Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Original article

COVID-19 and the Risk of Relapse in Multiple Sclerosis Patients: A Fight with No Bystander Effect?

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ABSTRACT

Background: COVID-19 is speculated to increase the likelihood of relapsing-remitting multiple sclerosis (RRMS) exacerbation.
Objective: To investigate the association between contraction of COVID-19 and incidence of acute MS attacks in RRMS patients six months post-infection.
Methods: This retrospective cohort study compares the risk of relapse in RRMS patients with (n=56) and without COVID-19 (n=69). Incidence of relapse was recorded for six-month following contraction of COVID-19. Incidence of RRMS exacerbation in patients with COVID-19 was compared to patients without COVID-19 (the independent control group) and the same patients six months prior to the COVID-19 pandemic.
Results: A lower incidence rate of RRMS exacerbation was observed in patients that contracted COVID-19 than in patients who did not contract COVID-19 (incidence rate ratio: 0.275; p=0.026). Self-controlled analysis showed no significant difference in relapse rates before the COVID-19 pandemic and after contracting COVID-19 (p=0.222). The relapse risk was not different between patients who had been hospitalized due to COVID-19 severity and those who had not (p=0.710).
Conclusion: COVID-19 contraction may not increase the risk of acute MS attacks shortly following contraction. We hypothesize that COVID-19-associated lymphopenia may partly preclude the autoreactive memory cells from expansion and initiating relapses through a so-called bystander effect of COVID-19 infection.

1. Introduction

The Coronavirus Disease-2019 (COVID-19) pandemic has rapidly spread across the globe, with the number of confirmed cases surpassing 100 million. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the responsible microbial agent, is an enveloped positive-sense single-stranded RNA virus and categorized in the beta coronavirus family (Zhu et al., 2020). COVID-19 can be clinically manifested through a wide range of symptoms with different degrees of severity from asymptomatic to severe. The majority of the infected individuals experience a relatively manageable disease course and do not require hospitalization or intensive care (Esakandari et al., 2020).

Since the onset of the COVID-19 outbreak, multiple sclerosis (MS) patients receiving disease-modifying therapies (DMTs) were considered at a higher risk for experiencing severe disease courses. MS is a chronic autoimmune-mediated neuroinflammatory disease of the central nervous system (CNS), characterized by inflammation, demyelination, gliosis, and neuroaxonal loss (Dendrou et al., 2015). MS is considered a

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multifactorial disease of unknown etiology, impacted by genetics and environmental factors, including viral infections (Donati, 2020). Certain viral infections that induce severe systemic inflammatory reactions are associated with a higher risk of MS relapses shortly following the infection (Sibley et al., 1985, Andersen et al., 1993, Panitch, 1994, Edwards et al., 1998, Buljevac et al., 2002, Correale et al., 2006, Tremlett et al., 2008). It is suggested that the proinflammatory milieu secondary to activation of host cellular and humoral immunity to the viral infection may promote migration of previously activated autoreactive T cells across the blood-brain barrier (BBB), resulting in CNS inflammation and exacerbations in relapsing-remitting MS (RRMS) patients (Marrodan et al., 2019).

SARS-CoV-2, similar to its phylogenetically identical strains, Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV), can promote a proinflammatory immune profile, characterized by elevated circulating level of interleukin-6 (IL-6) in the majority of COVID-19 patients (Cameron et al., 2008, Rokni et al., 2020, Rokni et al., 2020). This hyperinflammatory immunological profile, along with the reportedly high frequency of psychological disturbances in RRMS patients as a result of the ongoing pandemic (Stojanov et al., 2020), brought us to investigate the risk of relapses in RRMS patients following COVID-19 infection. To our knowledge, this is the first cohort study characterizing the risk of RRMS relapses following COVID-19.

2. Materials and Methods

2.1. Patients and study design

This retrospective cohort study included patients diagnosed with RRMS according to the 2017 McDonald criteria (Thompson et al., 2018), with a minimum disease duration of one year, as assessed by an expert neurologist. Participants were randomly selected from two groups 1) those who contracted COVID-19 during a period between March 1st, 2020 and June 1st, 2020 (COVID-19 group) and 2) RRMS patients who had no symptoms attributable to respiratory infections from February 1st, 2020 to November 1st, 2020 (non-COVID-19 group). Records of patients with COVID-19 were retrieved from two weeks before to six months after the onset of their COVID-19-related symptoms. Records from the patients without COVID-19 were retrieved from 6 months prior to November 1st, 2020. For the self-control comparison, we retrieved all patients' records from the last six months before the COVID-19 pandemic emergence in Iran, using the Isfahan MS Clinic registry. The first case of COVID-19 in Iran, according to the national officials, was confirmed on February 19th, 2020; therefore, the pre-COVID-19 pandemic period was defined as August 1st, 2019 to January 30th, 2020 (World Health Organization, 2020).

Inclusion criteria for all participants of this study were 1) a definite diagnosis of RRMS, made by a professional neurologist, according to the 2017 McDonald diagnostic criteria for MS, 2) minimum disease duration of one year, and 3) no missing data from the period under investigation. Inclusion criteria for the COVID-19 group was a positive Reverse Transcription-Polymerase Chain Reaction (RT-PCR) test result, between March 1st, 2020 to June 1st, 2020. The inclusion criteria for the non-COVID-19 group were: 1) absence of any reported symptoms attributable to respiratory infections during February 1st, 2020 and November 1st, 2020 and 2) negative results of RT-PCR test(s) (if performed).

From March 2020, biweekly telephone surveys following the set guidelines were conducted to identify signs of a possible MS relapse. In case of a suspected exacerbation patients were requested to make an additional visit to the clinic within 3 days. MS relapse-associated symptoms were assessed on average every two months and on additional visits in case of suspected exacerbation. Graphical abstract of the study timelines is presented in Figure-1.

2.2. Definitions

MS exacerbation was defined as development of a new neurologic abnormality, or worsening of a pre-existing one, for more than 24 hours. It must have been preceded by a stable or improving neurological state for at least 30 days, in the absence of concurrent fever, infection, or steroid withdrawal. COVID-19-related symptoms screened for included fever, anosmia, dysgeusia, myalgia, headaches, shortness of breath, diarrhea, nausea, sore throat, rhinorrhea, cough, vertigo, and chest pain.

2.3. Ethics

The ethical committee of Isfahan University of Medical Sciences approved this study and all patients signed informed consent letters for use of their clinical information.

2.4. Statistical analyses

The Pearson Chi-Square test, paired samples t-test, and independent samples t-test were used to analyze the intergroup differences based on variable types. A generalized linear regression model (Poisson regression) was performed to predict the incidence rate ratio (IRR) of MS relapses during six months based on age, gender, type of treatment regimen, MS duration, and COVID-19 contraction. Conditional logistic regression analysis through a 1-1 matched (self-controlled) analysis was performed to assess the impact of COVID-19 infection on relapse number in COVID-19 group patients before the pandemic and after COVID-19 contraction. A significance criterion of 0.05 was set. Data were gathered and analyzed using IBM SPSS v.23 for macOS.

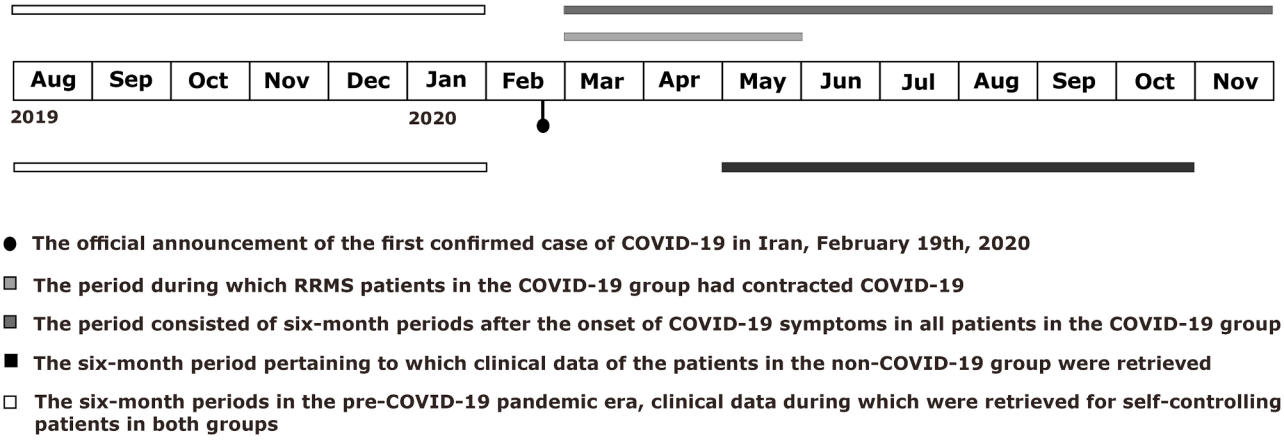

Figure 1. Summary of the timelines of the present retrospective cohort.

3. Results

3.1. Clinical and demographic findings

125 RRMS patients were included in this study, 56 of whom were included in the COVID-19 group and 69 in the non-COVID-19 group. There was no significant difference between the two groups in terms of mean age (p=0.746), while there was a higher proportion of females in the non-COVID-19 group (8.85:1 vs. 2.67:1, p=0.013). Demographic and clinical findings of the patients are presented in Table-1. There was no significant difference in terms of Expanded Disability Status Scale (EDSS) scores (p=0.126) or disease durations (p=0.745) between the two groups. Of note, treatment regimens differed between the two groups (p=0.002) (Table-1).

3.2. Relapse episodes in patients during the COVID-19 pandemic

3.2.1. Intergroup differences

Four patients in the COVID-19 group experienced a MS exacerbation within six months after the onset of COVID-19-associated symptoms (7.14%, 4/56). None of these relapse episodes occurred in the two weeks prior to COVID-19 symptoms manifestation. In RRMS patients without COVID-19, 18 patients (26.09%, 18/69) exhibited MS exacerbations during the monitored six months (from June 1st, 2020 to November 1st, 2020). Thus, a greater proportion of RRMS patients without COVID-19 had an exacerbation (p=0.006). Neurological symptoms associated with the episodes of relapse are presented in Table-1.

3.2.2. Generalized linear regression

The Poisson regression model showed that the incidence rate of acute MS relapses during six months was decreased by 72.5% in case of COVID-19 contraction (IRR: 0.275; 95% CI= 0.089 – 0.855; p=0.026). Age, sex, MS duration, and different categories of applied DMTs did not have a significant effect in this regression model.

3.2.3. Hospitalization and risk of relapse

One out of ten patients hospitalized due to severe COVID-19 experienced a relapse (1/10, 10%). Three out of 46 patients not hospitalized had a relapse episode after infection-associated symptoms onset (3/46, 6.98%). No difference in the relapse risk was observed between hospitalized and non-hospitalized patients (p=0.710).

3.2.4. Relapse episodes in patients before the COVID-19 pandemic

Patients of the two groups (i.e., the COVID-19 group and the non-COVID-19 group) were not significantly different concerning the number of MS attacks during the same last six months before the COVID-19 pandemic (14.29%, 8/56, in the COVID-19 group vs. 14.49%, 10/69, in the non-COVID-19 group, p=0.976).

3.2.5. Differences in the self-controlled model

The difference between the frequency of relapses in the COVID-19 group during six months before the pandemic and six months after their infection with SARS-CoV-2 was not significant (14.29%, 8/56 before the pandemic vs. 7.14%, 4/56 after contracting COVID-19, p=0.222). Clinical manifestations of the relapses in the COVID-19 group in both timelines are presented in table-2.

3.2.6. Conditional logistic regression

Conditional logistic regression for 1-1 matched (self-controlled) assessment with MS relapses as the outcome, showed no statistically significant effect of COVID-19 contraction (OR=0.462, 95% CI=0.131 to 1.632, p=0.230).

Table 1
Demographic, clinical, and treatment-associated findings of COVID-19 and non-COVID-19 groups

	COVID-19 group (n = 56)	Non-COVID-19 group (n = 69)	P-value
Mean age (±SD) [years]	36.89 (±9.06)	36.19 (±8.97)	0.746
Sex (Female/Male)	40/15	62/7	0.013 *
Mean disease duration (±SD) [years]	7.76 (±5.07)	8.12 (±6.60)	0.745
Median EDSS	1.5	1.5	0.126
MS relapses during the 6 months in the COVID-19 pandemic	4 (7.14)	18 (26.09)	0.006 *
Relapse symptoms (%)			
Lower extremity weakness	1 (25)	9 (50)	
Blurred vision	0	4 (22.22)	
Diplopia	1 (25)	1 (5.55)	
Gait ataxia	0	2 (11.11)	
Facial paresthesia	0	1 (5.55)	
Limbs paresthesia	2 (50)	0	
Vertigo	0	1 (5.55)	
Treatments (%)			
Oral medications:			
Teriflunomide	3 (5.36)	11 (15.94)	
Fingolimod	9 (16.07)	8 (11.59)	
Dimethyl fumarate	22 (39.28)	14 (20.29)	
Azathioprine	5 (8.93)	0 (0)	
Injectable medications:			
Interferon ß 1b	3 (5.36)	11 (15.94)	
Interferon ß 1a (weekly)	3 (5.36)	9 (13.04)	
Interferon ß 1a (every other day)	3 (5.36)	1 (1.45)	
Glatiramer acetate	3 (5.36)	11 (15.94)	
Infused monoclonal antibodies:			
Rituximab	3 (5.36)	3 (4.35)	
Natalizumab	2 (3.57)	1 (1.45)	

* statistically significant differences, with p values below 0.05

4. Discussion

This retrospective cohort study showed that COVID-19 contraction did not alter relapse rates in the same patients and that RRMS patients without clinical or laboratory findings suggestive of SARS-CoV-2 infection had a higher risk of experiencing MS relapses during the COVID-19 pandemic. Additionally, hospitalization due to COVID-19 severity was not associated with a change in the relapse rate in RRMS patients.

4.1. Viral respiratory tract infections and MS relapses

Several studies in the literature suggest that viral respiratory tract infections increase the risk of MS exacerbations and relapses (Sibley et al., 1985, Andersen et al., 1993, Panitch, 1994, Edwards et al., 1998, Buljevac et al., 2002, Correale et al., 2006, Tremlett et al., 2008). However, one should practice caution when interpreting the data from the currently existing literature. A considerable proportion of these studies date back to the pre-DMT era, and the investigated participants were not receiving the DMTs that are widely applied in modern practice (Sibley et al., 1985, Andersen et al., 1993). Further, no firm conclusions

Table-2
. MS exacerbations of COVID-19 group patients during six months after contracting COVID-19 and six months before contracting COVID-19

	COVID-19 group, after contracting COVID-19	COVID-19 group, before the pandemic
MS relapses during 6 months	4 (7.14)	8 (14.29)
Relapse symptoms (%)		
Lower extremity weakness	1 (25)	2 (25)
Blurred vision	0	4 (50)
Diplopia	1 (25)	1 (12.5)
Gait ataxia	0	1 (12.5)
Limbs paresthesia	2 (50)	0

can be drawn from the studies on patients taking DMTs, concerning the effect of these therapies on infection-induced risk of relapse, with these papers either reporting contrary results (Panitch, 1994, Buljevac et al., 2002) or not being able to explore such effects due to the scant number of their patients who were not taking DMTs (Correale et al., 2006, Tremlett et al., 2008).

Nevertheless, potential mechanisms for the suggested increased risk of relapse, following infection with viral agents, include the detection of viral epitopes, activation of host's T cells, and secretion of proinflammatory cytokines, including IL-1β, IL-6, and tumor necrosis factor (TNF)-α. This proinflammatory profile increases the expression of endothelial adhesion molecules and increases BBB permeability, allowing for transmigration of previously activated, autoreactive T-cells across the BBB. Moreover, these proinflammatory cytokines contribute to the activation of CNS glial cells and macrophages, as well as expression of major histocompatibility complexes I/II and co-stimulatory molecules, promoting T cells reactivation and localized inflammation (Marrodan et al., 2019). IL-1β and TNF-α may further maintain the migration and recruitment of autoreactive T cells into the sites of inflammation by increasing chemokine (e.g., CCL2 and CCL20) production by astrocytes and microglia cells (Marrodan et al., 2019, Steelman, 2015).

4.2. Human coronaviruses and MS

Some strains of human coronaviruses may be associated with stimulation of autoimmune demyelination in MS through toll-like receptors (TLRs) activation (Montalvan et al., 2020). Nevertheless, there is limited data regarding an association between SARS-CoV-2 and MS progression or relapse.

4.3. Current knowledge on SARS-CoV-2 and MS-associated demyelination

It was speculated that COVID-19 contraction could increase the risk of clinical exacerbations in patients with RRMS. Proposed mechanisms for this risk included 1) autoimmune response following activation of TLRs by SARS-CoV-2, 2) initiation of an immune cell response following infection with a subsequent autoreactive outbreak in RRMS patients, 3) CNS inflammation and BBB disruption due to cytokine storm in severe cases of COVID-19, and 4) direct CNS damage by the virus (Sadeghmousavi and Rezaei, 2020).

However, to date, few reports concerning the development of MS-associated demyelination in COVID-19 patients shortly following the infection have been published (Palao et al., 2020, Domingues et al., 2020, Moore et al., 2021) (summarized in Table-3). Kataria et al. have reported three RRMS patients who experienced worsening clinical symptoms following the COVID-19 contraction. They reported weakness, fatigue, and shortness of breath, with no corresponding positive radiological findings on their MRI scans. All patients tested positive for COVID-19 infection via RT-PCR. All patients' EDSS scores improved back to baseline after appropriate medical management for COVID-19; thus, the worsening of their symptoms was equated to pseudo-exacerbations rather than MS relapses (Kataria et al., 2020).

The limited number of reports on COVID-19 contraction and MS relapses shortly following the infection may suggest no association between SARS-CoV-2 infection and MS relapse. However, the present study is the first cohort study to investigate whether COVID-19 contraction in RRMS increases the exacerbation risk within 6 months of infection.

4.4. COVID-19 infection and risk of relapse in MS patients in this study

To our surprise, when compared to an independent control group (i.e., the non-COVID-19 group), RRMS patients who had contracted COVID-19 had significantly fewer relapse episodes (p=0.006). When analyzing the relapse rates between the COVID-19 group and the independent control group, we observed that contracting COVID-19 was associated with a 72.5% decrease in the IR of relapses (p=0.030). Possible confounding factors such as age, gender, treatment regimens, and MS duration had no effects on the relapse risk. Interestingly, RRMS patients in the COVID-19 group had similar relapse rates prior to COVID-19 contraction.

4.5. SARS-CoV-2 effects on immune system components: is COVID-19-associated lymphopenia the missing piece of the puzzle?

IL-6 elevation is commonly observed in COVID-19 patients (Rokni et al., 2020). Increased levels of IL-2, IL-7, IL-10, granulocyte colony-stimulating factor (G-CSF), interferon gamma-induced protein 10 (IP-10), CCL2, CCL3, and TNF-α, have been observed in most hospitalized patients with a relatively severe course of COVID-19 infection, experiencing cytokine storm syndrome (Rokni et al., 2020, Conti et al., 2020, Wong et al., 2004). Given this proinflammatory profile, increased risk of MS relapse is expected in patients with severe COVID-19 infection. However, relapse risk was not increased in either comparison type in this study (i.e., independent controls or self-controls). Moreover, no increased risk of relapse was observed in patients who had been hospitalized with a severe course of infection.

CD8+ and CD4+ T cells, B cells, and macrophages are the key components of MS relapses; Th1 and Th17 cells are the main coordinators of the autoimmune responses in MS (Chihara, 2018). Interestingly, COVID-19-associated transient lymphopenia drastically decreases the number of CD8+ and CD4+ T cells (Liu et al., 2020). Several explanations respecting the reduction of the circulating T cell count in COVID-19 patients, which is indeed shown to be negatively correlated with the severity of infection (Tan et al., 2020), exist, including 1) elevated levels of IL-6, TNF-α, and Fas-FasL-mediated apoptosis of peripheral T cells, which is supported by the reported efficacy of tocilizumab (an IL-6 antagonist) in reversing the COVID-19-associated lymphopenia (Tavakolpour et al., 2020), 2) exhaustion of both CD4+ and CD8+ T cells, independent of regulatory T cells as a result of COVID-19 infection, which is characterized by down-regulated expression of T cell activation markers (e.g., CD107a and IFN-γ) and up-regulated expression of T cell exhaustion markers (e.g., PD-1, Tim-3, and NKG2A) on the surface of these T cell subsets

Table-3
. Reported cases of MS-associated demyelinating events in COVID-19 patients in the literature

	Age/ sex	Demyelination symptoms	Interval between COVID-19 and demyelination symptoms	COVID-19 severity	Utilized treatment/ Result
Palao et al. (2020)	29/F	Visual acuity loss and field defects, Pyramidal dysfunction	~ 1-2 weeks	Mild, disappearing in a week	Methylprednisolone/Improved and discharged
Domingues et al. (2020)	42/F*	Hemiparesthesia of the face, upper limb, and thorax	3 weeks	Mild	-/full recovery after 3 weeks
Moore et al. (2020)	28/M	Nystagmus and ophtalmoplegia	2 weeks	Mild, Nasopharyngeal PCR test was still positive at the time of admission	Methylprednisolone/Improved and discharged

* this case was diagnosed as clinically isolated syndrome, since the patient did not fulfill the criteria for dissemination in space, and oligoclonal bands were not detected.

(Tavakolpour et al., 2020, Diao et al., 2020), and 3) COVID-19-induced disruption of proliferation and expansion of T cells, as the expression of some genes responsible in this regard (e.g., MAP2K7 and SOS1) are shown to be down-regulated in COVID-19 patients as long as they have not recovered from the infection (Ouyang et al., 2020).

We hypothesize that COVID-19-associated lymphopenia in RRMS patients may be partially involved in precluding the expansion and proliferation of autoreactive T cells. Thus, it may decrease the likelihood of cytokine-induced transmigration of these cells into the CNS parenchyma and initiation of acute MS exacerbations.

4.6. Chronic stress during the COVID-19 pandemic and considerations in MS patients

Recently, Bonavita et al. have surveyed a large number of MS patients to assess perceived stress, depression, and perceived social support. Unfortunately, a significantly higher proportions of MS patients, compared to healthy controls, were depressed (43.1% vs. 23.1%; $p<0.001$), experienced high levels of stress (58% vs. 39.8%; $p<0.001$), and less perceived social support ($p<0.001$) (Bonavita et al., 2020). These patients may experience high levels of chronic stress because of the pandemic, their clinical condition, and their immunosuppressive treatment regimens. Due to the retrospective nature of our study the psychological status of our patients could not be assessed during the recording of their relapses. Whether or not chronic stress predisposes MS patients to higher risks of developing relapses is controversial, partly due to the inter-study differences in terms of stress definition and measurement methods (Xie et al., 2020). However, we speculate that this evident psychological stress on RRMS patients (Stojanov et al., 2020, Bonavita et al., 2020) may have had an impact, at least partially, on the activity of their disease during this period, and it was more significant in patients who had not contracted COVID-19 during those times, probably facing chronically elevated levels of stress during the 9-10 months recorded in our study.

4.7. Limitations

Limitations of this study include its retrospective nature and the potential for errors in the registry system used for data collection. However, restrictive measures were taken to reduce such errors. Furthermore, assessing serological findings and psychological stimulators of MS relapses during the recording of relapse episodes was not possible.

5. Conclusion

Our results suggest that COVID-19 infection, regardless of its severity, was not associated with an increased risk of relapse shortly following infection. However, should there be a long-term latent SARS-CoV-2 infection in the CNS parenchyma, its reactivation over long periods of time may hypothetically cause neurodegeneration and disease progression in MS patients. Thus, further long-term studies are needed to investigate in this regard. Additionally, studies assessing the effect of psychological inducers of MS relapses and the immune profile (e.g., lymphocytes count, proinflammatory cytokines levels, and T-cell exhaustion markers) on the risk of relapse in the context of COVID-19 contraction are warranted. Moreover, interdisciplinary measures should be taken to provide patients diagnosed with chronic autoimmune diseases, including MS, with psychological monitoring and support during the ongoing pandemic.

6. Credit author statement

Masoud Etemadifar: Conceptualization, Resources, Supervision; **Nahad Sedaghat:** Formal analysis, Writing - Original Draft; **Ali Aghababaee:** Methodology, Writing - Review & Editing; **Parisa K Kargaran:** Writing - Review & Editing; **Mohammad Reza Maracy:** Methodology, Formal analysis; **Mazdak Ganjalikhani-Hakemi:** Writing - Review & Editing; **Milad Rayani:** Investigation, Project administration; **Amir Parsa Abhari:** Investigation; **Reza Khorvash:** Investigation; **Mehri Salari:** Writing - Review & Editing, Supervision; **Hosein Nouri:** Methodology, Formal analysis, Investigation, Writing - Original Draft, Writing - Review & Editing.

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Conflict of interest

The authors have no conflict of interest to disclose.

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