treatment against HP infection can affect other gut bacteria. So, these results may be due to eradication of other bacteria. Taken together, more investigation is needed to reveal role of HP infection in CIS disease.

Although the rate of HP seropositivity in patients with RRMS was higher than controls, this difference was not statically significant. There are controversial reports about the frequency and role of HP infection in RRMS. HP histological survey among Greek MS-afflicted showed more abundance of HP infection within patients with RRMS compared to control group who were chosen from patients with anemia.[17] Also, Long et al. reported higher prevalence of HP seropositivity in Chinese patients with MS compared to HCs. In this study, clear association

between HP infection across MS disorder pathogenesis was not found.[18] Due to probable dependent mechanism, including plethora of platelet coagulation, increased reactive oxygen metabolites, production of factors which lead to increased fibrin status, and managed cell death and degeneration, HP infection may have association with MS.[16]

On the other hand, in a number of studies, it has been shown that HP infection may have protective role against MS disease.[16,25,29,30] In studies among Japanese patients, high rate of HP seropositivity in the patients with CMS and MS cases with positive aquaporin-4 (AQP4) has been shown. However, in both studies, frequency of HP seropositivity was similar between controls and patients with MS collectively.[16,29] A systematic literature review concluded that HP infection might have reverse association with MS. However, none of the studies enrolled in the systematic review had assessed frequency of HP infection in patients with SPMS and patients with CIS.[31] Therefore, the result of this study cannot be generalized to all types of MS.

Exact reasons upon the argument between HP and MS are not clear enough. Race diversity may be recognized as a probable reason of this issue. Regardless of the same community of assessment, our study is in contradiction with other studies which assessed frequency of HP infection in Iranian patients with MS.[30,32] Generally, there is still no rational evidence into the race diversity impression on this difference.[33] Detection methods can be named as another possible cause of this argument, since variable methods have been used in many studies. In this study, both IgM and IgG Abs against HP were detected. We assessed IgM Ab to discriminate between current and past HP infection. HP IgM Ab seropositivity was similar among groups of study and had no association with variables.

A low sample size can be numbered as one of the study limitations. High sensitivity and low specificity and accuracy of enzyme-linked immunosorbent assay (ELISA) test, besides its great false positive rate, accompanied our sort of results. In our study, duration of disease was not similar among patients. Also, age of patients with SPMS was higher than patients with CIS. It has been suggested that immunosuppressive treatment may influence HP infection.[34] In the current study, most of patients with MS used immunosuppressive treatment. So, our results may be affected by immunosuppressive treatment.

## Conclusion

SPMS type showed more HP IgG prevalence compared to HC group and other MS clinical courses. So, the similar causal factors may cause susceptibilities to both SPMS and HP infection. Various studies have reported different outcomes regarding the role of HP infection in development of MS and the definite role of the infection in development of disease, particularly CIS and SPMS, is still unknown. Cohort study with high sample size on different races is needed to determine HP infection role in MS disease.

## Conflict of Interests

The authors declare no conflict of interest in this study.

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