





Original Article

Impact of Alcohol Consumption on Multiple Sclerosis Using Model-based Standardization and Misclassification Adjustment Via Probabilistic Bias Analysis

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Abstract

Background: The etiology of multiple sclerosis (MS) is still not well-demonstrated, and assessment of some risk factors like alcohol consumption has problems like confounding and measurement bias. To determine the causal effect of alcohol consumption on MS after adjusting for alcohol consumption misclassification bias and confounders.

Methods: In a population-based incident case-control study, 547 patients with MS and 1057 healthy people were recruited. A minimally sufficient adjustment set of confounders was derived using the causal directed acyclic graph. The probabilistic bias analysis method (PBAM) using beta, logit-logistic, and triangular probability distributions for sensitivity/specificity to adjust for misclassification bias in self-reporting alcohol consumption and model-based standardization (MBS) to estimate the causal effect of alcohol consumption were used. Population attributable fraction (PAF) estimates with 95% Monte Carlo sensitivity analysis (MCSA) intervals were calculated using PBAM and MBS analysis. Bootstrap was used to deal with random errors.

Results: The adjusted risk ratio (95% MCSA interval) from the probabilistic bias analysis and MBS between alcohol consumption and MS using the three distribution was in the range of 1.93 (1.07 to 4.07) to 2.02 (1.15 to 4.69). The risk difference (RD) in all three scenarios was 0.0001 (0.0000 to 0.0005) and PAF was in the range of 0.15 (0.010 to 0.50) to 0.17 (0.001 to 0.47).

Conclusion: After adjusting for measurement bias, confounding, and random error alcohol consumption had a positive causal effect on the incidence of MS.

Keywords: Alcohol consumption, G-formula, Model-based standardization, Monte Carlo sensitivity analysis, Multiple sclerosis, Probabilistic bias analysis

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Introduction

Multiple sclerosis (MS) is the most common non-traumatic disabling disease in young adults.^{1,2} Life expectancy in these patients is 10 years less than the normal population.³ Despite its low prevalence, a similar increasing trend has been reported in almost all parts of the world. From 1990 to 2016, the age-standardized prevalence of the disease increased by 10.4%.⁴ Iran has a medium-to-high prevalence of MS; nevertheless, a dramatic increase has been recently reported in its incidence and prevalence.⁵⁻⁷

Numerous studies have been performed to determine the risk factors of MS, but its etiology is still not well-demonstrated. Vitamin D deficiency,⁸ exposure to ultraviolet B (UVB) light,⁹ Epstein-Barr virus (EBV) infection,¹⁰ smoking,¹¹ waterpipe smoking,¹² diet¹³ and drug abuse¹⁴ are all associated with the disease. Another suggested risk factor is alcohol consumption. However, there is no conclusive evidence about the possible

association between alcohol intake and MS.^{15,16}

The underlying social stigma in societies like Iran may result in the possibility of misclassification or underreporting bias when investigating the consumption of illegal substances including alcohol intake or drug abuse.¹⁷ Thus, appropriate control for this type of misclassification bias is prudent for a correct causal analysis of alcohol intake and MS diagnosis. The probabilistic bias analysis method (PBAM) is one of the recently emerging methods which provides bias-corrected effect estimates using prior distribution for sensitivity and specificity of exposure misclassification.¹⁸⁻²⁰ Bayesian methods (BM) and PBAM often provide similar results though the latter is more straightforward and accessible than BM.^{21,22}

There are several causal methods including inverse probability-of-treatment weighting (IPTW), and model-based standardization (MBS), known as parametric g-formula in the time-varying setting, for estimating

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the marginal causal effects in cohort and case-control studies.^{14,23-29} These methods might be appropriate for estimating the causal effect of alcohol consumption on MS, as policy interventions for reducing excessive alcohol consumption at the population level could be more effective.³⁰ Therefore, by conducting a large population-based incident case-control study with known case and control sampling fractions, we aimed to evaluate the causal effect of alcohol consumption on MS after adjusting for misclassification bias and confounders using PBAM and MBS.

Materials and Methods

Design and Sampling

This case-control study was conducted in Tehran, Iran.^{12,31} All participants provided verbal informed consent, and all stages of this study were based on the Helsinki Declaration. The study base was individuals aged 15–50 years who were residents in Tehran between August 2013 and February 2015. The case group consisted of 547 new cases with MS, definitively diagnosed by at least one neurologist using the 2010 McDonald criteria as well as MRI confirmation. A random-digit dialing (RDD) sampling technique was used for control selection, and 1057 alive person aged 15–50 years were selected. The international physical activity and a validated Persian version of EnvIMS-Q questionnaires along with the neurologist's opinion were used to prepare the MS comprehensive checklist.³²⁻³⁵ Lifestyle data and other confounding variables were collected via interviews. Ten interviewers were identified based on their skill set and trained to use the standardized data collection procedures. Phone interviews were conducted and we monitored the data collection activities for any interviewer bias by randomly recording interviews. To decrease the possibility of misclassification of undetected cases, the clinical signs and characteristics of MS were explained to the control

sample. Data gathering in case and control groups was accomplished with the same protocol. Drinking any type of alcohol (beer, wine, liquor, and the other types) for at least 6 times in at least a six month period was considered as the life time alcohol consumption. Life events were defined as significant stressful occurrences in the past 4-5 years, including but not limited to divorce, migration, and loss of loved ones.

Statistical Analysis

A literature review was performed to determine the potential confounders of the causal relationship between alcohol consumption and MS. The causal directed acyclic graph³⁶⁻⁴⁴ for the effect of alcohol consumption on MS is presented in Figure 1. We used Pearl's back-door criterion to identify a minimally sufficient set of confounders for adjustment. All analyses were performed using the R statistical software.

Bias and Causal Analysis Using PBAM and MBS

Step 1: To parameterize probability distributions for sensitivity/specificity, the literature was systematically reviewed in Scopus, PubMed, and Web of Science using the keywords “accuracy”, “measurement error”, “measurement bias”, “sensitivity”, “specificity”, “validity”, “self-reported alcohol”, and “multiple sclerosis”. Sensitivity and specificity estimates along with their 95% confidence intervals (CIs) were extracted from the studies. Pooled sensitivity and specificity values were calculated using the random-effects model.⁴⁵

Step 2: Six studies with eight sensitivity and specificity values were derived based on the literature review.⁴⁶⁻⁵¹ Pooled sensitivity and specificity estimates with 95% CIs were 0.79 (0.72, 0.86) and 0.84 (0.80, 0.89), respectively. These studies included patients who visited the emergency department, individuals with addiction, patients infected with HIV, pregnant women, students, and the general

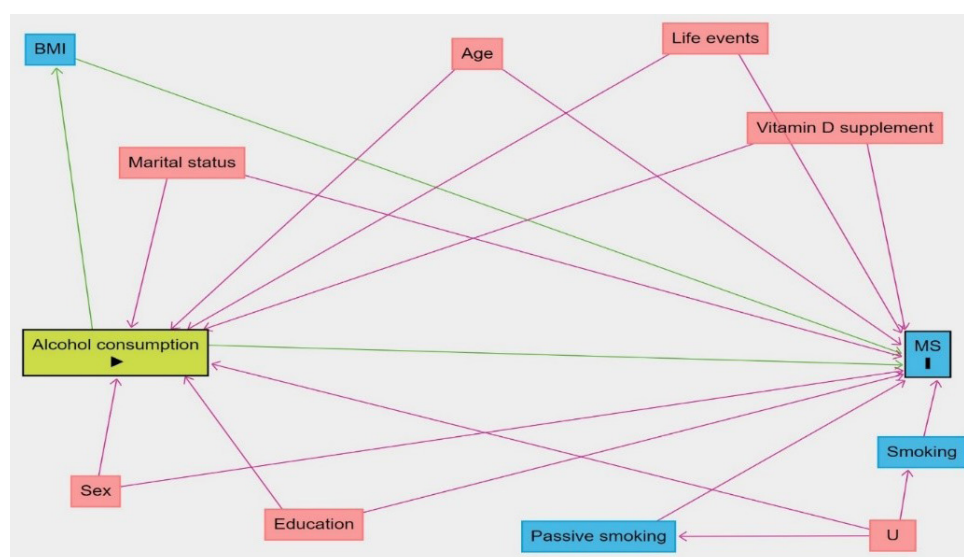


Figure 1. Causal Directed Acyclic Graph for the Effect of Alcohol Consumption on Multiple Sclerosis. The minimally sufficient adjustment set of confounders consists of age, sex, marital status, education, smoking, passive smoking, life events and vitamin D supplement

population. Since none of the studies included patients with MS, we were unable to estimate differential misclassification, and also none of these studies were conducted in Iran. Objective biomarkers, such as hair analysis tests and various blood tests, served as the gold standard for determining alcohol consumption.

Step 3: Three probability distributions, namely beta, logit-logistic, and triangular, were specified to represent a diverse range of choices in the absence of empirical information (Supplementary file 1, Figure S1). They were specified so that their median (2.5th and 97.5th percentiles) was equal to the pooled estimate (95% CI) obtained in the previous step. Parameters for triangular, beta, and logit-logistic distributions are shown in Table 1.

Step 4: The sensitivity and specificity matrix as well as the numbers of reported exposed and unexposed cases were used to obtain the expected and unexposed true number of cases (for more explanations, see Figure S1). Sensitivity and specificity values were randomly selected from the probability distributions discussed in the third step.

Step 5: Positive predictive value (PPV) and negative predictive value (NPV) were obtained (for more explanations, see Figure S1). Negative or zero A or B values were discarded and the fourth and fifth steps were repeated.

Step 6: The expected exposure status for each person was obtained using the observed exposure status, PPV, and NPV values. This variable was assumed to be Bernoulli-distributed with the probability parameters equal to PPV and NPV for exposed and unexposed cases. So, we generated a random variable with a uniform distribution (U_i) between the values of zero and one. For the exposed case (reported alcohol), the exposure status was set to be 0 if $U_i > PPV$; otherwise, the exposure status was not changed. For the unexposed cases, the exposure status was set to be 1 if $U_i > NPV$; otherwise, the exposure status was not changed.

Step 7: A multivariable logistic regression model was fitted with case/control status as the response variable, and the imputed exposure status derived in the previous step, as well as confounders as predictors. Fractional polynomials were used to assess the linearity assumption for the variable age.

Step 8: Using the logistic regression model from the previous step, the MBS was performed by calculating the standardized risks in the exposed and unexposed over

the confounders' distributions in the study base of the case and control groups, obtained by model-intercept correction. First, the bias in the intercept due to case-control sampling was corrected by subtracting the log (sampling fraction in case/sampling fraction in control) i.e. $\log\left(\frac{0.96}{1057/5115679}\right) = 8.44$, from the apparent intercept. The sample fraction in the case group refers to the ratio of the number of cases to the total number of individuals with MS, and the sample fraction in the control group represents the ratio of the number of controls to the number of general population aged between 15 and 50 years. Second, the standardized risk in the exposed was calculated by predicting the probability of outcome based on the observed confounder values and setting all participants to be exposed and then averaging the predicted risks, weighted by inverse sampling fractions in the case and control groups. The standardized risk in the unexposed was calculated similarly by setting all unexposed. Marginal risk ratio (RR) and risk difference (RD) were obtained by dividing and subtracting the calculated standardized risks in the exposed and unexposed.

Step 9: The results of the previous step constitute one round. Steps 4–8 were repeated 1000 times to obtain a simulation interval using probabilistic bias analysis via Monte Carlo simulation from the distributions mentioned in step 3: the median (50th percentile), and 2.5 and 97.5 percentiles of the RRs and RDs obtained were considered as the point estimate and Monte Carlo sensitivity analysis (MCSA) limits, respectively.

By now, we corrected misclassification bias and confounding, but random error should be addressed as well. Therefore, all steps 4 to 9 were performed in each of the 500 bootstrap sample, reconstructed through separately sampling by replacement from cases and controls with the same original sizes, yielding 500 000 RRs and RDs corrected for both misclassification/confounding and random error.

Population Attributable Fraction

To determine the fraction of all MS patients in the population that might be attributable to alcohol consumption, we calculated population attributable fraction (PAF) as follows⁵²⁻⁵⁴:

$$PAF = \frac{\Pr[Y = 1] - \Pr[Y^{a=0} = 1]}{\Pr[Y = 1]}$$

where $\Pr[Y = 1]$ is the observed risk and $\Pr[Y^{a=0} = 1]$ refers to the risk that would have been observed if everybody had received $a = 0$ or no alcohol consumption. $\Pr[Y^{a=0} = 1]$ was calculated as the standardized risk in the unexposed, explained in step 8. For conventional analysis, we used the PAF formula above, provided that there was no adjustment for misclassification in calculating observed risk and risk under no alcohol consumption assumption i.e. the analysis starts from step 7 above using

Table 1. Probability Distributions Parameters for Triangular, Beta and Logistic Distributions in Case and Control Groups

Bias Parameters	Triangular Distribution (Minimum; Maximum; Mode)	Beta Distribution (Alpha; Beta)	Logit-Logistic Distribution (Location; Scale)*
Sensitivity	0.72, 0.86, 0.79	79.79, 20.32	0.79, 0.004
Specificity	0.80, 0.89, 0.84	88.75, 16.03	0.84, 0.003

*The location and scale for logistic distribution are presented, and the logit-logistic distribution is the expit transformation of this distribution.

the observed exposure (instead of the imputed exposure) and continues through step 8 in which no Monte Carlo simulation was performed, and CI was obtained using 500 bootstrap samples.

Results

This case-control study included 547 cases and 1057 controls, of whom 401 (73.3%) and 544 (51.5%) were female, respectively. The mean age (SD) was 30.5 (7.53) for cases and 31.3 (9.33) for controls. The characteristics of both groups are presented in Table 2. According to Figure 1, the variables age, sex, marital status, education, smoking, passive smoking, life events, and vitamin D supplement were considered to be confounders for the effect of alcohol consumption on MS.

The confounder-adjusted odds ratio (OR) obtained from the conventional logistic regression analysis for the effect of alcohol consumption on MS was 1.75 (95% CI: 1.28 to 2.30). Table 3 presents the results of the PBAM-and-MBS analysis. After adjustment for confounding and misclassification bias, the RR estimates (95% MCSA interval) were 2.02 (1.15 to 4.69), 1.99 (1.06 to 5.54), and 1.93 (1.07 to 4.07), considering triangular, beta and logit-logistic distributions for bias parameters, respectively. The distribution of misclassification bias-and confounders-adjusted RRs using different bias parameters is demonstrated in Figure 2.

The PAF (95% CI) for alcohol assumption was 0.12 (0.05 to 0.18) using conventional analysis. Table 4 shows PAF estimates with a 95% MCSA interval using PBAM and MBS analysis. PAF (95% MCSA interval) was 0.17

(0.001 to 0.47) using triangular parameter distribution, 0.16 (0.014 to 0.47) using beta and 0.15 (0.010 to 0.50) logit-logistic bias parameter distribution.

Discussion

By conducting a large population-based incident case-control study, we assessed the causal effect of alcohol consumption on MS after adjusting for three main sources of error i.e. misclassification, confounding, and random error. Based on our study, after adjusting for errors, alcohol consumption has a causal effect on MS. The PBAM was used to address misclassification in the self-reported alcohol consumption.²¹ This method depends on the sensitivity and specificity estimates obtained from resources such as a literature review and meta-analysis.^{21,55} Three different distributions were used to assess the sensitivity of the results to such choices.

PBAM has been used to correct misclassification in some epidemiological studies. Livingston et al compared three methods of regression calibration, multiple imputations for measurement error, and PBAM to correct measurement errors in self-reported adolescent alcohol use.⁵⁶ The results of this study indicate that PBAM is not a good method for the correction when the sample size is small. Due to the sparseness of the crosstab cells used to estimate the sensitivity and specificity, the performance of the PBAM varied greatly with the sample size. Also, PBAM had great performance when sensitivity and specificity were high. Pakzad et al assessed the association between smoking and breast cancer adjusted for confounders and self-reported smoking misclassification using PBAM.²⁰ In that study, OR estimate increased from 0.64 for conventional analysis to ranges of 2.63–2.69 and 1.73–2.83 for non-differential and differential misclassification in PBAM. So, non-significant negative adjusted association between smoking and breast cancer changed to a significant positive adjusted association. In a recent study by Pakzad et al, adjustment for misclassification in the self-reported alcohol consumption using PBAM changed no evidence against independence between alcohol consumption and breast cancer to a substantial positive association.⁵⁷ Bodnar et al applied PBAM to correct misclassification in self-reported pre-pregnancy BMI category in the assessment of the association between BMI and pregnancy outcomes, and showed that misclassification adjustment attenuates the unadjusted association.⁵⁸

To our knowledge, this study is the first which combines PBAM with MBS to estimate the causal effect of alcohol consumption on MS. Observational studies are prone to confounding bias, and association does not ensure causation.⁵⁹ IPTW, MBS, and targeted maximum likelihood estimation (TMLE) are the methods that can be used in the case-control studies to estimate the so-called marginal (population-averaged) causal effects.⁶⁰ MBS is a generalization of classical standardization which uses standard outcome regression modeling and standardization.^{61,62}

Table 2. Characteristics of Cases and Controls

Variables	MS cases	Controls
Age (years); mean (SD)	30.5 (7.5)	31.3 (9.3)
Gender (female)*	401 (73.3)	544 (51.5)
Marital status		
Single	246 (45.1)	486 (46.2)
Married	300 (54.9)	567 (53.8)
Educational year; mean (SD)	13.8 (3.3)	13.4 (3.2)
Smoking (yes)	108 (19.7)	211 (19.9)
Passive smoking (yes)	285 (52.1)	396 (37.5)
Life event (yes)	442 (80.8)	866 (81.9)
Vitamin D supplement (yes)	14 (0.02)	80 (0.07)

MS, multiple sclerosis; SD, standard deviation.

* No. (%) was reported unless otherwise stated.

Table 3. Adjusted Risk Ratio and Risk Difference Estimates with 95% MCSA Interval Using Probabilistic Bias and MBS Analyses

Bias Parameter Distribution	Effect Measure Estimate (95% MCSA)	
	RR	RD
Triangular	2.02 (1.15 to 4.69)	0.0001 (0.0000 to 0.0005)
Beta	1.99 (1.06 to 5.54)	0.0001 (0.0000 to 0.0005)
Logit-logistic	1.93 (1.07 to 4.07)	0.0001 (0.0000 to 0.0005)

CI, confidence interval; MCSA, Monte Carlo sensitivity analysis; RR, risk ratio; RD, risk difference.

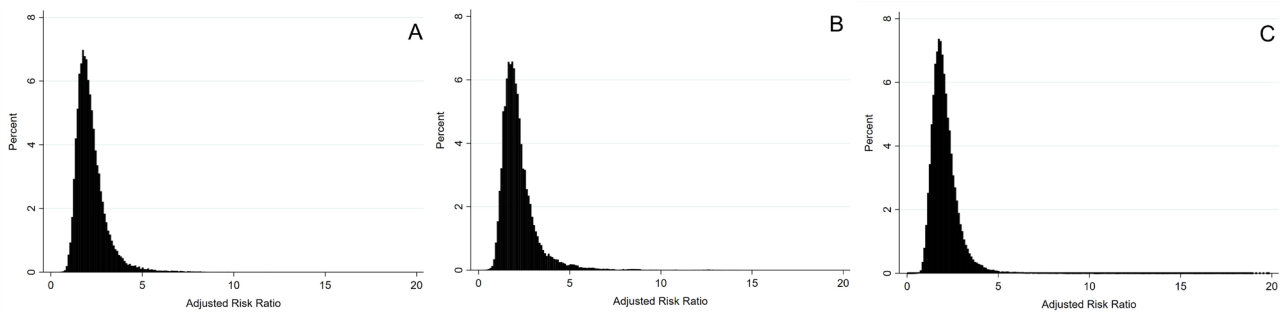


Figure 2. Triangular (A), Beta (B) or Logit-Logistic (C) Distributions of RRs, Adjusted for Measurement Bias, Confounding and Random Error

Table 4. Estimates of Population Attributable Fraction with 95% MCSA Intervals Using Probabilistic Bias and MBS Analyses

Bias Parameter Distribution	Bias Analysis (95% MCSA)
Triangular	0.17 (0.001 to 0.47)
Beta	0.16 (0.014 to 0.47)
Logit-logistic	0.15 (0.010 to 0.50)

Parametric g-formula has been used in some epidemiological studies for calculating the causal effects. Taubman et al performed the first large-scale application of the parametric g-formula in 2009, using data from the Nurses' Health Study to estimate lifestyle interventions on the risk of coronary heart disease, and facilitated future use by making the software available.⁶³ Some other researchers like Jain et al,⁶⁴ Westreich et al,⁶⁵ Garcia-Aymerich et al,⁶⁶ Edwards et al,⁶⁷ Murray et al,⁶⁸ and Young et al,⁶⁹ used g-formula and described its pros and cons. In several studies, Mansournia and colleagues applied MBS in case-control studies and parametric g-formula in cohort studies in the fixed and time-varying settings.^{23,70-74}

In this study, we used MBS after probabilistic bias correction of the exposure and obtained RR estimates in range of 1.93–2.02 based on three bias parameter distributions. In fact, alcohol consumption misclassification led to the underestimation in the association of alcohol consumption and MS, and adjusted estimates were increased after correction (OR estimate was 1.75 in conventional analysis). Based on our study results, there is sufficient evidence against the independency of alcohol consumption and MS, and alcohol consumption had a causal effect on MS incidence. A few studies have examined the effect of alcohol consumption on the risk of MS, and reported inconsistent results. A case-control study in Serbia reported a significant association between the consumption of hard liquor per day and the risk of MS (OR=6.7).⁷⁵ Foster et al showed a relationship between the duration of alcohol consumption and disability and MRI measures in MS. The study included two separate cohorts from Nurses' Health Study and Nurses' Health Study II and reported no association between alcohol consumption and MS risk.⁷⁶ On the other hand, Hedström et al merged two case-control studies (EIMS and GEMS study) and concluded that there is an inverse dose-dependent association between alcohol consumption

with MS. Women and men who reported high alcohol consumption had lower risk of developing MS compared with nondrinking women and men.¹⁵

In this study, we calculated PAF for alcohol consumption based on its definition, i.e. $(O - E)/O$ where O is the observed number of cases and E is the expected number under no exposure in the population. Measurement error in O was adjusted with PBAM and E was calculated using MBS analysis; in our study, measurement error is adjusted with PBAM, and the risk ratio is calculated from the MBS analysis. Based on our result, the PAF estimate for alcohol consumption was in the range of 0.15 to 0.17. No other study has calculated the PAF for alcohol consumption in MS.

The strengths of this study included a systematic search for bias parameters and using different distributions for them, using fractional polynomials to adjust for age, identification of confounders using a causal diagram, correction of the intercept for using the MBS in the case-control study, and finally, unifying the PBAM and MBS for the causal analysis of case-control studies for the first time.

The study suffers from some limitations. First, because of the absence of a study reporting alcohol consumption sensitivity and specificity in people with MS, we performed bias correction only under the non-differential scenario; a differential scenario may have had different results. However, the impact of cultural and religious norms and values on alcohol drinking is expected to be independent of MS status and therefore non-differential. Second, alcohol consumption was considered dichotomous which could reduce the study's statistical power and result in a biased impression of dose-response.²⁶ Another limitation is the possibility of unmeasured confounders, as well as measurement error in the confounders such as smoking which may result in residual confounding, and the direction of bias cannot be predicted due to the correlation between measurement errors in alcohol consumption and smoking. This confounding could be assessed in future studies.

Conclusion

Bias and causal analysis in this study showed that alcohol consumption doubles the risk of MS, and a significant proportion of MS cases in Iran are linked to alcohol consumption.

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Authors' Contribution

Conceptualization: Mohammad Ali Mansournia, Saharnaz Nedjat, Ibrahim Abdollahpour, Maryam Nazemipour.

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Methodology: Mohammad Ali Mansournia, Maryam Nazemipour, Pooneh Malekifar.

Project administration: Mohammad Ali Mansournia, Pooneh Malekifar.

Supervision: Mohammad Ali Mansournia, Saharnaz Nedjat.

Validation: Mohammad Ali Mansournia, Saharnaz Nedjat, Ibrahim Abdollahpour.

Visualization: Saharnaz Nedjat, Ibrahim Abdollahpour, Maryam Nazemipour, Saeed Malekifar.

Writing—original draft: Ibrahim Abdollahpour, Saeed Malekifar, Pooneh Malekifar.

Writing—review & editing: Mohammad Ali Mansournia, Saharnaz Nedjat, Maryam Nazemipour.

Competing Interests

The authors have no conflicts of interest.

Ethical Approval

The ethics committee at Tehran University of Medical Sciences approved the protocol of this study with an ethics code of IR.TUMS.SPH.REC.240.1039.

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Supplementary Files

Supplementary file 1 contains Figure S1.

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