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Research Paper

COVID-19 Infection and Seropositivity in Multiple Sclerosis Patients in Guilan in 2021

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ABSTRACT

Background: Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system. COVID-19 has presented a significant challenge to the care providers of patients with MS.

Objectives: The present study aimed to investigate the frequency of COVID-19 infection and its seropositivity in MS patients in Guilan, Iran, in 2021.

Materials & Methods: In this analytical-cross-sectional study, all patients with relapsing-remitting MS registered in the Guilan MS Association with an expanded disability status scale of less than 5 who were referred for evaluation participated in the study. Information related to the clinical and serological symptoms of COVID-19 infection, changes in drug use, and the occurrence of new attacks were collected. Serological results of COVID-19 (IgG) among them were registered.

Results: In total, 260 patients with MS (78.8% women, and 21.2% men) with a Mean±SD age of 38.7±9.9 years, and a Mean±SD duration of MS of 8.9±4.9 years were investigated. The most commonly used drugs were Dimethyl fumarate, Interferon, and Rituximab, respectively. Thirty-three patients (12.6%) had a clinical COVID-19 infection, of which 32 people had a mild and only one had a critical infection. Eight patients (1.3%) had positive COVID-19 IgG tests. No significant relationship was found between the COVID-19 infection with the type of medication, medication change, clinical attack of MS, and co-morbidities (P>0.05).

Conclusion: A few patients had positive COVID-19 IgG tests and clinical COVID-19 infection. The vast majority had mild disease, and the clinical attack was not related to COVID-19 infection.

Keywords: COVID-19, Multiple sclerosis, Infection

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Highlights

• COVID-19 could provoke the immune system or multiple sclerosis (MS) to predispose patients more to COVID-19 infection.

• But a few patients had positive COVID-19 IgG tests and clinical COVID-19 infection.

• The vast majority of patients with MS and COVID-19 had mild disease, and the clinical attack was not related to COVID-19 infection.

Introduction

Multiple sclerosis (MS) is a demyelinating, inflammatory, and chronic degenerative disease of the central nervous system [1, 2] characterized by recurrent episodes of neurological impairment and disability, which may be progressive sometimes [1]. This disorder is the most common progressive neurological disability in young adults [3]. The activation of the immune system against myelin antigen has a role in developing this disorder [4]. Currently, more than 1.3 million people worldwide have been involved in MS [3]. Iran is one of the countries where the prevalence of MS is high, and it is the second cause of disability among young people in this country [5].

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a human coronavirus that started the COVID-19 pandemic in December 2019 [6]. A significant number of sufferers, especially those with severe forms of Coronavirus disease 2019 (COVID-19) infection, have underlying diseases such as arterial hypertension, cardiovascular disease, chronic lung disease, diabetes, Body mass index (BMI) greater than 40, immunodeficiency, and malignancies, which in some cases have been up to 50% of patients [7]. According to initial reports from China, about 81% of patients with COVID-19 have mild flu-like symptoms or mild pneumonia, and 19% have a severe disease [8].

COVID-19 is a multidimensional and unpredictable syndrome whose outcomes are largely determined by the host's immune response. Compared to other respiratory viruses, this virus induces a stronger and more prolonged invasive inflammatory response [9], which is stimulated by widespread cytokine release and, in severe cases, impairs coagulation function and causes multiorgan failure [10]. As with other coronaviruses which have been isolated from the brain and cerebrospinal fluid of MS patients [11-13], pericytes and astrocytes of the blood-brain barrier may represent entry points for this virus [14].

According to the reports, neurological symptoms were reported in more than 80% of cases [15-20]. Most of the neurological manifestations of COVID-19 shared a common immune substrate. Indeed, the brain lesions associated with COVID-19 reflected vascular and demyelinating pathology and were mainly attributed to severe activation of the immune system with massive production of neurotoxic cytokines (especially IL1-beta and IL6) [21].

During the first outbreak of the COVID-19 pandemic, limited studies were conducted about the effects of MS and MS drugs on the COVID-19 virus and also the effect of COVID-19 on MS. In addition, many people with MS needed access to regular medical services (infusions, physical therapy, occupational therapy, botulinum toxin injections for spasticity, and home care services), which may have been disrupted by changes in health care delivery as a result of the COVID-19 pandemic [22]. It was necessary to consider the potential risk of complications and possible mortality for any patient with MS, who might become infected with SARS-CoV-2 and develop COVID-19. Aspects that should be considered when evaluating respiratory viral infection in patients with MS include smoking, mobility status, age, weight, underlying respiratory diseases, and other diseases (smoking, less mobility, higher age and weight, asthma or chronic obstructive pulmonary disease (COPD), fatigue, and pain increase the risk of COVID-19 infection and its severity). On the other hand, the number of lymphocytes less than 1100/mm^3 was associated with an increased risk of infection and death due to infection. This risk is greatly increased, especially when the lymphocyte count falls below 800/mm^3 (>50% risk) [23-25].

Various drugs, mainly immune system regulators, are used to control MS disease. There were some theories about the effect of MS medication on susceptibility to COVID-19 infection. The classification of MS

treatments includes [1] Disease Modifying Therapies (DMTs), which regulate the body's immune system and generally do not suppress the body's immune system not putting the patient at risk for most infections including Glatiramer acetate, Interferon, and Natalizumab; [2] Some DMTs are immunomodulators, but they limit the immune system's ability to respond to infection and may therefore increase the risk of infections including Dimethyl Fumarate, Fingolimod, and Siponimod; and [3] Some treatments that work in stages with lymphocyte depletion could be dangerous in these patients, including Hematopoietic stem cell transplantation, Alemtuzumab, Mitoxantrone, Cladribin, Rituximab, and Ocrelizumab. Therefore, the recommendations regarding the use of different MS drugs in the crisis of the COVID-19 virus were different [23, 26-28].

Considering all the above cases, we decided to examine the frequency of clinical infection with the COVID-19 virus, its severity, and seropositivity in the population of MS patients in Guilan province, and also make a comparison between different groups of patients (based on the medication they were taking or possibly stopping or not taking the medication). This study could also be indicative of the effects of MS drugs in the face of COVID-19 and help to design the new guidelines for deciding how to continue, stop, or change the medication, or its drugs in the critical situation of facing COVID-19 and or similar viruses.

Materials and Methods

Participants

In this analytical-cross-sectional study, all patients with MS of relapsing-remitting (RRMS) type who were registered in the MS national registry system of Iran, Guilan MS Association branch, were included after obtaining informed consent. The inclusion criteria were as follows: RRMS type of MS based on 7 modified McDonald's criteria, Expanded Disability Status Scale (EDSS) less than 5, and being able to refer to the Guilan MS Association. The exclusion criteria were as follows: unwillingness to participate in the study, suffering from autoimmune diseases and cancer, and taking immunosuppressive drugs.

The data collection tool was a checklist including demographic information (age, gender, duration of MS, the patient's medications, and background disorders) and information related to the clinical signs, symptoms, and serology of COVID-19, changes in medications, and occurrence of new attacks. Serological testing of COVID-19 (IgG test) was performed on all patients participating in the project.

After calling the patients and completing the aforementioned checklist, they were asked about infection with COVID-19 and the symptoms of the disease, and the severity of the disease was determined. The severity of the disease was considered as mild to moderate (fever, cough, myalgia, fatigue), severe (with an increase in respiratory rate >30 per minute and a drop in blood oxygen saturation <93% and <300 mmHg), and critical (respiratory failure requiring mechanical ventilation and septic shock, dysfunction of other organs requiring ICU).

Laboratory exams

The serum of 1cc of patients' blood was separated after centrifugation and stored at a temperature of -20 degrees Celsius. At the desired time, IgG antibody against COVID-19 was determined using the SARS-CoV-2 IgG ELISA Kit manufactured by PISHTAZ TEB DIAGNOSTICS manufactury. This test had a sensitivity of 94.1% and a specificity of 98.3%, and it was qualitative and the results were interpreted based on the cut-off index. Values >1.1 were considered positive, between 1.1 and 0.9 suspicious or equivocal, and less than 0.9 were considered negative.

Statistical analysis

The collected data were coded and entered into SPSS software version 22. Mean±SD were used to describe quantitative variables with normal distribution, and median and interquartile range was used for quantitative variables with non-normal distribution. Also, qualitative variables were reported as numbers and percentages. The normal distribution of quantitative study variables was measured using Kurtosis and Skewness values, Q-Q Plot, Box plot, and Shapiro-Wilk test. The Chi-square test or Fisher's exact test was used to compare the clinical and serological frequency of COVID-19 infection according to qualitative variables.

Results

In this study, 260 patients with MS (pwMS) were examined, of which 205 were women (78.8%) and 55(21.2%) were men. The mean age of them was 38.7±9.9(64-19) years and the average duration of MS was 8.9±4.9(25-1) years. Only one patient was not taking medication for MS (0.4%) and 24 patients (9.2%) had underlying diseases including diabetes or arterial hypertension.

Table 1 shows the frequency of MS medications used in patients. The most used drugs were Dimethyl Fumarate, Interferon, and Rituximab, respectively. Twenty-eight patients (10.8%) changed their medication during the first year of the COVID-19 pandemic. Thirty-three (12.6%) people had a clinical infection, of which 32 people had a mild illness and only one person had a critical illness.

As Table 2 shows, there was no significant relationship between the age group, gender, and comorbidities in terms of COVID-19 infection (P>0.05).

Table 3 shows that there was no significant relationship between the COVID-19 infection with MS medication, type of medication, and change in medication (P>0.05).

Table 1. The frequency of the type of MS medicine in pwMS

Variables		No. (%)
Medication type	Gelatirameracetat	18(6.9)
	Interferon	55(21.2)
	Natalizumab	3(1.2)
	Fingolimod	42(16.2)
	Dimethyl Fumarate	75(28.8)
	Teriflunomide	13(5)
	Rituximab	49(18.8)
	Ocrelizumab	5(1.9)
	Total	260(100)

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Table 2. Comparison of demographic characteristics and comorbidities based on COVID-19 infection in pwMS

Variables (Categories)		Clinical Infection		P
		No. (%)		
		Yes	No	
Age (y)	18-30	5(15.15)	49(21.58)	0.643
	30-45	18(54.54)	121(53.3)	
	>45	10(30.30)	57(25.11)	
	Total	33(100)	227 (100)	
Gender	Female	26(78.78)	179(78.84)	0.999
	Male	7(21.21)	48(21.14)	
	Total	33(100)	227(100)	
Comorbidity	Positive	30(90.9)	206(90.74)	0.999
	Negative	3(9.09)	21(9.25)	
	Total	33(100)	227(100)	

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Table 3. Comparison of medication status based on clinical infection of COVID-19 in pwMS

Drug	Variables	Clinical Infection No. (%)		P
		Yes	No	
Type	Gelatirameracetat	3(9.09)	15(6.6)	0.894
	Interferon	6(18.18)	49(21.58)	
	Natalizumab	0(0)	3(1.32)	
	Fingolimod	5(15.15)	37(16.29)	
	Dimethyl-Fumarate	10(30.3)	65(28.63)	
	Teriflunomide	3(9.09)	10(4.4)	
	Rituximab	6(18.18)	43(18.94)	
	Ocrelizumab	0(0)	5(2.2)	
	Total	33(100)	227(100)	
Change	Yes	2(6.06)	26(11.45)	0.548
	No	31(93.93)	201(88.54)	
	Total	33(100)	227(100)	

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Among all pwMS, only 8 patients (3.1%) had a positive COVID-19 IgG (Figure 1). Among 33 patients who had clinical signs and symptoms of COVID-19 infection, 7 patients were seropositive and among 227 non-clinically infected patients, only 1 patient was seropositive.

Most of the patients (239[91.9%]) did not have a clinical attack of MS and only 21(8.1%) had a clinical attack. Out of 21 patients who experienced an MS attack during the first time of the COVID-19 pandemic, IV Methylprednisolon was prescribed for 18 patients (90.0%) and IVIG for 2 patients (10.0%), and one patient did not receive any treatment. Also, none of these patients (who had a relapse) interrupted the treatment. Among those infected with COVID-19, only one person (3.03%), and among those non-infected with COVID-19, 20 patients

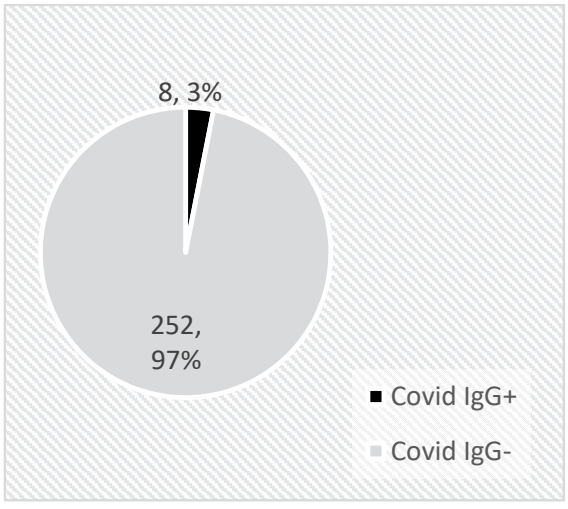

Figure 1. Frequency of serological results of COVID IgG test in pwMS

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Table 4. Comparison of the frequency of variables based on COVID-19 seropositivity in pwMS

Variables(Categories)		COVID-19 Seropositivity No. (%)		P
		Yes	No	
Age(y)	18-30	2(25)	52(20.63)	0.636
	30-45	3(37.5)	136(53.96)	
	>45	3(37.5)	64(25.39)	
	Total	8(100)	252(100)	
Gender	Female	8(100)	197(78.17)	0.209
	Male	0(0)	55(21.82)	
	Total	8(100)	252(100)	
Drug type	Gelatiramerastat	1(12.5)	17(6.74)	0.004
	Interferon	1(12.5)	54(21.52)	
	Natalizomab	0(0)	3(1.19)	
	Fingolimod	2(25)	40(15.87)	
	Dimethyl Fumarate	1(12.5)	74(29.36)	
	Triflunomide	3(37.5)	10(3.96)	
	Rituximab	0(0)	49(19.44)	
	Ocrelizumab	0(0)	5(1.98)	
	Total	8(100)	252(100)	
Comorbidity	Yes	8(100)	228(90.47)	0.99
	No	0(0)	24(9.52)	
	Total	8(100)	252(100)	
Clinical attack	Yes	0(0)	21(8.33)	0.99
	No	(100)	231(91.66)	
	Total	8(100)	252(100)	
Discontinue treatment	Yes	0(0)	0(0)	0.99
	No	8(100)	252(100)	
	Total	8(100)	252(100)	

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(8.81%) had an MS attack. There was no significant relationship between the COVID-19 infection and the clinical attack of MS (P=0.490).

Table 4 shows that there was no significant relationship between age group, sex, a drug used, comorbidity, MS clinical attack, and discontinuation of treatment with serological infection of COVID-19 (P>0.05). This is while a significant relationship was observed between the type

Table 5. Comparison of the frequency of demographic characteristics and comorbidities based on the severity of COVID-19 in pwMS

Variables (Categories)		COVID-19 Severity No. (%)		P
		Mild	Critical	
Age (y)	18-30	5(15.62)	0(0)	0.669
	30-45	17(53.12)	1(100)	
	>45	10(31.25)	0(0)	
	Total	32(100)	1(100)	
Gender	Female	25(78.12)	1(100)	0.99
	Male	7(21.87)	0(0)	
	Total	32(100)	1(100)	
Comorbidity	Yes	29(90.62)	1(100)	0.99
	No	3(9.37)	0(0)	
	Total	32(100)	1(100)	

of drug and COVID-19 seropositivity (P=0.004) so most patients with a positive serological test used Teriflunomide and most patients with a negative serological test used Dimethyl Fumarate.

Table 5 shows that no significant relationship was found between the demographic characteristics and comorbidities based and the severity of the COVID-19 infection (P>0.05). No mortality was observed among MS patients with COVID-19 infection.

Discussion

While MS does not seem to be related to the severity or mortality caused by COVID-19, due to the need to comprehensively investigate the devastating effects of COVID-19 on various diseases, especially MS, this study was conducted on pwMS. The results showed that the majority of patients were women and the mean age of the patients was 38.7 years.

Most patients were taking prophylactic medications for MS. The most common drugs used were Dimethyl Fumarate, Interferon, and Rituximab, respectively. In this study, 33(12.6%) patients had a clinical COVID-19 infection, among which 32 people had a mild infection and only one person had a critical infection. In addition, 8 patients (1.3%) had a positive IgG test. Of the 21(8.1%) patients who had a clinical attack, 20 patients were treated, including 18 patients (90.0%) who received IV Methylprednisolon and 2 patients (10.0%) received IVIG, and none of these patients discontinued their previous treatment.

The results of this study showed that there was no significant relationship between medication use, type of medication and change of medication, clinical attack of MS, and comorbidity with COVID-19 infection. Also, the examination of the variables separately from the clinical and serological results indicated that there was no significant relationship between age group, gender, drugs used, comorbidity, clinical attack of MS, and discontinuation of treatment with serological infection of COVID-19 (P>0.05). This is while a significant relationship was observed between the type of medication and posit-ive serological test (P=0.004) so most patients with the positive serological test used Teriflunomide and most patients with the negative serological test used Dimethyl Fumarate.

As observed in the present study, the results of recent studies do not show that the probability of COVID-19 infection in people with MS was increased compared to the general population [29-32], which is due to the strict adherence to the protocol in the COVID-19 crisis by these patients and not leaving the house except for essential conditions. However, before the COVID-19 pandemic, people with MS were 2-4 times more likely to be hospitalized with a serious infection [33-35].

Similar to our study, Iaffaldano et al. showed that people with MS who were younger, female, had comorbidities, were receiving treatments, and needed to go to medical centers, were more likely to be infected with SARS-CoV2 [36]. Since young people are often exposed to MS and also this age group can include the active and working age group who are required to be in more contact with the outside environment, more cases of COVID-19 can be expected.

In contrast to our study, in Zhang et al. study of 882 MS patients in eight Chinese cities, including Wuhan, the results showed that no MS patient was infected with COVID-19. The researchers attributed this result to the preventive strategies and precise timing of this study, early in the epidemic with data collected before June 2020 [37]. Certainly, the role of compliance with protocols and the use of preventive methods in preventing the infection of this unknown virus, especially in MS patients, can not be neglected.

As it was also determined in this study, the severity of COVID-19 was not related to demographic characteristics and comorbidities in MS patients. The study by Richer et al. also showed that the severity, hospitalization rate, and intensive care unit admission rate related to COVID-19 infection did not increase among MS patients in general [38].

In the present study, most of the subjects who were infected with COVID-19 had mild to moderate disease and only one patient was in a critical condition. However, previous studies have shown that several risk factors among people with MS influence the risk of severe COVID-19. Like the multicenter prospective cohort study of Chaudhry et al. in 2020, this study examined 40 patients with MS and COVID-19. The severity of COVID-19 infection was based on the need for hospitalization. In sum, 19.40(47.5%) had a mild, 15.40(37.5%) had a moderate, and 6.40(15%) had a severe course. In this study, greater severity of the COVID-19 infection was associated with older age, progressive MS phenotype, and a higher degree of MS disability and was not associated with DMT consumption. Of course, the classification of the severity of COVID-19 was somewhat different from our study. In that study, the mild course was defined as the patient not needing to be hospitalized, the moderate course was defined as the need to be hospitalized in the general category, and the severe course was defined as the need for intensive care or death. Also, patients with any type of MS (including RRMS and PMS) with any EDSS level were included in that study [39].

Several large national and international studies were conducted to track risk factors associated with COVID-19 infections in the first year of the pandemic in people with MS. Male sex, older age, cardiopulmonary diseases, progressive MS course, and higher disability have been identified as the risk factors for a more severe course of COVID-19 [22, 38, 40]. Salter et al. also determined these risk factors, especially the level of disability, with increased mortality of COVID-19 [38].

As mentioned, in our study, no significant relationship was observed between the incidence of clinical MS attack and COVID-19 infection from the clinical point of view and serologic exam. A comprehensive study by Garjani et al. showed that the majority of MS patients who became infected with COVID-19 reported clinical worsening of their previous neurological symptoms, and 20%-35% had new MS symptoms that were mainly motor or sensory in nature, which could appear after the acute infectious phase [41]. These attacks were defined by pwMS as worse than attacks experienced without COVID-19 infections. Accordingly, Parrotta reported a relapse rate of 21.1% in a study in New York [42].

In our study, the most commonly used drugs in pwMS were Dimethyl Fumarate, Interferon, and Rituximab, respectively. Although no significant relationship was found between COVID-19 clinical infection and the type of drug used. In Berger et al.'s 2020 study investigating the effect of MS DMTs on the expression of COVID-19, although data were limited, DMTs did not increase the risk of symptomatic SARS-CoV-2 infection, and the severe morbidity and mortality of SARS-CoV-2 were more than the result of an overactive immune response and the result of uncontrolled viral replication [29]. In several other studies, no significant association of DMTs with the severity of COVID-19 was found. No DMT had a higher risk for severe COVID-19 outcomes [30, 31, 39, 42, 43].

Of course, in the current study, there was a significant relationship between the type of drug and positive serologic test, so most patients with the positive serological test used Teriflunomide, and most patients with the negative serological tests used Dimethyl Fumarate. A study by Sormani et al. showed that the use of beta interferons reduced the risk of COVID-19 infection in pwMS [44]. However, studies in patients with severe COVID-19 show defective production of IFN-I, resulting in delayed and uninhibited T-cell responses. This process increases both the viral spread and cytokine release, which is predisposed to multiorgan failure [45, 46].

Coronaviruses can interfere with the production and function of IFN-I through several nonstructural proteins. SARS-CoV-2 antagonizes IFN-I secretion and signaling more efficiently than SARS-CoV-1 and MERS-CoV [47]. If the host has a weak IFN system, these intrinsic viral properties are dangerously enhanced. Zhang et al. showed enrichment in genetic variants impaired IFN-I immunity in critically ill patients with COVID-19 [48], while Bastard et al. reported increased levels of neutralizing IFN-I antibodies in patients with severe COVID-19 infection [49]. Therefore, these data can imply that people who are at risk of developing MS may be more exposed to the adverse effects of the virus.

For this reason and according to some studies, the use of IFN-beta to fight against COVID-19 can be considered if administered early in the infection, as a "supplement" to help suppress the virus [50, 51]. Riva et al. showed that in addition to interferons, DMTs protect against relapses caused by COVID-19. Indeed, MS patients receiving DMT were less likely to develop new MS symptoms during COVID-19 compared with untreated patients [52].

Limitations

One of the limitations of this study was the lack of a control group to compare with MS patients. Another limitation was the completion of information through a telephone call, which was used due to the coincidence of the COVID-19 pandemic and to prevent patients from getting infected. Although the importance of data collection in person and through interviews cannot be ignored, the telephone method has been an accepted method during the sampling period.

The other limitation was the number of questionnaires and the multiplicity of questions could be a deterrent factor in providing the correct answer for the people to answer. Before the data collection, the necessary explanations were given to the patients regarding the importance of the correct answer of the patients in expressing the results.

Conclusion

This study concluded that only a few patients had positive COVID-19 IgG tests and clinical COVID-19 infection. The vast majority had mild disease, and the clinical attack was not related to COVID-19 infection. More investigations are still required regarding the recognition of this virus and its short and long-term effects on the chronic and acute diseases of patients.

Ethical Considerations

Compliance with ethical guidelines

All study procedures complied with the ethical guidelines of the Declaration of Helsinki 2013. Ethical approval was obtained from the Ethics Committee of Guilan University of Medical Sciences (GUMS) (Code: IR.GUMS.REC.1400.451). Informed consent was obtained from all participants included in the study.

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Authors contributions

Conceptualization: Amirreza Ghayeghran, Alia Saberi, Samaneh Ghorbani Shirkoohi, Rita Khayami; Methodology: Enayattollah Homaee Rad; Data collection: Elahe Ghahramani, Mehri Fallahi, Fatemeh Shafaei, Parisa Shahshahani; Data analysis: Enayattollah Homaee Rad; Writing-original draft: Elahe Ghahramani, Alia Saberi and Zoheir Reihanian; Writing-editing & review: Alia Saberi and Zoheir Reihanian; Supervision: Amirreza Ghayeghran, Alia Saberi, Hamidreza Hatamian. All authors contributed and approved the final manuscript.

Conflict of interest

The authors reported no conflict of interest.

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