

## Main Article

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**Cite this article:** Iravani K, Malekpour B, Rasekhi A, Faramarzi A, Soltaniesmaeili A, Golkhar B, Jahanandish F, Babaei A. Functional magnetic resonance imaging in coronavirus disease 2019 induced olfactory dysfunction. *J Laryngol Otol* 2024;**138**:178–183. <https://doi.org/10.1017/S0022215123001652>

Received: 27 May 2023

Revised: 28 July 2023

Accepted: 11 August 2023

First published online: 5 October 2023

### Keywords:




Coronavirus; diagnostic imaging; magnetic resonance imaging; smell; quality of life

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# Functional magnetic resonance imaging in coronavirus disease 2019 induced olfactory dysfunction

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## Abstract

**Objective.** To evaluate the functional magnetic resonance imaging changes in the olfactory structures of coronavirus disease 2019 patients experiencing olfactory dysfunction.

**Methods.** This study included patients aged 25–65 years who presented with a sudden loss of smell, confirmed coronavirus disease 2019 infection, and persistent olfactory dysfunction for a minimum of 2 months without any treatment.

**Results.** Irrespective of the side of brain activation, the analysis of the cumulative maximum diameter of the activation zones revealed significantly lower activation in the upper frontal lobe ( $p = 0.037$ ) and basal ganglia ( $p = 0.023$ ) in olfactory dysfunction patients. Irrespective of the side of activation, the analysis of the number of activation points demonstrated significantly lower activation in the upper frontal lobe ( $p = 0.036$ ) and basal ganglia ( $p = 0.009$ ) in olfactory dysfunction patients.

**Conclusion.** Patients with coronavirus-triggered olfactory dysfunction exhibited lower activity in their basal ganglia and upper frontal lobe.

## Introduction

Olfactory and gustatory deficits are two prominent and well-recognised symptoms of the coronavirus disease 2019 (Covid-19) infection, yet smell seems to be more compromised than taste.<sup>1</sup> Approximately half of the affected Covid-19 individuals show evidence, suggested by a meta-analysis, of a conductive mechanism of olfactory dysfunction localised within the olfactory cleft.<sup>2</sup> It is now established that anosmia or hyposmia serve as typical symptoms beneficial for the diagnosis of Covid-19. Acute olfactory dysfunction is characterised by a diminished or altered sense of smell persisting for 14 days or fewer, in the absence of chronic rhinosinusitis, previous head trauma or neurotoxic drug use.<sup>3</sup>

Evaluations of the olfactory structures in individuals with olfactory dysfunction can be conducted using computed tomography (CT) and magnetic resonance imaging (MRI), tools capable of differentiating between different aetiologies and contributing to the prediction of clinical outcomes. The olfactory system can be thoroughly assessed by MRI, especially in cases of traumatic, viral, metabolic, mental and neurodegenerative illnesses that result in olfactory dysfunction.<sup>4,5</sup>

Currently, olfactory imaging is not a routine procedure for Covid-19 patients with olfactory dysfunction. However, observed abnormalities of the olfactory sulcus, olfactory bulb, olfactory tract and olfactory cleft on imaging have been receiving more attention in relation to Covid-19-associated olfactory dysfunction.<sup>6</sup> These imaging results may shed light on the mechanisms of Covid-19-associated olfactory dysfunction,<sup>7</sup> as well as the potential involvement of the brain and olfactory pathways, and the likely entryway of the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Additionally, the information from these results could equip clinical professionals to better predict the clinical course and develop personalised therapies to treat Covid-19-associated olfactory dysfunction.<sup>8</sup>

Olfactory bulb imaging related to Covid-19 olfactory impairment has thus far only been minimally explored in case reports or series presented in the literature. For a more comprehensive understanding of the pathophysiology associated with Covid-19-induced anosmia, an imaging investigation that incorporates unbiased clinical correlation is necessary.

In our study, we employed functional MRI, a method that identifies changes in real-time brain activity by measuring fluctuations in blood flow, to evaluate alterations in the olfactory structure of Covid-19 patients suffering from olfactory dysfunction. Contrasting with traditional static imaging modalities, functional MRI provides a

dynamic overview of brain activity. This functionality was instrumental in our choice of functional MRI for this study, given its potential to delineate the specific neural pathways implicated in Covid-19-induced olfactory dysfunction.

## Materials and methods

### Study design

This observational study implemented a case–control approach. Patients who tested positive for SARS-CoV-2 RNA through real-time polymerase chain reaction formed the study's demographic. This research received approval from the local institutional review board (approval code: IR.SUMS.MED.REC.1399.135). Prior to participation, all patients provided their informed consent.

### Setting

Patients presenting with olfactory dysfunction following Covid-19 infection were referred to the Motehari Clinic. The clinic is an affiliate of Shiraz University of Medical Sciences (Shiraz, Iran). The referral appointments took place between March and September 2022.

### Participants

The Covid-19-related olfactory dysfunction group comprised patients aged 25–65 years, all of whom exhibited olfactory dysfunction subsequent to Covid-19 infection at our clinic. The inclusion parameters for this case group were: (1) patient reports of sudden loss of smell; (2) substantiated olfactory dysfunction as per the University of Pennsylvania Smell Identification Test ('UPSIT') (score of  $\leq 18$ ); (3) verification of Covid-19 infection during initial symptoms through a nasopharyngeal and throat swab polymerase chain reaction test; and (4) persistence of olfactory dysfunction for a duration of at least two months and no longer than six months, without any intervention for olfactory dysfunction.

The control group's inclusion criteria were: (1) absence of smell loss complaints; (2) demonstrable normal olfactory function according to the University of Pennsylvania Smell Identification Test (score of  $\geq 19$ ); and (3) Covid-19 infection confirmation during initial symptoms via a nasopharyngeal and throat swab polymerase chain reaction test.

The exclusion criteria omitted: participants with ongoing Covid-19 neurological symptoms (other than olfactory dysfunction, such as memory loss, headaches, isolated dysgeusia or ageusia), those with prior smell and taste impairment or head trauma history, those with allergic rhinitis and chronic rhinosinusitis, individuals with neurological or psychiatric problems, and patients with a general contraindication to MRI.

### Olfactory evaluation

The University of Pennsylvania Smell Identification Test, applied in this study, encompassed 24 culturally recognisable odours (Magnolia, Saveh, Iran): vinegar, coffee, mint, banana, garlic, coconut, curd, cinnamon, apple, menthol, pineapple, cucumbers, lemon, saffron, orange, smoke, cardamom, rose-water, honey, hazelnut, vanilla, cantaloupe, onion and butter.<sup>9,10</sup> Research has demonstrated that these odours are well-known to Iranian individuals.<sup>11</sup> Test results were conveyed as a numerical value ranging from 0 to 24, indicative

of olfactory function.<sup>12</sup> This scale measures: anosmia (scores of 0–9), severe microsmia (scores of 10–13), mild microsmia (scores of 14–18) and normosmia (scores of 19–24).<sup>13</sup>

These evaluations were carried out in a sufficiently ventilated space by a resident doctor in otolaryngology.

### Magnetic resonance imaging protocol

The MRI scan of the olfactory bulb was conducted using a 1.5T scanner (Magnetom Avento; Siemens, Erlangen, Germany) equipped with an 18-channel head coil. Along with the conventional sequences for the entire brain, specific sequences for the olfactory structures featured high-resolution T2-weighted Sampling Perfection with Application optimised Contrast using different flip angle Evolution ('SPACE') sagittal images and coronal T2-weighted images. The field of view encapsulated the anterior pole of the olfactory bulb to the primary olfactory area.

Functional images utilised gradient-recalled echo-planar images, with a repetition time of 3000 ms and an echo time of 50 ms. The field of view measured  $220 \times 220$  mm<sup>2</sup>, the slice thickness/gap was set at 4/0 mm, and the image collection included 38 slices. In total, 760 brain volume sequences were gathered in 10 measurements, taken during 24 seconds of rest and a 6-second task. The slice thickness was set at 4 mm, with a flip angle of 90 degrees, a voxel size of  $3.4 \times 3.4 \times 4$ , and a paradigm size of 10.

### Olfactory bulb magnetic resonance imaging

For the ultra-high-resolution T2-weighted Sampling Perfection with Application optimised Contrast using different flip angle Evolution sagittal images, the settings included a repetition time of 1000 ms, an echo time of 136 ms, a flip angle of 90° and a slice thickness of 2 mm. There was no slice oversampling. The field of view measured  $200 \times 200$  mm, the matrix was  $320 \times 320$ , phase oversampling was 30 per cent and the bandwidth was 150 Hz/pixel. The voxel size was set at  $0.6 \times 0.6 \times 0.6$  mm, the time of acquisition was 6.08 minutes and the echo train duration was 440 ms.

Coronal T2-weighted images spanned the anterior pole of the olfactory bulb to the primary olfactory region, with the settings including a repetition time of 6550 ms, an echo time of 99 ms, a flip angle of 150° and a slice thickness of 1 mm. The distance factor was 0, the field of view was  $100 \times 100$  mm<sup>2</sup>, the matrix was  $269 \times 384$ , phase oversampling was 56 per cent and the bandwidth was 289 Hz/pixel. The voxel size was  $0.3 \times 0.3 \times 1$  mm, the time of acquisition was 8.19 minutes and the turbo factor was 17.

### Magnetic resonance imaging evaluation

A singular radiologist conducted the volumetric and morphological analyses. The volumes of the olfactory bulbs were determined by summing the manually measured values of length, depth and width, each multiplied by one another and then divided by two. The signal intensity of the olfactory bulbs was appraised on both the coronal T2-weighted and the three-dimensional fluid-attenuated inversion recovery ('FLAIR') images, utilising the contralateral gyrus rectus as the reference for signal intensity. A solitary instance of anomalous signal intensity was not deemed abnormal, given the susceptibility of the olfactory bulbs to artefacts. Locations of signal

abnormalities in the olfactory bulb were evaluated, specifically in the rostral, central and caudal areas.

### Fusion functional magnetic resonance imaging data interpretation

The fusion process was executed in the advanced perfusion mode, utilising 50 per cent blending following alignment. Positive activity was defined as artefact-free regions exhibiting a blood-oxygen-level-dependent ('BOLD') activity that exceeded 10 voxels post-fusion. In order to quantify the activated areas, we calculated the total of the maximum diameters of these areas, in centimetres.

### Statistical methods

Categorical variables were represented as frequency and percentage values. Quantitative parameters were conveyed as mean ( $\pm$  standard deviation) values. Independent *t*-tests were used to analyse parametric and non-parametric continuous parameters, with Mann–Whitney *U* tests being applied where appropriate. *P*-values that were less than 0.05 were interpreted as statistically significant. SPSS version 25 statistical software (SPSS, Chicago, Illinois, USA) was employed for the analysis.

### Results

This study incorporated a total of 20 patients. Of these, 15 were identified as suffering from olfactory dysfunction (cases), while the remaining 5 showed no signs of olfactory dysfunction (controls). Within the case group, there were nine males (60 per cent) and six females (40 per cent), whereas

the control group comprised three males (60 per cent) and two females (40.0 per cent) ( $p = 1.000$ ). The average age for the case and control groups was  $33.31 \pm 10.90$  years and  $33.33 \pm 1.53$  years, respectively ( $p = 0.312$ ). The mean University of Pennsylvania Smell Identification Test score across all subjects was found to be  $11.64 \pm 5.18$ , with a range of 4–18. The mean interval from the onset of olfactory dysfunction until the administration of the functional MRI scan was approximately  $3.13 \pm 1.06$  months.

When considering the side of activation, the analysis of the summation of the maximum diameter of the activation zones revealed significantly lower activation in the left upper frontal lobe ( $p = 0.026$ ), right basal ganglia ( $p = 0.013$ ) and left basal ganglia ( $p = 0.018$ ) in patients with olfactory dysfunction (Table 1). Without factoring in the side of activation, the same analysis showed markedly lower activation in the upper frontal lobe ( $p = 0.037$ ) and basal ganglia ( $p = 0.023$ ) in olfactory dysfunction patients (Table 2).

When considering the side of activation, the analysis of the number of activation points showed significantly lower activation in the right upper frontal lobe ( $p = 0.043$ ), left upper frontal lobe ( $p = 0.025$ ), right basal ganglia ( $p = 0.017$ ) and left basal ganglia ( $p = 0.005$ ) in olfactory dysfunction patients (Table 3). Without factoring in the side of activation, the analysis of the number of activation points showed that there was significantly lower activation in the upper frontal lobe ( $p = 0.036$ ) and basal ganglia ( $p = 0.009$ ) in olfactory dysfunction patients (Table 4).

### Discussion

Our functional MRI analysis revealed significantly diminished activity within the superior frontal lobe and basal ganglia

**Table 1.** Summation of maximum diameter of activation zones with consideration of side

Zone	Maximum diameter (mean (SD); mm) by group		<i>P</i> -value*
	With olfactory dysfunction	Without olfactory dysfunction	
Rt cerebellum	48.8 (60.00)	44.0 (3.50)	0.858
Lt cerebellum	54.1 (70.70)	35.0 (34.00)	0.855
Pons	6.7 (12.90)	4.7 (8.10)	0.944
Rt occipital lobe	43.5 (47.30)	73.0 (57.90)	0.439
Lt occipital lobe	57.7 (61.70)	49.3 (33.80)	0.952
Rt temporal lobe	28.6 (31.10)	65.3 (42.80)	0.108
Lt temporal lobe	41.6 (51.70)	48.7 (33.90)	0.507
Rt upper frontal lobe	7.2 (14.20)	30.3 (38.00)	0.158
Lt upper frontal lobe	9.5 (17.50)	33.0 (9.50)	0.026
Rt lower frontal lobe	17.3 (22.60)	21.7 (30.10)	0.704
Lt lower frontal lobe	23.7 (37.10)	14.0 (24.20)	0.724
Rt basal ganglia	6.3 (12.10)	33.7 (25.30)	0.013
Lt basal ganglia	6.5 (11.50)	30.7 (18.60)	0.018
Rt parietal lobe	63.6 (80.60)	90.3 (58.50)	0.283
Lt parietal lobe	46.5 (61.40)	94.7 (52.60)	0.131
Rt olfactory bulb size	39.77 (22.07)	67.68 (27.20)	0.138
Lt olfactory bulb size	38.13 (24.05)	25.97 (14.49)	0.260

\*Mann–Whitney *U* test. SD = standard deviation; Rt = right; Lt = left

**Table 2.** Summation of maximum diameter of activation zones without consideration of side

Zone	Maximum diameter (mean (SD); mm) by group		P-value*
	With olfactory dysfunction	Without olfactory dysfunction	
Cerebellum	102.9 (114.60)	79.0 (31.20)	0.859
Occipital lobe	101.3 (104.70)	122.3 (90.40)	0.766
Temporal lobe	70.2 (75.10)	114.0 (71.80)	0.311
Upper frontal lobe	16.7 (24.90)	63.3 (41.30)	0.037
Lower frontal lobe	41.1 (57.20)	35.7 (54.20)	0.950
Basal ganglia	12.8 (22.20)	64.3 (43.70)	0.023
Parietal lobe	110.1 (137.90)	185.0 (52.80)	0.109
Olfactory bulb size	38.95 (20.67)	46.82 (20.18)	0.767

\*Mann-Whitney U test. SD = standard deviation

**Table 3.** Analysis of number of activation points with consideration of side

Zone	Number of activation points (mean (SD)) by group		P-value*
	With olfactory dysfunction	Without olfactory dysfunction	
Rt cerebellum	2.87 (3.29)	3.00 (1.73)	0.631
Lt cerebellum	2.60 (3.44)	1.33 (1.15)	0.854
Pons	0.40 (0.63)	0.33 (0.58)	0.943
Rt occipital lobe	2.73 (2.63)	5.00 (4.00)	0.280
Lt occipital lobe	2.93 (2.79)	3.00 (2.00)	0.810
Rt temporal lobe	1.73 (1.91)	3.33 (2.52)	0.201
Lt temporal lobe	2.40 (2.69)	2.67 (1.53)	0.586
Rt upper frontal lobe	0.73 (1.33)	2.33 (1.53)	0.043
Lt upper frontal lobe	0.47 (0.92)	1.67 (0.58)	0.025
Rt lower frontal lobe	1.07 (1.28)	1.67 (2.08)	0.525
Lt lower frontal lobe	1.40 (2.10)	1.67 (2.08)	0.543
Rt basal ganglia	0.40 (0.74)	1.67 (0.58)	0.017
Lt basal ganglia	0.27 (0.46)	1.67 (0.58)	0.005
Rt parietal lobe	3.87 (4.91)	5.67 (3.06)	0.189
Lt parietal lobe	2.47 (3.27)	3.00 (1.73)	0.427

\*Mann-Whitney U test. SD = standard deviation; Rt = right; Lt = left

among patients with olfactory dysfunction when compared to the control group, specifically in regard to the quantity and maximum diameter of activation zones. This observed pattern echoes imaging results found in other neurological conditions associated with olfactory dysfunction, which exhibit decreased activity in similar brain areas.

The association between Covid-19 and both olfactory and gustatory deficits is well-established, and these are recognised as fundamental symptoms, although the impairment of smell appears more pronounced than that of taste. According to a 2022 meta-analysis, among patients with Covid-19 infection and olfactory dysfunction, 55.6 per cent and 43.5 per cent displayed morphological anomalies in the olfactory bulb and

**Table 4.** Analysis of number of activation points without consideration of side

Zone	Number of activation points (mean (SD)) by group		P-value*
	With olfactory dysfunction	Without olfactory dysfunction	
Cerebellum	5.47 (5.89)	4.33 (0.58)	0.676
Occipital lobe	5.67 (5.29)	8.00 (6.00)	0.510
Temporal lobe	4.13 (4.19)	6.00 (3.61)	0.339
Upper frontal lobe	1.20 (1.82)	4.00 (2.00)	0.036
Lower frontal lobe	2.47 (3.29)	3.33 (4.16)	0.526
Basal ganglia	0.67 (1.05)	3.33 (1.15)	0.009
Parietal lobe	6.33 (7.98)	8.67 (3.79)	0.191

\*Mann-Whitney U test. SD = standard deviation

olfactory nerve, respectively. Concurrently, 60.0 per cent demonstrated atypical olfactory bulb volumes.<sup>2</sup>

Significantly decreased olfactory bulb volumes have been noted in various disorders, including specific cases of post-infectious olfactory dysfunction observed after certain viral infections, as well as neurodegenerative diseases. The identification of these imaging patterns has proven invaluable in these conditions, contributing to early diagnosis and improved understanding of disease progression, and facilitating the development of targeted therapies.<sup>14</sup>

A comparative evaluation of olfactory bulb volume and intensity between participants with and without anosmia subsequent to Covid-19 infection revealed no significant differences.<sup>15</sup> A large-scale cohort study that compared longitudinal brain MRI changes in 713 participants pre- and post-SARS-CoV-2 infection arrived at a similar conclusion.<sup>16</sup>

A solitary case study exploring the utilisation of functional MRI in anosmia related to Covid-19 revealed an elevated blood oxygen level-dependent signal in the piriform and right uncus cortices.<sup>17</sup>

Kandemirli *et al.* examined 23 patients with persistent Covid-19 olfactory dysfunction. Their analysis of CT and MRI results indicated that Covid-19 anosmia is linked with abnormalities in the olfactory cleft and bulb. Notably, they found evidence of olfactory bulb degeneration in a significant portion of the patient population.<sup>7</sup> Separately, Eliezer *et al.* discovered transient olfactory cleft oedema in 20 Covid-19 patients suffering from olfactory function loss, based on their MRI findings.<sup>18</sup>

Yildirim *et al.* analysed the olfactory functional MRI results of 97 individuals experiencing post-infectious olfactory dysfunction, in addition to 31 patients exhibiting chronic Covid-19-associated olfactory dysfunction.<sup>19</sup> Their study concluded that the olfactory bulb volumes were noticeably larger in Covid-19-associated olfactory dysfunction cases than in post-infectious olfactory dysfunction cases. However, they found no statistically significant difference regarding the lack of activity in the orbitofrontal and entorhinal regions. Importantly, their imaging approach for the study paralleled the one that we adopted.<sup>19</sup>

Contrasting with 23 healthy controls, Burulday *et al.* found that 23 individuals with Covid-19 displayed significantly diminished olfactory volumes in their cerebral MRI scans.<sup>20</sup> Conversely, Altundag *et al.* concluded that there was no

perceptible difference between olfactory bulb volumes and sulcus depths, as revealed by MRI examinations.<sup>21</sup>

- Olfactory dysfunction is an obvious and well-known cardinal symptom of coronavirus disease 2019 (Covid-19) infection
- There was significantly lower activation in the upper frontal lobe and basal ganglia in patients with olfactory dysfunction
- Olfactory bulb size is not the primary cause of long-term olfactory dysfunction in Covid-19 patients, according to functional magnetic resonance imaging results

Frosolini *et al.* examined the pre- and post-coronavirus olfactory bulb volume in a case series of five patients who underwent MRIs before and after Covid-19 infection, noting ranges of 40.58–116.4 mm<sup>3</sup> and 19.44–55.04 mm<sup>3</sup>, respectively.<sup>22</sup> Consequently, it was suggested that patients with protracted Covid-19, as characterised by olfactory dysfunction, may exhibit a decreased olfactory bulb volume, which can serve as a radiological marker.<sup>22</sup> These authors also conducted a literature review, investigating the radiological images obtained via MRI, CT or positron emission tomography for 246 patients testing positive for Covid-19. Among the six articles reviewed, the olfactory bulb was found to be reduced in volume and asymmetrical in 46 patients. Notably, these studies revealed a decrease in metabolic activity in the tertiary olfactory cortex – implicated in quality processing and emotional response to odours – without any concurrent reduction in volume.<sup>22</sup> Contrarily, in 11 studies included in their review, the olfactory bulb volume was found to be normal during the early stages of Covid-19 infection. Interestingly, according to Laurendon *et al.*, one patient was found to have a larger olfactory bulb volume along with a hyperintense signal.<sup>23</sup>

In research by Lu *et al.*, it was observed that recovered Covid-19 patients had a higher likelihood of exhibiting larger volumes in their olfactory cortices, hippocampi, insulas, Heschl's gyri, Rolandic opercula and cingulate gyri compared to control subjects, alongside decreased diffusion tensor imaging values.<sup>24</sup> Regarding the central olfactory pathways, no significant volumetric or signal anomalies were discerned in our study.

In the most recent systematic review and meta-analysis of 10 studies, there were no significant differences noted between the evaluations of right and left olfactory bulb volumes. Similarly, when compared to non-Covid-19 controls, the depths of the right and left olfactory sulcus in individuals with Covid-19 did not demonstrate substantial changes.<sup>25</sup>

To our knowledge, this is the inaugural original study utilising functional MRI in patients exhibiting persistent olfactory dysfunction following Covid-19 infection. The efficacy of functional MRI in patients with Covid-19 remains, at this point, inadequately established.

Firstly, the modest sample size, particularly in the non-olfactory dysfunction group, could potentially affect the validity of the statistical comparisons made, thus indicating a limitation in our study. In light of this, for future studies, it would be prudent to employ larger sample sizes, particularly in the non-olfactory dysfunction group, to ensure more robust statistical results and to increase the generalisability of our findings. Secondly, our research is a retrospective case-control study, a design that could impose another constraint which may affect the analysis of the study's outcomes. The study groups' heterogeneous sizes further underscore this limitation. A significant drawback is the inability to measure the olfactory cleft width.

Although functional MRI necessitates higher costs and resources, it provides unique insights into the neural basis of olfactory dysfunction induced by Covid-19, disclosing compensatory neural adaptations and informing prognosis and therapeutic strategies. Its utility as a first-line tool for olfactory assessment may be limited because of cost and resource constraints, yet the potential value of functional MRI in research and intricate clinical scenarios is considerable. Notwithstanding these limitations, the holistic information gleaned from functional MRI could substantially enhance our comprehension of persistent olfactory dysfunction post-Covid-19, advocating its prudent use in future research and clinical contexts. Further research is essential in order to elucidate the radiological abnormalities and involvement of the peripheral and central olfactory pathways in individuals experiencing post-Covid-19 olfactory alterations, to guide therapy and rehabilitation procedures.

## Conclusion

Based on the observations from this case-control study, individuals suffering from Covid-19-induced olfactory dysfunction exhibited decreased activity in their basal ganglia and upper frontal lobe. Functional MRI results suggest that olfactory bulb size is not the principal contributor to long-term olfactory dysfunction in patients with Covid-19.

**Acknowledgements.** This article was supported by the Vice-Chancellor for Research of Shiraz University of Medical Sciences (grant number: 99-01-01-22555). The authors would like to thank Shiraz University of Medical Sciences, Shiraz, Iran, the Center for Development of Clinical Research of Nemazee Hospital, and Dr Nasrin Shokrpour for editorial assistance.

**Competing interests.** None declared

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