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Research Article

The Relation Between Air Pollution and Multiple Sclerosis Hospitalization in Kerman

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Abstract

Background: Air pollutants may harm the nervous system and act as environmental risk factors for increased hospitalizations and relapses in multiple sclerosis (MS).

Objectives: This study aimed to assess the potential association between MS hospitalizations and ambient air pollutants, including CO, O_3, SO_2, NO_2, PM_{10}, and $PM_{2.5}$, in Kerman, Iran.

Methods: This ecological study used air pollution and meteorological data obtained from the Kerman Environmental Protection Agency and the Kerman Meteorology Organization, respectively. Multiple sclerosis hospitalization data were obtained from the Shafa Hospital MS Registry in Kerman. Generalized additive models (GAMs) were used to estimate rate ratios (RRs) for air pollutants in predicting MS hospitalization after adjusting for temperature, relative humidity, seasonality, weekdays, and long-term trends, using lags of up to 7 days.

Results: During 2008 - 2020, 4,913 MS hospitalizations occurred among patients with MS in Kerman, of which 3,739 were in females. Significant associations were observed between MS hospitalization and CO in individuals aged < 30 years (RR = 1.5647 at lag 0), O_3 in individuals aged > 50 years (RR = 1.0161 at lag 5), SO_2 in individuals aged > 50 years (RR = 1.0253 at lag 5), NO_2 in females (RR = 1.0121 at lag 0), PM_{10} in individuals aged > 50 years (RR = 0.9828 at lag 3), and $PM_{2.5}$ in individuals aged > 50 years (RR = 0.9832 at lag 5).

Conclusions: Ambient O_3 and NO_2, and more consistently, CO and SO_2, were associated with increased MS hospitalizations in Kerman.

Keywords: Air Pollutants, Multiple Sclerosis, Environmental Factors, Rate Ratio, Kerman Province

1. Background

Multiple sclerosis (MS) is an inflammatory disease in which myelinated axons in the central nervous system (CNS) are damaged (1), leading to neurological disability. It is more common among adults aged 20 - 40 years (2). Multiple sclerosis is a global health problem, and the number of patients with MS increased to 2.8 million in 2020 (3). Epidemiological studies have shown that the number of patients with MS has also increased in Iran over the past two decades (4). The prevalence of MS in Kerman, Iran, was 57.3 per 100,000 people in 2011 (5).

Studies have shown that air pollutants may affect the CNS and lead to hospital admissions for neurological diseases (6-8). Although the main etiology of MS has not yet been identified (9), several environmental risk factors for MS have been reported, including seasonal

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changes, weather conditions, and air pollutants (10-12). Other studies have suggested that MS relapse varies by season (13); for example, in Kerman, Iran, most cases occur in winter and spring (14).

Oikonen et al. reported an association between MS and particulate matter in Finland (15). In a systematic review, the authors concluded that air pollutants such as NO_2 and PM may be associated with MS (4). In addition, Heydarpour et al. showed that exposure to SO_2, PM_{10}, NO_2, and NOx might be related to MS relapses in Tehran (12).

Despite these findings, evidence regarding the effects of air pollution on CNS diseases such as MS remains limited. Kerman is a city in southeastern Iran with both air pollution and variable rates of MS incidence (14).

2. Objectives

This study aimed to determine whether short-term associations exist between air pollutants (CO, O_3, NO_2, SO_2, PM_{10}, and $PM_{2.5}$) and hospital admissions for MS in Kerman, Iran.

3. Methods

3.1. Study Design and Setting

This ecological study was conducted in Kerman, Iran. Hourly ambient city-wide air pollutant measurements for CO, O_3, NO_2, SO_2, PM_{10}, and $PM_{2.5}$ in Kerman were obtained from the Kerman Environmental Protection Agency from September 2008 to March 2020. Daily averages were calculated from the hourly data. In Kerman, air pollution is monitored by a single station located at Shohada Square. Measurements were performed using standard monitoring instruments in accordance with relevant guidelines. In this study, when hourly data were unavailable, missing values were imputed using the expectation-maximization (EM) algorithm.

Meteorological variables, including daily temperature and relative humidity, were obtained from the Kerman Meteorology Organization.

3.2. Multiple Sclerosis Hospitalization Data

Multiple sclerosis incidence and relapse data, as daily counts, were obtained from Kerman's Shafa Hospital MS Registry under ICD-10 code G35. Shafa Hospital is the main referral center for neurological patients in Kerman, and the MS data center is located at this hospital.

Incidence data were obtained anonymously by sex and age group. Most MS hospitalizations were due to MS attacks, relapse, or complications; however, the exact reason for admission was not recorded.

3.3. Statistical Analysis

Generalized additive models (GAMs), as shown in the equations below, were used to estimate the RRs of air pollutants and MS hospitalization for a 1-unit increase in CO and a 10-unit increase in all other pollutants. The models were adjusted for temperature, relative humidity, seasonality, weekdays, and long-term trends, with lags of up to 7 days. This study evaluated only short-term effects; therefore, effects only up to 7 days were examined. The time unit was day. Analyses were performed using R 4.5.2 software.

$$Y_t \sim \text{Poisson}\,(\mu_t)$$

$$\text{Log}\,\mu_t = \alpha + \sum \beta_i\,(X_i) + \sum S_j\left(X_j\right) + \text{season} + \text{day of week} + \text{long term trend}$$

In this model, Y_t denotes the daily number of MS hospitalizations in the total population and by sex and age group. β_i is the coefficient for air pollutants and denotes the log of the RR, and S_j (X_j) represents the smoothing functions of meteorological variables, including temperature and relative humidity.

4. Results

During the 12-year study period, 4,913 hospitalizations for MS were recorded at Shafa Medical Center, of which 3,739 (76%) were in females and 1,174 (26%) were in males. Most admissions (59%) occurred in the 30 - 50-year age group. MS hospitalization counts are presented in Table 1. Table 2 shows the mean±standard deviation of air pollutants in Kerman, during the years under study.

Descriptive statistics for the air pollutants and meteorological variables are presented in Table 3. Correlations among air pollutants in Kerman are shown in Table 4. Many air pollutants were significantly correlated; therefore, only single-pollutant models were constructed.

Table S1 in the supplementary file and Figure 1 present the GAM results for evaluating the impact of air pollutants on MS hospitalizations.

Table 1. Counts of Multiple Sclerosis Hospitalization From 2008 to 2020 in Different Population Subgroups

Variables	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	Total
Female	36	178	199	234	201	197	269	333	370	452	497	671	102	3739
Male	14	62	67	57	58	76	87	121	128	143	152	180	29	1174
< 30 years	22	105	102	92	95	97	127	163	166	198	189	256	55	1667
30 - 50 years	23	123	149	183	152	164	211	274	302	347	391	508	62	2889
> 50 years	5	12	15	16	12	12	18	17	30	50	69	87	14	357
Sex Ratio (F/M)	2.57	2.87	2.97	4.10	3.46	2.59	3.09	2.75	2.89	3.16	3.26	3.72	3.51	3.18

Table 2. Presents the Mean ± Standard Deviation of Air Pollutants in Kerman During the Study Years [a, b]

Variables	O_3 (ppb)	CO (ppm)	NO_2 (ppb)	SO_2 (ppb)	PM_{10} (µg/m^3)	$PM_{2.5}$ (µg/m^3)
2009	20.03 ± 1.06	0.91 ± 0.36	18.79 ± 4.57	8.03 ± 3.58	130.10 ± 41.57	42.82 ± 18.88
2010	26.47 ± 17.18	1.03 ± 0.54	20.81 ± 9.21	9.98 ± 6.37	118.32 ± 51.29	45.25 ± 26.88
2011	29.99 ± 6.61	0.94 ± 0.43	16.24 ± 4.49	12.87 ± 4.22	101.63 ± 26.56	26.24 ± 9.77
2012	34.42 ± 13.53	0.78 ± 0.38	12.68 ± 4.84	7.93 ± 5.14	67.32 ± 40.33	20.53 ± 15.61
2013	33.66 ± 11.89	0.92 ± 0.39	12.77 ± 5.10	16.73 ± 9.01	67.4 ± 24.21	25.35 ± 12.70
2014	30.51 ± 7.35	1.13 ± 0.38	15.35 ± 2.99	25.04 ± 6.19	68.94 ± 17.55	24.34 ± 8.32
2015	32.83 ± 11.94	0.91 ± 0.56	7.62 ± 6.89	24.21 ± 10.33	60.88 ± 29.37	28.21 ± 13.52
2016	30.08 ± 11.49	0.97 ± 0.52	16.56 ± 14.24	52.04 ± 22.80	66.92 ± 43.60	24.62 ± 10.65
2017	32.67 ± 11.22	1.02 ± 0.49	23.01 ± 7.56	49.99 ± 19.96	48.85 ± 21.03	21.52 ± 9.38
2018	30.72 ± 11.84	1.48 ± 1.39	14.75 ± 6.39	35.43 ± 18.13	26.45 ± 21.03	23.37 ± 11.72
2019	33.66 ± 8.36	1.62 ± 0.78	14.93 ± 4.07	46.66 ± 11.62	27.44 ± 24.64	22.20 ± 9.45

[a] Values are expressed as mean ± SD.

[b] Data was not available for all months of 2008 and 2020 and thus these years were not listed in the table.

Table 3. Descriptive Statistics of Daily Air Pollution and Meteorological Variables in Kerman (2008 - 2020)

	Mean	SD	Min	Median	25th Percentile	75th percentile	98th percentile	Max
O_3 (ppb)	30.21	11.91	1.92	29.72	22.24	37.42	58.70	79
CO (ppm)	1.07	0.69	0.03	0.92	0.66	1.34	2.54	12.27
NO_2 (ppb)	15.82	7.96	0	15.41	11.71	19.29	36.69	78.45
SO_2 (ppb)	26.12	20.64	0	21	9.12	41.64	82.76	128.46
PM_{10} (µg/m^3)	71.11	47.45	0	63.48	36.71	97.94	194.61	382.76
$PM_{2.5}$ (µg/m^3)	27.47	16.18	0	24.20	17.57	32.91	78.55	112
Temperature(°C)	16.75	8.10	-12.1	17.2	9.7	23.80	30.20	41
Humidity (%)	31.15	17.30	1	27	18	41	75	100

Carbon monoxide, O_3, and SO_2 were directly associated with MS hospitalizations at certain lags in males. Significant associations were observed at lag 1 for CO (RR = 1.0113, 95% CI: 1.0099 - 1.0123), lag 3 for O_3 (RR = 1.0110, 95% CI: 1.0051 - 1.0171), and lag 5 for SO_2 (RR = 1.0135, 95% CI: 1.0106 - 1.0163).

Carbon monoxide, O_3, SO_2, and NO_2 were also directly associated with MS hospitalization rates at certain lags in females. Associations were observed at lag 0 for CO (RR = 1.4784, 95% CI: 1.1884 - 1.8401), lag 3 for O_3 (RR = 1.0101, 95% CI: 1.0061 - 1.0122), lag 1 for SO_2 (RR = 1.0135, 95% CI: 1.0124 - 1.0160), and lag 0 for NO_2 (RR = 1.0121, 95% CI: 1.0050 - 1.7080).

Table 4. Spearman Correlation Coefficients Between Air Pollutants in Kerman (2008 - 2020)

	CO	NO_2	SO_2	PM_{10}	$PM_{2.5}$	
O_3	1					
CO	-0.548 [a]	1				
NO_2	-0.454 [a]	0.399 [a]	1			
SO_2	0.205 [a]	0.233 [a]	0.181	1		
PM_{10}	-0.107 [a]	-0.231 [a]	0.158 [a]	-0.399 [a]	1	
$PM_{2.5}$	-0.1 [a]	-0.079 [a]	0.051 [a]	-0.141 [a]	0.486 [a]	1

[a] $P < 0.001$.

Across many age groups, CO, O_3, and SO_2 showed direct associations with MS hospitalizations. The strongest association was observed in individuals aged < 30 years at lag 0 for CO (RR = 1.5647, 95% CI: 1.2610 - 1.3711).

Among all pollutants listed in Table S1 in the supplementary file, CO and SO_2 were more consistently associated with increased MS hospitalizations than the other pollutants.

In this study, PM_{10} and $PM_{2.5}$ were inversely associated with MS hospitalizations in several subgroups. The strongest significant associations were observed for PM_{10} in individuals aged > 50 years at lag 3 (RR = 0.9828) and for $PM_{2.5}$ in individuals aged > 50 years at lag 5 (RR = 0.9832).

5. Discussion

Few studies worldwide have examined the relation between air pollution and MS (15-21). In this study, significant associations were observed between short-term exposure to some air pollutants and MS hospitalization in Kerman, Iran. Watad et al. also suggested that MS recurrence may be associated with environmental factors such as climate variables and air pollution (22).

In this study, increased CO was associated with a higher number of MS hospitalizations across different subgroups. A case-control study in the United States also reported a significant relation between ambient CO and MS in children (OR = 3.85, 95% CI: 1.34 - 11.1) (20). However, in Tehran, Iran, CO was not related to MS recurrence, which may have been due to the short study period (2011 - 2012) and small sample size (21).

In this study, O_3 was significantly associated with MS hospitalizations across many subgroups and lags. Consistent with these findings, Jeanjean et al. showed that O_3 was related to MS relapse during the hot season in France after adjustment for meteorological variables (OR = 1.16, 95% CI: 1.07 - 1.25) (19). However, these results differ from a study conducted in Tehran, which found no significant relation between O_3 and MS attacks (21). One possible reason is that, in the current study, the average concentration of O_3 was 30.21 ± 11.91 ppb, which was higher than that reported in the Tehran study (25.79 ± 16.11 ppb) (21). Meanwhile, ozone levels in the hot season in France were even higher than those in Kerman (86.85 ± 30.89 ppb), which might explain the association observed between O_3 and MS in the French study (19). However, in a study conducted in Spain with O_3 levels similar to those in Kerman (35.7 ± 18.11 ppb), no association was found between O_3 and MS admissions (17).

In this study, significant associations between SO_2 and MS hospitalizations were observed in many subgroups. Other researchers have also reported relations between sulfur dioxide and MS (12, 15, 20). In Tehran, Iran, researchers observed that MS cases were more exposed to SO2 than controls (12). Lavery et al. also showed that SO_2 was associated with increased pediatric MS recurrence in the United States (OR = 3.14, 95% CI: 1.13 - 8.72) (20). In this study, the average concentration of SO_2 was 26.12 ± 20.64 ppb, which is higher than the WHO-recommended level (23), but lower than the level reported in the Tehran study (58 ppb), which also found a significant association (12).

In the current study, NO_2 was significantly related to MS hospitalizations in several subgroups. Similarly, other studies have reported that nitrogen dioxide may be related to the recurrence of MS attacks (12, 15, 16, 19, 21). A systematic review conducted by Farahmandfard et al. (4) also concluded that NO_2 and NOx may be related to MS prevalence or relapse. In France, increased NO_2

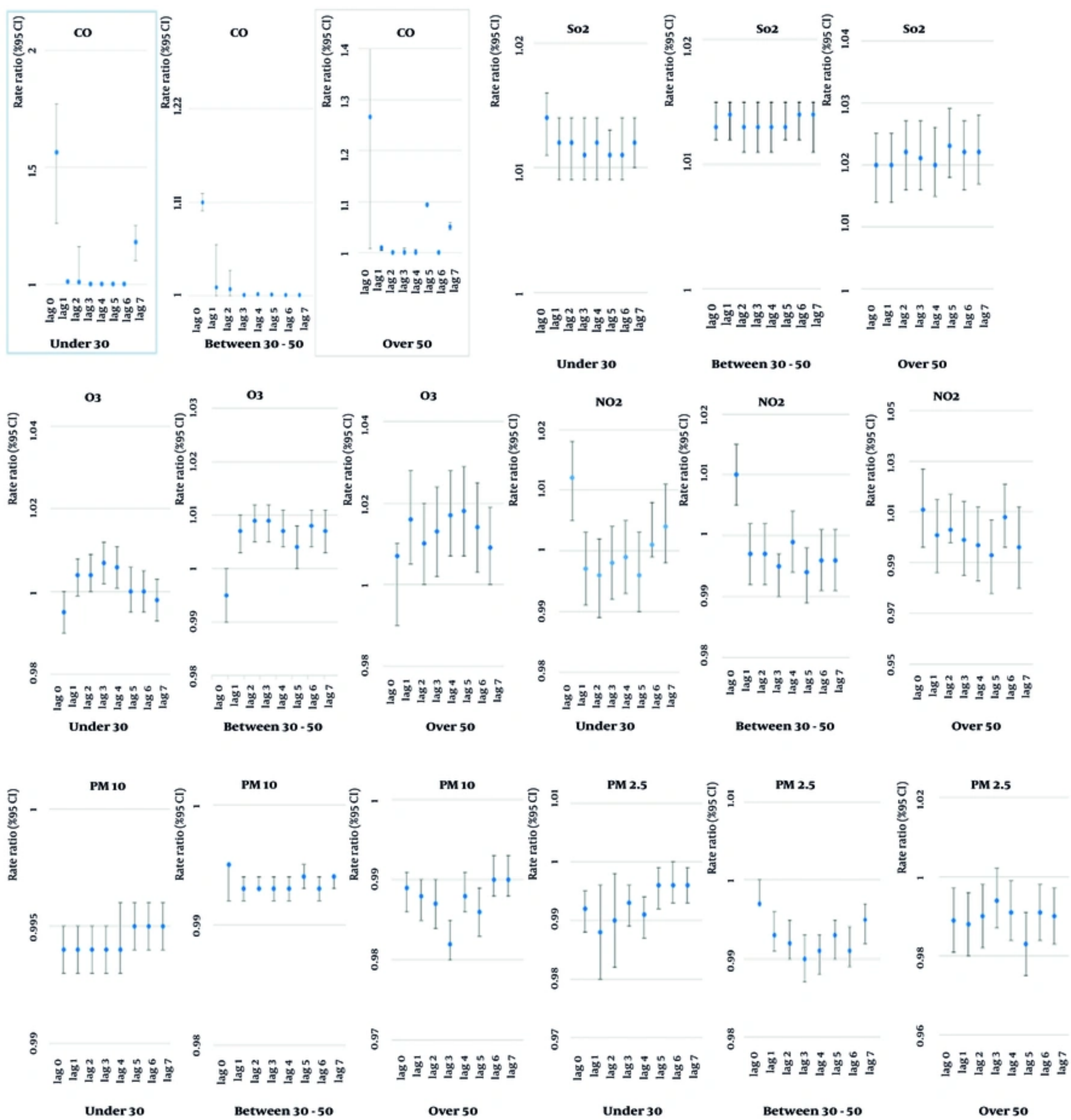

Figure 1. Association between air pollutants (CO, O_3, NO_2, SO_2, PM_{10}, $PM_{2.5}$) and multiple sclerosis hospitalization in age groups with up to 7-day lags in Kerman, Iran, September 2008 - March 2020.

after a 0 - 3-day lag was related to MS relapse in winter (OR = 1.08, 95% CI: 1.03 - 1.14) (19), and in Tehran, NO_2 was related to MS relapse (r = 0.27) (21). However, Gregory et al. did not find a significant relation between NO_2 and MS relapse in the United States (18). In Spain, Carmona et al. also showed no association between traffic-related air pollutants, including nitrogen oxides, and MS hospitalizations (17).

In this study, PM_{10} and $PM_{2.5}$ were inversely related to MS hospitalizations in all subgroups. This finding may have several explanations. Similar counterintuitive findings have been reported in studies conducted in regions with substantial dust storms or non-combustion particulate sources (19, 24, 25). In cities such as Kerman, the chemical composition of particulate matter in arid environments is often dominated by crustal or mineral dust rather than traffic- or industry-related particles, and these components may have different inflammatory potentials. In addition, extreme dust events can lead to substantial changes in population mobility, school and workplace closures, or altered health-care-seeking behavior at the population level, none of which can be fully accounted for in ecological models. However, other studies have shown relation between PM_{10} and MS (12, 15, 16, 18, 19, 24-26). In Finland, increased PM_{10} concentrations after a 1-month lag increased the risk of MS relapse (OR = 4.14, 95% CI: 1.61 - 10.63) (15). In the study by Gregory et al., PM_{10} was directly related to MS prevalence rates in the total population in the United States (β = 0.276) (18). In Italy, MS relapse was directly related to PM_{10} exposure in two studies (24, 25). Roux et al. showed a significant direct association between PM_{10} and the risk of MS relapse after a 1 - 3-day lag in the cold season in Strasbourg, France (OR = 1.40, 95% CI: 1.08 - 1.81) (26). In Jeanjean et al.'s study, PM_{10} after a 0 - 3-day lag was associated with increased MS relapse in winter in Paris, France (OR = 1.06, 95% CI: 1.01 - 1.11) (19). However, other studies found no association (17, 27).

In this study, the average concentration of PM_{10} was 71.11 ± 47.45 $\mu g/m^3$, which was higher than the levels measured in Italy (42.48 ± 28.6 $\mu g/m^3$) (24) and France (23.70 ± 12.69 $\mu g/m^3$) (19), but lower than the level measured in Tehran, Iran (99.1 $\mu g/m^3$) (12). Therefore, it is not reasonable to attribute these conflicting results to ambient dust concentrations alone.

One study showed that $PM_{2.5}$ was associated with increased recurrence of MS among children in the United States (OR = 3.96, 95% CI: 1.42 - 11.1) (20), and another study observed that MS prevalence was directly related to $PM_{2.5}$ exposure in Italy (28). However, in Canada, $PM_{2.5}$ exposure did not increase the risk of MS (HR = 0.96, 95% CI: 0.86 - 1.07) (29). In Italy, people with lower $PM_{2.5}$ exposure were less likely to develop MS (30).

Some studies have reported that patients with MS have lower vitamin D levels during relapses. This may be related to the role of vitamin D in immune system balance (31, 32). Sunlight exposure can increase vitamin D production in the human body, but air pollutants reduce exposure to ultraviolet radiation and decrease vitamin D production (33, 34). Nevertheless, vitamin D is discussed here only to suggest a biological rationale, as air pollution has been shown to reduce solar radiation and may affect vitamin D synthesis. This might help explain how industrialization, urbanization, and lifestyle changes are related to MS (35-37).

5.1. Study Limitations

Important limitations of this study include the use of aggregated data and the possibility that hospital admissions may not reflect all MS relapses. Diagnostic variability and changes in health-care access may also have occurred during the 12-year period. Because of multicollinearity concerns, single-pollutant models were used; however, pollutant effects may have been confounded by other pollutants. In addition, not all meteorological factors were adjusted for in the analysis. Another limitation is that only short-term effects, with lags of up to 7 days, were evaluated.

Many studies have examined associations between ambient pollutants, environmental risk factors, and health outcomes (38-42), but these studies cannot demonstrate causation. More research is needed to draw causal inferences.

There are limited studies on the effects of air pollutants on MS. This study was innovative because it included approximately 12 years of air pollution and MS hospital admission data and used GAMs to adjust for nonlinear confounder variables.

5.2. Conclusions

Ambient O_3, NO_2, and, more consistently, CO and SO_2 were associated with increased MS hospitalization in Kerman. However, potential confounders, the aggregated nature of the data, collinearity between pollutants, and the limited generalizability of the results should be considered. This evidence emphasizes the need to control and reduce air pollutants.

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Supplementary Material

Supplementary material(s) is available here [To read supplementary materials, please refer to the journal website and open PDF/HTML].

Footnotes

AI Use Disclosure: The authors declare that no generative AI tools were used in the creation of this article.

Authors' Contribution: Mohammad Amin Farahmandfard: conceptualization, methodology, validation, statistical analysis, writing the original draft; Narges Khanjani: Supervision, conceptualization, writing, review, editing, project supervision; Hossein Ali Ebrahimi: Conceptualization, editing; Moghaddameh Mirzaee: Statistical analysis, editing; Hoda Kamali: Data curation, editing

Conflict of Interests Statement: The authors declare no conflict of interersts.

Data Availability: The dataset presented in the study is available upon reasonable request from the first author. The data are not publicly available.

Ethical Approval: The Ethics in Research Committee of Kerman University of Medical Sciences approved the study protocol under code IR.KMU.REC.1398.583. All methods were performed in accordance with the relevant guidelines and regulations.

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