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# Investigating the Relationship between Seasonal Fluctuations and the Number of Relapsing-Remitting Multiple Sclerosis Attacks in Qom

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**Abstract**

**Background:** Multiple sclerosis (MS) is a chronic autoimmune disease that affects the central nervous system (CNS). Environmental factors such as seasonal changes and air pollution play a significant role in the progression and relapse of this disease. This study aimed to investigate the impact of seasonal changes and air pollution on the frequency and severity of MS attacks in patients from Qom province.

**Methods:** This cross-sectional analytical study included 491 patients with relapsing-remitting MS (RRMS) registered with the MS Association of Qom province from 2016 to 2021. Data on temperature, humidity, and air pollutants (PM2.5, PM10, and O3) were collected from the Meteorological Organization and the Environmental Protection Agency of Qom province. Missing data were estimated using the Multiple Imputation method. Data were analyzed using the Generalized Additive Model (GAM) and R software.

**Results:** The mean number of relapses was 0.68 ± 5.21. The results showed that increased temperature was directly correlated with a higher number of relapses (r = 0.46, $P$ < 0.001), while increased relative humidity was associated with a decrease in relapses (r = -0.35, $P$ = 0.006). Additionally, PM10 and PM2.5 pollutants were directly related to an increase in relapses. Comorbid autoimmune diseases and family history of MS were also significantly associated with the number of relapses ($P$ = 0.000).

**Conclusion:** This study emphasizes the complexity of relationships between environmental factors, demographic characteristics, and the onset of MS relapses, underscoring the need for integrated strategies in managing MS patients.

**Keywords:** MS, Multiple sclerosis, Relapsing, Seasonal fluctuations

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## Introduction

Multiple sclerosis (MS) is an autoimmune disease that is the most common inflammatory disease of the central nervous system (CNS). It is caused by autoimmune T-cells demyelinating the CNS nerve cells (1,2). According to the statistics of the World Health Organization, more than two million and three hundred thousand people in the world are suffering from MS. The incidence rate of this disease in the world is 2.5 per 100 000 people (per year), and its prevalence rate is 30 per 100 000 people. The geographical region of Europe has the highest incidence and prevalence of MS globally.

The geographical region of Iran is located in areas with moderate prevalence of this disease (3,4). Recent studies have shown that the prevalence of MS has increased in Iran and Arab countries, especially in the last decade. The prevalence of this disease in Iran ranges from 5.3 to 74.28 per 100 000 people, depending on the provinces (5). A wide range of genetic and environmental factors, including bacterial infection, viral infection (such as Epstein-Barr virus and influenza), fungal infection, seasonal changes, and vitamin D deficiency, affect the development and recurrence of this disease (6-10). One of the important and determining factors in the development and recurrence of

MS is seasonal changes.

Seasonal changes are well detected by the skin through the amount of light radiation. The amount of light radiation is one of the most important factors of seasonal changes. It has a direct relationship with the level of inflammation in the skin and other parts of the body, including the CNS. Additionally, it has an inverse relationship with the body's melatonin level. It has been proven that melatonin plays an important role in the severity and relapse of MS. The amount of vitamin D in the body, the prevalence of viral infections, and air pollution change with seasonal changes, which can be effective in the development and occurrence of attacks of this disease (11-13). Due to the importance of seasonal changes, air pollutants, and the high prevalence of MS disease in the central regions of Iran, along with the lack of domestic research in this field and the increasing daily pollutants in the air worldwide, we decided to investigate the effect of seasonal changes on attacks and severity of MS. The rising prevalence of MS in Iran and the role of environmental factors such as seasonal changes and air pollution in exacerbating the disease highlight the need for domestic research to better understand these relationships. This study, by investigating the impact of these factors on relapse and disease severity, can contribute to the development of preventive strategies and improved patient care.

**Methods**

This study was conducted as a cross-sectional analytical research. In this study, data from all individuals diagnosed with MS who were registered with the MS Association from 2016 to 2021 were included. Additionally, information on temperature and humidity variables for the study years was obtained from the Meteorological Organization, and air pollution indices were sourced from the Environmental Protection Agency of Qom province. The sampling method used in this study was convenient sampling from all registered patients with MS in Qom province.

After the proposal was approved and the ethical code (IR.MUQ.REC.1399.115) was obtained, as well as informing the patients about the study, the patients were examined. The inclusion criteria for the study included: being diagnosed with relapsing-remitting type according to the standard ICD-10 definition "G35.1", residing (or having lived for at least 5 years) in Qom city, providing informed consent to participate in the study, and having complete information available for the patients under review in the MS Association of Qom from 2016 to 2021. Also, the exclusion criteria included: withdrawing from the plan and the occurrence of an attack while not living in Qom. Patients were classified as relapsing-remitting MS (RRMS). Then, the files of patients registered in the MS Association of Qom province, which have been fully documented since 2016, were examined over 5 years in different seasons. This examination took into account the recorded weather conditions (humidity, temperature) and air pollution data (PM2.5, PM10, O3) documented by the Environmental Protection Agency. The relationship between the number of attacks in these patients and the weather and air pollution indices was analyzed across different seasons during these 5 years. Ultimately, the data in each group were analyzed using appropriate statistical tests and the R software. Considering that in some cases there were missing data in the temperature and humidity variables, amounting to 20%-30%, the missing data were estimated using the statistical method of Multiple Imputation. To describe quantitative and qualitative data, the mean and standard deviation were used for quantitative data, while frequency and percentage were used for qualitative data. The Spearman correlation test was employed to examine the relationships. To investigate the connection between climatic variables, pollutants, and the number of MS attacks, the Generalized Additive Model (GAM) was utilized for time series regression. To evaluate the model fit, the Akaike information criterion (AIC) was used, and to control for confounding effects such as temporal trends and air pollutants, the penalized smoothing spline function was employed, following recent time series studies. The data were analyzed using R software version 3.5.3 with the MGCV package. The number of disease recurrences was analyzed monthly.

**Results**

In total, the data collection was completed, and all data were finalized. However, in some cases, such as temperature and humidity = 8%, PM2.5 = 32%, and PM10 = 28%, the data were incomplete. Since the number of missing data points is all below 35%, the missing data were estimated using the multiple imputation method. A total of 491 patients were included in the study, of which 100 (20.3%) were male and 391 (79.7%) were female. Out of this total, 404 (82%) were married and 87 (18%) were single patients. Regarding the presence of comorbidities, it was found that 151 (30.8%) of the patients had comorbid conditions such as diabetes, hypertension, etc. Among these, 58 (11.9%) had autoimmune diseases like lupus, rheumatoid arthritis, etc., while 340 (69.2%) did not have any comorbidities. The family history among patients was as follows: 363 (73.9%) patients had no family history of MS, while 128 (26.1%) had a family history of the disease. An assessment of the disability levels in MS patients using the Modified Rankin Scale indicated that MS had not caused disability in 50 (10.2%) patients, whereas it had led to varying degrees of disability in 441 (89.8%) patients. The mean number of relapses was 0.68 ± 5.21. The mean temperature was 1.30 ± 19.16, with a minimum of 4.12 and a maximum of 34.75. The mean relative humidity was 2.25 ± 40.93, with a minimum of 16.87 and a maximum of 70.38. The mean PM2.5 was 10.95 ± 38.58, with a minimum of 1.06 and a maximum of 495.41. The mean PM10 was 11.55 ± 10.55, with a minimum of 4.34 and a maximum of 475.34. Finally, the mean O3 was 0.007 ± 0.04, with a minimum of 0.002 and a maximum of 0.284. In the time series analysis of relapses, the overall results showed that during the periods of March 2016 and November 2016, as well as in 2017 and 2018, the relapses were at their lowest point, reaching zero. However, in the period of March 2020, the relapses peaked at their highest level. Other trends can be observed in the chart below (Figure 1).

The rate of relapses was also examined in the time series by gender. In women, the lowest rates were observed in March, November 2016, 2017, and 2018, while the highest rate was recorded in March 2020. In men, the lowest rates were seen in March, May, July, November, January 2016, as well as in May, November, January, May, November 2018, January, July, November 2019, and November, May, January 2020, and January 2021. The highest rate for men was observed in September 2020 (Figure 2).

The temporal trend of relapse cases was also examined in relation to temperature and relative humidity variables. The results indicated that temperature and relative humidity had an inverse relationship based on the climatic conditions of our study area (Qom province). However, different climatic conditions may yield results that differ from our findings. Additionally, as can be observed schematically in the chart below, every time there was an increase in temperature, the number of relapses also increased correspondingly, sometimes with a delay in the rise of relapse cases (Figure 3).

The temporal trend of relapse cases was also examined in relation to the air pollutants present. The results indicated that the number of relapses had a direct relationship with the examined pollutants (PM10, PM2.5). Wherever these pollutants showed an increasing trend, the number of relapses also increased (Figure 4).

In terms of the correlation between variables, the results showed a direct correlation between the number of relapses and temperature, meaning that as the temperature increased, the number of relapses also showed an increasing trend ($r = 0.46$, $P < 0.001$). However, compared with humidity levels, this relationship was inverse; as relative humidity increased, the number of relapses showed a decreasing trend ($r = -0.35$, $P = 0.006$). Additionally, there was no correlation between air pollutants (O3, PM10, and PM2.5) and the number of relapses ($P = 0.627$, $P = 0.509$, and $P = 0.531$) (Table 1).

In this study, the percentage of changes in the recurrence risk was examined daily and cumulatively. The results were as follows: in the daily examination, on a separate day, for each unit of change in temperature on day 0, the percentage of changes in the occurrence of MS relapse (0.81, 9.72) was 5.17 times, and one day later, the percentage of changes in the occurrence of MS relapse (1.75, 7.90) became 4.78 times, and in the next 2 days (-0.82, 3.59), it became 1.36 times.

The findings indicated that over time, the impact of temperature on the percentage of relapse changes decreased and even became negative. Additionally, in the cumulative review, for each unit change in temperature, on days 1 and 0, the cumulative percentage of relapse

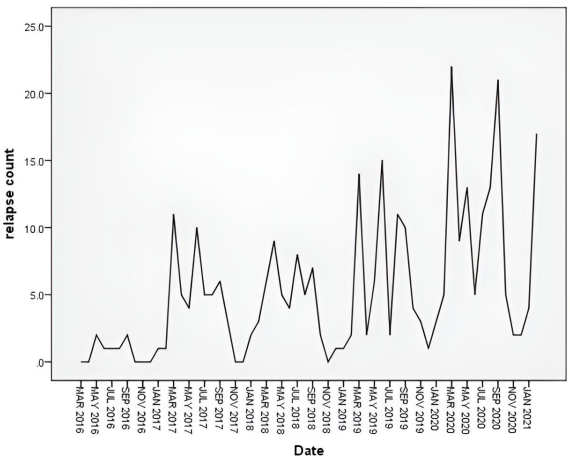


**Figure 1.** Time series chart of relapse cases (total)

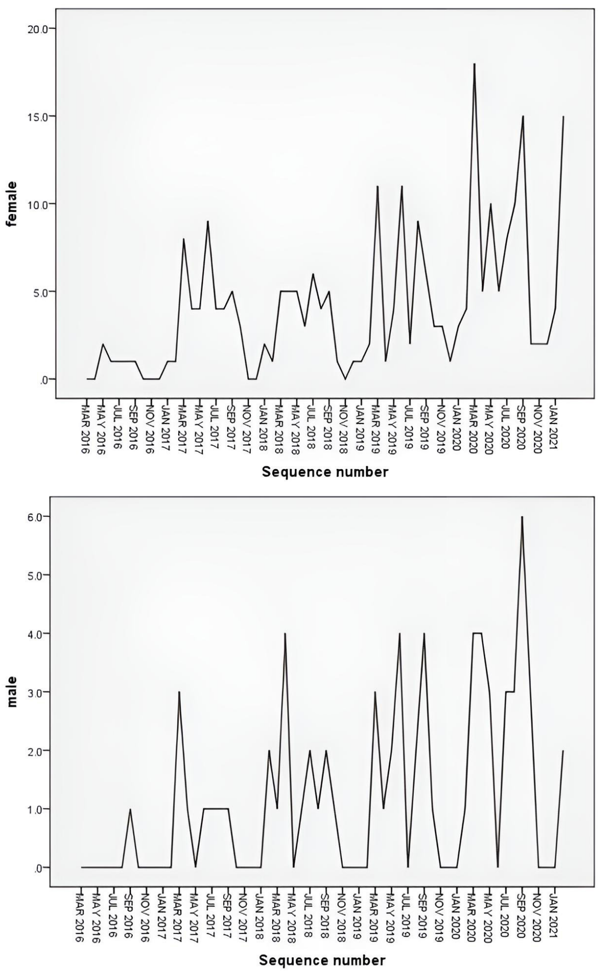


**Figure 2.** Time series chart for women and men

changes in MS was (1.91, 11.34), increasing by a factor of 6.52. In the subsequent 2 days, the cumulative percentage of relapse changes was (1.86, 9.19), increasing by a factor of 5.46, and in the following 3 days, the cumulative percentage of relapse changes was (1.08, 7.62), increasing by a factor of 4.29.

The findings also indicated that as time goes on, the effect of temperature on the percentage of relapse decreases. In the daily review, for every 1% increase in humidity, the risk of disease relapse was as follows: on day zero, there was an increase of 5.5 (4.67, 6.41), and then, it decreased on subsequent days, showing a decrease of -1.75 (-3.05, -0.44) on day one and -0.86 (-1.91, 0.20) on day two. This indicates an inverse relationship between the increase in relative humidity and the percentage of changes in relapse rates of MS, as shown in Table 2 and Figure 3.

The study revealed that 174 patients had no history of relapse, and among the 309 patients who had a relapse

**Table 1.** Correlation between variables

| | | | Relapse count | Temperature (°C) | RH | O3 | PM10 | PM2.5 |
|---|---|---|---|---|---|---|---|---|
| Spearman's rho | Relapse count | Correlation coefficient | 1.000 | 0.460** | -0.354** | -0.064 | -0.087 | 0.082 |
| | | Sig. (2-tailed) | . | 0.000 | 0.006 | 0.627 | 0.509 | 0.531 |
| | | N | 60 | 60 | 60 | 60 | 60 | 60 |
| | Temperature (°C) | Correlation coefficient | 0.460** | 1.000 | -0.912** | 0.145 | 0.256* | 0.261* |
| | | Sig. (2-tailed) | 0.000 | . | 0.000 | 0.268 | 0.048 | 0.044 |
| | | N | 60 | 60 | 60 | 60 | 60 | 60 |
| | Relative humidity (%) | Correlation coefficient | -0.354** | -0.912** | 1.000 | -0.197 | -0.326* | -0.279* |
| | | Sig. (2-tailed) | 0.006 | 0.000 | . | 0.132 | 0.011 | 0.031 |
| | | N | 60 | 60 | 60 | 60 | 60 | 60 |
| | O3 | Correlation coefficient | -0.064 | 0.145 | -.197 | 1.000 | 0.007 | 0.288* |
| | | Sig. (2-tailed) | 0.627 | 0.268 | .132 | . | 0.957 | 0.025 |
| | | N | 60 | 60 | 60 | 60 | 60 | 60 |
| | PM10 | Correlation coefficient | -0.087 | 0.256* | -.326* | 0.007 | 1.000 | 0.168 |
| | | Sig. (2-tailed) | 0.509 | 0.048 | .011 | 0.957 | . | 0.200 |
| | | N | 60 | 60 | 60 | 60 | 60 | 60 |
| | PM2.5 | Correlation coefficient | 0.082 | 0.261* | -.279* | 0.288* | 0.168 | 1.000 |
| | | Sig. (2-tailed) | 0.531 | 0.044 | .031 | 0.025 | 0.200 | . |
| | | N | 60 | 60 | 60 | 60 | 60 | 60 |

** Correlation is significant at the 0.01 level (2-tailed).
* Correlation is significant at the 0.05 level (2-tailed).

**Table 2.** Percent change (percentage) in MS relapse risk counts based on meteorological variables

| Variables | Lag structure | Lags | | | | | |
|---|---|---|---|---|---|---|---|
| | | 0 | 1 | 2 | 3 | 4 | 5 |
| Temperature (°C) | SDL | 5.17 (0.81, 9.72) | 4.78 (1.75, 7.90) | 1.36 (-0.82, 3.59) | 1.64 (-0.43, 3.76) | -1.48 (-3.46, 0.53) | -2.59 (-5.78, 0.70) |
| | MDAL | | 6.52 (1.91, 11.34) | 5.46 (1.86, 9.19) | 4.29 (1.08, 7.62) | 1.84 (-1.48, 5.29) | 3.48 (-0.18, 7.28) |
| Relative humidity (%) | SDL | 5.5 (4.67, 6.41) | -1.75 (-3.05, -0.44) | -0.86 (-1.91, 0.20) | 1.00 (-0.12, 2.15) | 0.71 (-0.39, 1.83) | 0.43 (-1.45, 2.35) |
| | MDAL | | -3.48 (-6.02, -0.87) | -2.19 (-4.15, -0.19) | -1.90 (-3.71, -0.06) | -1.51 (-3.41, 0.43) | -0.03 (-2.03, 2.00) |

SDL: single day lag; MDAL: multiple day average lag

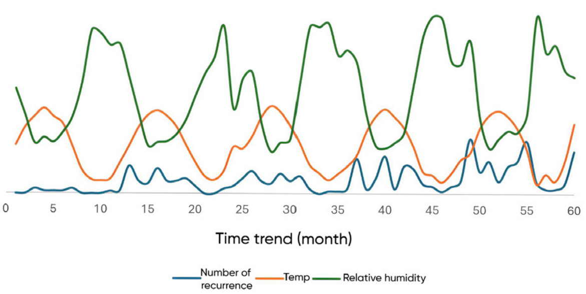


**Figure 3.** Time trend of the number of recurrences with temperature and relative humidity variables

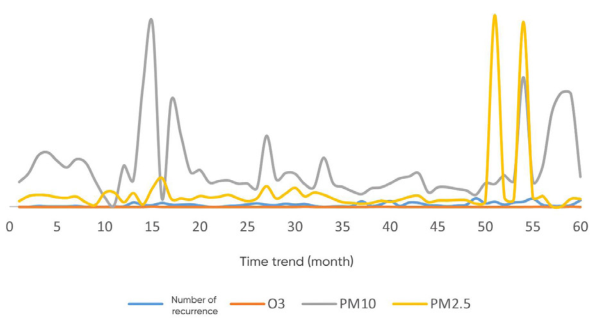


**Figure 4.** Time trend diagram of the number of relapses with atmospheric pollutants

in the last 5 years, 69 were male and 240 were female. Statistically, no significant relationship was found between gender and the number of relapses ($P = 0.272$). The examination of the relationship between accompanying autoimmune diseases and the number of relapses showed that among the 309 patients with a history of relapse in the last 5 years, 40 had accompanying autoimmune diseases, and there was a statistically significant relationship between accompanying autoimmune diseases and the number of relapses ($P = 0.000$) (Table 3). The investigation of the relationship between family history and relapses in the last 5 years also indicated that out of the 309 patients with a relapse history in the last 5 years, 483 had a family history, and there was a statistically significant relationship between family history and the occurrence of relapses in the last 5 years ($P = 0.000$). However, no significant relationship was found between family history and the number of relapses, although it was very close to a significant level ($P = 0.059$).

## Discussion

MS is a chronic autoimmune disease that extensively damages the CNS. Environmental factors, including climatic fluctuations and air pollution, can have a significant impact on disease progression and the number of attacks. In this discussion, we will examine the relationship between these factors and the number of MS attacks in central Iran, referencing findings from other studies. Temperature and humidity fluctuations are key factors in the onset of autoimmune diseases such as MS. Studies have shown that temperature changes can act as a trigger for MS attacks. Specifically, rising temperatures appear to correlate with an increase in the number of attacks. In central Iran, climatic fluctuations are pronounced. This relationship may hold significant importance. Studies indicate that on hot and dry days, the incidence of attacks may rise, which could be due to physiological changes in patients' bodies. Air pollution is also recognized as an important environmental factor in the onset of autoimmune diseases. Numerous studies have demonstrated a connection between pollution from vehicles and industries and the increasing incidence of MS. In central Iran, pollutants such as particulate matter (PM10 and PM2.5), nitrogen dioxide, and ozone gases have been on the rise. These pollutants can induce inflammation in the immune system, increasing the risk of disease attacks. Conflicting results from various studies have demonstrated that a precise understanding of the effects of air pollution on MS necessitates further research. Additionally, other results indicated that temperature and relative humidity had an inverse relationship based on the climatic conditions of our study area (Qom province). However, it is possible that under different climatic conditions, the results may differ from our findings. Additionally, based on our study findings, whenever we experienced an increase in temperature, the number of relapses also increased accordingly, sometimes with a delayed effect. It seems that sunlight exposure and skin inflammation may be among the triggering factors for immune system activation, leading to the onset and relapse of MS. Moreover, T lymphocytes appear to be one of the key cells in the pathogenesis of this disease. The number of relapses had a direct relationship with the analyzed pollutants (PM10, PM2.5), and wherever these pollutants showed an increasing trend, the number of relapses also increased. In line with our study results, Blatt et al demonstrated that seasonal variations in sunlight exposure lead to environmental (cutaneous) inflammation, which results in the production of cytokines that attract T lymphocytes. When this inflammation subsides, these lymphocytes return to the bloodstream, and some ultimately migrate to the brain, where they may potentially cause inflammation (14). In another study consistent with ours, Jeanjean et al published an article in 2018 titled "Are ozone, NO2, and PM10 associated with the onset of MS relapses?" The researchers ultimately stated that air pollutants can be a factor in increasing MS attacks, and seasonal variations in pollution levels can also lead to changes in the severity of the disease and the frequency of its attacks (1). Additionally, Templer DI et al, in their article titled "Birth Season and Multiple Sclerosis in Scandinavia," stated that the monthly distribution of births among individuals with MS significantly differs from that of the general population (15). MS patients were more likely to be born in March, April, May, and June. Infection was suggested as a possible explanation for this phenomenon. Ultimately, the researchers concluded that the birth month and associated factors, such as seasonal infections, are important influences on the onset of MS. Tataru et al (16) conducted a study titled "The limited impact of the summer heat wave in France (2003) on the admission and relapse of multiple sclerosis in the hospital."

**Table 3.** Examining the relationship between patients' gender and autoimmune disease with disease recurrence

| Variable | | Recurrence | | | | | *P* value |
|---|---|---|---|---|---|---|---|
| | | One | Two | Three | Four | Five | |
| Gender | Men | 32 (46.4) | 13 (18.8) | 14 (20.3) | 7 (10.1) | 3 (4.3) | 0.272 |
| | Woman | 103 (42.9) | 72 (30) | 35 (14.6) | 15 (6.3) | 15 (6.3) | |
| Autoimmune Disease | No | 118 (43) | 75 (27) | 42 (15) | 20 (7) | 14 (5) | 0.001 |
| | Yes | 17 (42) | 10 (25) | 7 (17) | 2 (5) | 4 (10) | |

They stated that patients with MS often report worsening symptoms with increasing ambient temperature. The results showed a significant reduction in MS hospital admissions during the winter season, particularly in December, but no significant peak was observed in any season or month. There was no statistically significant relationship between the average ambient temperature and the number of admissions and relapses. The adverse symptoms associated with high temperatures that are typically observed in MS patients may require a rapid increase in moderate ambient temperature or the body's internal temperature to manifest. This study provides valuable insights into the relationship between environmental factors (e.g., temperature, humidity, and air pollution) and the frequency of MS relapses, but it has some limitations. Firstly, conducting the study in a specific geographic region (Qom province) may limit the generalizability of the findings. Secondly, the retrospective design and reliance on pre-existing data may introduce bias into the results. Additionally, the lack of consideration for confounding factors such as lifestyle and socioeconomic status, as well as the exclusive focus on RRMS, are other limitations of this study. To address these limitations, future studies are recommended to be multi-center and prospective to enhance the generalizability and accuracy of the results. Furthermore, investigating confounding factors, longer-term follow-up, and including other MS subtypes (such as progressive MS) can provide a more comprehensive understanding of the impact of environmental factors on disease relapse. Additionally, conducting laboratory research to explore the biological mechanisms linking environmental factors to MS relapses is suggested.

## Conclusion

In summary, this study highlights the multifaceted nature of MS, where environmental factors, especially temperature and relative humidity, significantly affect relapse rates. Comorbid autoimmune diseases and family history also emerge as critical factors influencing disease dynamics. These findings could inform future studies and clinical approaches aimed at managing and mitigating the impact of MS, emphasizing the need for holistic patient care that considers both environmental influences and underlying health conditions.

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**Competing Interests**

The authors declared no conflict of interest.

**Ethical Approval**

The Ethics Committee of Qom University of Medical Sciences approved this study (Ethical code: IR.MUQ.REC.1399.115).

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