Depression links with the non-motor symptoms of Parkinson's disease

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Abstract

Background: The non-motor symptoms (NMS) of Parkinson's disease (PD) and their potential role in early diagnosis are recent debates. Herein, we aimed to investigate the association between depression and non-motor symptoms of PD including sleep disorders, hyposexuality, hyposmia, constipation, and orthostatic hypotension.

Methods: After obtaining written informed consent, the diagnosis was confirmed using the criteria developed by the United Kingdom PD Society Brain Bank for the clinical diagnosis of PD. The stage and the severity of the disease were determined using the UPDRS and Hoehn & Yahr criteria. Demographics as well as the family history, habitual history, and past medical history data were obtained. Depression was determined through a psychiatric consultation based on DSMV criteria and Beck Depression Inventory (BDI). Sleep quality was assessed using the Pittsburgh Sleep Quality (PSQ), and Epworth and REM Sleep Behavior Disorder Sleep Questionnaire (RBDSQ) was applied to investigate daytime sleepiness and REM sleep disorders, respectively. Cognitive disorders were also investigated using Montreal cognitive assessment (MoCA).

Results: 93 patients were enrolled. The BDI score was significantly correlated with hyposexuality, MoCA scores, and PSQ scores. Depression was significantly more severe in those with hyposexuality (p-value = 0.018). After adjustments, a significant association existed between the BDI score and the MoCA score and hyposexuality.

Conclusions: Besides the known correlations of depression with cognitive decline in PD, depression is also significantly associated with hyposexuality in these patients. The etiological underpinnings of these associations are to be explored in the future.

Introduction

Early diagnosis and prognostics evaluation is a crucial concern in neurodegenerative diseases that have prompted many pursuits in proposing potential predictors (1). As one of the most common progressive neurodegenerative disorders worldwide, chiefly among the elderly population, Parkinson's disease (PD) is characterized by piecemeal loss and death of the substantia nigra pars compacta neurons and aggregation of the alpha-synuclein protein (α-syn) in the central nervous system (2, 3). This pathophysiology clinically manifests through common motor symptoms, including resting tremor, bradykinesia, gait difficulties, muscle rigidity, and postural instability, which interferes with activities of daily living (4). However, although PD is mainly known by motor symptoms, many non-motor symptoms (NMS), ranging from sensory abnormalities, cognitive impairment, sleep disturbances (insomnia, REM sleep behavior disorder (RBD), Excessive daytime sleepiness, painful dystonia), autonomic dysfunction (orthostatic hypotension, obstipation), psychosis are proposed to be correlated with PD (4).

Former works have suggested that at least one NMS manifests in PD patients (5). The prevalence of depressive disorder PD patients is about 40%, but because of overlapping symptoms of PD and depression, it is primarily undiagnosed (5). Sleep disorders prevalence is about 90%, and some of the studies suggest that RBD is connected with a higher risk of developing PD in the future (6) NMSs in PD patients have a vast unfavorable impact on Prognosis and the quality of life in patients, such as faster motor and cognitive deterioration (7). Despite their great impact on patients' quality of life, clinical diagnosis challenges remain regarding the diagnosis of NMSs, that is partly due to the dominance of other symptoms in PD. Therefore, determining clinical red flags of NMSs could help with promoting a more thorough investigation for these symptoms in a certain group of patients. This is particularly of significance since the NMSs of PD are known to precede the disease by years and detecting them might help earlier diagnosis (8).

As a disabling comorbidity in PD, depression is remarkably prevalent. This might be due to the potential involvement of joint neural microstructural pathophysiology between depression and PD (9). Although the pathophysiological underpinnings are yet unclarified, the current literature strongly suggest that depression is indeed associated with increased risk of PD (8), while depression is also remarkably more prevalent in patients with PD (10). Therefore, herein, we aimed to investigate whether depression in patients with PD is associated with a range of NMSs.

Methods

Design and Participants

All patients referring to two university referral clinics between March 2021 and December 2021 with a diagnosis of PD who gave their written informed consents for inclusion in the study were initially found eligible. Those with any other prior psychiatric or neurologic disorders were excluded. A total of 93 patients were enrolled in the study.

Measurements and Definitions

The diagnosis was confirmed using the criteria developed by the United Kingdom Parkinson's Disease Society Brain Bank for the clinical diagnosis of PD.

The stage and the severity of the disease were determined using the unified Parkinson's disease rating scale (UPDRS) (11) and Hoehn & Yahr scale (12). Demographic information was extracted using an appropriate questionnaire. The data regarding family history, habitual history (smoking and alcohol consumption), and past medical history were obtained. Depression was evaluated using Beck Depression Inventory (BDI) (13) which has been tested for validity and reliability in PD (14). The BDI has been widely used as an assessment instrument for intensity of depression in patients who meet clinical diagnostic criteria for depressive syndromes, in which, scores from 0 through 9 indicate no or minimal depression; scores from 10 through 18 indicate mild to moderate depression; scores from 19 through 29 indicate moderate to severe depression; and scores from 30 through 63 indicate severe depression. The PD's NMS were considered hyposmia, orthostatic hypotension, and constipation, hyposexuality, and sleep disturbances. Hyposmia was evaluated clinical history accompanied by testing the patients' sense of smell using three odorous substances, including coffee, cinnamon, and mint. A diagnosis of hyposmia was

established if the patient was incapable of detecting two out of three odors. Orthostatic hypotension was also evaluated by a physician clinically, defined as a decrease in systolic blood pressure of 20 mm Hg or more, or a decrease in diastolic blood pressure of 10 mmHg or more, or an increase in heart rate by more than 20 beats per minute, within three minutes of standing compared with sitting or supine position. Sleep quality was assessed using the Pittsburgh Sleep Quality (PSQ) (15) and Epworth sleepiness scale (ESS) (16) to investigate daytime sleepiness, and REM Sleep Behavior Disorder Sleep Questionnaire (RBDSQ) (17) was applied to investigate REM sleep disorders. Eventually, cognitive evaluation was conducted using Montreal cognitive assessment (MoCA) (18).

Ethical Considerations

The study proposal was evaluated ethically at the ethics committee of Tehran University of Medical Sciences and was approved with the ethics code of IR.TUMS.MEDICINE.REC.1398.455. The protocol of this study corresponded to the 2013 Helsinki declaration. All participants gave written informed consent and were considered anonymous and all data registered confidentially with no personal information.

Statistical Analysis

We described continuous variables as mean with standard deviation and categorical variables as numbers (percentage). The binary logistic regression model was applied to assess the association of binominal non-motor symptoms and BDI score and demographics, and the estimated effect was reported as odds ratio (OR) with 95% confidence interval (CI). Association between scale non-motor variables and BDI score and demographics were also investigated by using the linear regression analysis. Variance inflation factor (VIF) was considered in the adjusted regression model to determine any possible multicollinearity. Age, gender, Parkinson's disease duration, and Hoehn and Yahr classification were considered as probable confounders and adjusted in multivariate logistic regressions. Data analyses were done using IBM SPSS Statistics for Windows, version 25.0 (Armonk, NY: IBM Corp.). Statistical significance was considered as P-value less than 0.05.

Results

A total of 93 idiopathic PD patients were enrolled with a mean age of 66.38 ± 8.21 years old (range: 51–80 years). Among these, 63 (67.7%) were male, and 30 (32.3%) were female. Mean PD duration was 5.33 ± 4.74 years (range: 1–25 years). Demographics and clinical characteristics of patients are detailed in Table 1.

Table 1
Demographics, clinical characteristics, and non-motor symptoms in study population.

Clinical Characteristics	N = 93
Age (Years)	66.38 (8.21)
Gender	
Male	63 (67.7%)
Female	30 (32.3%)
Past Medical History	
Yes	50 (53.8%)
No	43 (46.2%)
Alcohol Consumption	
Yes	6 (6.5%)
No	87 (93.5%)
Smoking	
Yes	21 (22.6%)
No	72 (77.4%)
Family History	
Yes	20 (21.5%)
No	73 (78.5%)
Hoehn and Yahr	
0.5	10 (10.8%)
1	28 (30.1%)
1.5	27 (29.0%)
2	19 (20.4%)
2.5	7 (7.5%)
3	2 (2.2%)
Parkinson's Disease Duration (Years)	5.33 (4.74)
Depression Duration (Years)	6.80 (3.69)
Parkinson's Disease Drug	
Levodopa	62 (66.7%)
Levodopa + Pramipexole	28 (30.1%)
Levodopa + Benserazide	3 (3.2%)
Depression Drug	
Serteraline	48 (51.6%)
Bupropione	45 (48.4%)
ESS Score	7.77 (4.96)
ESS Class	
Lower Normal	31 (33.3%)
Higher Normal	40 (43.0%)
Mild Excessive	10 (10.8%)
Moderate Excessive	5 (5.4%)
Severe Excessive	7 (7.5%)

Abbreviations: ESS: Epworth Sleepiness Scale; PSQ: Pain and Sleep Questionnaire; RBSQ: REM Sleep Behavior Disorder Screening Questionnaire; MoCA: Montreal Cognitive Assessment.

Data are presented as mean (standard deviation) and number (%)

Clinical Characteristics	N = 93
PSQ Score	11.10 (3.44)
PSQ Class	
Weak	87 (93.5%)
Good	6 (6.5%)
RBDSQ	8.00 (2.42)
MoCA	20.29 (3.73)
BDI Score	35.80 (12.15)
BDI Class	
Mild Depression	11 (11.8%)
Moderate Depression	19 (20.4%)
Severe Depression	63 (67.7%)
Hyposmia	
Yes	28 (30.1%)
No	65 (69.9%)
Orthostatic hypotension	
Yes	39 (41.9%)
No	54 (58.1%)
Constipation	
Yes	51 (54.8%)
No	42 (45.2%)
Hyposexuality	
Yes	45 (48.4%)
No	48 (51.6%)
Abbreviations: ESS: Epworth Sleepiness Scale; PSQ: Pain and Sleep Questionnaire; RBSQ: REM Sleep Behavior Disorder Screening Questionnaire; MoCA: Montreal Cognitive Assessment.	
Data are presented as mean (standard deviation) and number (%)	

Among the study population, 28 (30.1%) patients have experienced hyposmia, 39 (41.9%) patients have experienced orthostatic hypotension, 51 (54.8%) patients have reported constipation, and 45 (48.4%) patients have reported hyposexuality. The mean BDI score for depression was 35.80 ± 12.15. Eleven (11.8%) patients had mild depression, 19 (20.4%) patients had moderate depression, and 63 (67.7%) patients had severe depression according to the BDI questionnaire. Mean ESS score, PSQ score, RBDSQ score, and MoCA score were 7.77 ± 4.96, 11.10 ± 3.44, 8.00 ± 2.42, and 20.29 ± 3.73, respectively (Table 1).

Associations between demographics and NMS are shown in Tables 2 and 3. There was a positive significant correlation between ESS and Hoehn and Yahr staging (p-value = 0.009). PSQ score showed significant associations with Hoehn and Yahr staging, PD duration, depression duration, and PD drugs (p-value = 0.012, 0.001, 0.030, and 0.039, respectively). PD drugs was also associated with MoCA score (p-value = 0.047). Additionally, orthostatic hypotension was associated with depression duration (p-value = 0.019) and was significantly more prevalent in patients who used sertraline (p-value = 0.001). Gender and PD stage were contributed to hyposexuality (p-value = 0.048 and 0.035, respectively).

Table 2
Association between non motor symptoms and demographics

Demographics	ESS			PSQ			RBDSQ			MoCA		
	B	CI	P	B	CI	P	B	CI	P	B	CI	P
Age	-0.031	-0.144/0.107	0.770	-0.112	-0.134/0.040	0.285	0.183	-0.006/0.114	**0.079**	-0.169	-0.170/0.016	0.10
Gender	0.155	-0.537/3.807	0.138	-0.068	-2.017/0.023	0.518	0.010	-1.022/1.022	0.928	0.184	-0.163/3.087	**0.07**
Past Medical History	0.125	-0.828/3.310	0.237	0.199	-0.041/2.744	**0.057**	0.095	-0.549/1.473	0.367	0.045	-1.223/1.898	0.66
Alcohol Consumption	-0.183	-7.792/0.435	**0.079**	-0.020	-3.180/2.617	0.847	-0.091	-2.921/1.139	0.386	-0.103	-4.687/1.572	0.32
Smoking	0.009	-2.351/2.565	0.931	0.060	-1.210/2.191	0.568	0.043	-0.951/1.443	0.684	0.013	-1.731/1.965	0.90
Family History	0.109	-1.180/3.794	0.299	-0.183	-3.299/0.180	**0.079**	-0.174	-2.220/0.181	**0.095**	-0.013	-1.996/1.766	0.90
Hoehn and Yahr	0.270	0.579/3.900	**0.009***	0.258	0.327/2.636	**0.012***	-0.098	-1.230/0.443	0.352	-0.147	-2.197/.369	0.16
Parkinson's Disease Duration	0.071	-0.143/0.292	0.498	0.339	0.104/0.388	**0.001***	0.110	-0.049/0.162	0.294	-0.104	-0.245/0.081	0.32
Depression Duration	-0.005	-0.287/0.273	0.963	0.255	0.021/0.399	**0.030***	0.155	-0.033/0.236	0.139	-0.116	-0.326/0.092	0.27
Parkinson's Disease Drug	0.022	-1.005/1.245	0.832	0.214	0.041/1.565	**0.039***	0.103	-0.275/0.816	0.327	-0.207	-1.668/-0.012	**0.04**
Depression Drug	-0.047	-2.521/1.588	0.653	-0.115	-2.206/0.625	0.270	-0.161	-1.764/0.214	0.123	0.121	-0.634/2.436	0.24

Abbreviations: ESS: Epworth Sleepiness Scale; PSQ: Pain and Sleep Questionnaire; RBSQ: REM Sleep Behavior Disorder Screening Questionnaire; MoCA: Montreal Cognitive Assessment; B: Regression Coefficient; CI: Confidence Interval; P: P-value

P-value < 0.1 are bolded

*P-value < 0.05

Table 3
Association between non motor symptoms and demographics

Demographics	Hyposmia			Orthostatic hypotension			Constipation			Hyposexuality		
	OR	CI	P	OR	CI	P	OR	CI	P	OR	CI	P
Age	0.966	0.914/1.021	0.221	1.017	0.967/1.070	0.515	1.022	0.972/1.075	0.390	0.991	0.943/1.042	0.723
Gender	0.638	0.252/1.614	0.343	1.125	0.464/2.725	0.794	0.484	0.196/1.198	0.117	2.500	1.009/6.194	**0.048***
Past Medical History	0.568	0.230/1.406	0.221	0.563	0.244/1.298	0.177	0.880	0.385/2.012	0.763	0.774	0.340/1.762	0.542
Alcohol Consumption	2.480	0.469/13.126	0.285	1.417	0.270/7.422	0.680	0.388	0.067/2.230	0.298	1.071	0.205/5.605	0.935
Smoking	0.909	0.311/2.654	0.862	0.814	0.300/2.205	0.686	1.892	0.683/5.237	0.220	0.961	0.363/2.543	0.963
Family History	0.725	0.235/2.235	0.575	0.519	0.180/1.502	0.227	1.008	0.373/2.725	0.987	0.841	0.311/2.270	0.732
Hoehn and Yahr	0.578	0.264/1.267	0.578	1.985	0.966/4.077	**0.062**	1.643	0.809/3.337	1.169	2.184	1.055/4.524	**0.035***
Parkinson's Disease Duration	0.980	0.888/1.082	0.690	1.069	0.975/1.171	1.154	1.110	0.996/1.237	**0.059**	1.026	0.940/1.119	0.569
Depression Duration	0.926	0.815/1.052	0.239	1.153	1.023/1.298	**0.019***	0.992	0.887/1.108	0.884	0.982	0.878/1.097	0.982
Parkinson's Disease Drug	1.015	0.625/1.646	0.953	1.390	0.885/2.182	0.152	0.885	0.566/1.383	0.591	0.876	0.560/1.371	0.563
Depression Drug	0.727	0.298/1.776	0.484	0.231	0.095/.563	**0.001***	0.627	0.275/1.426	0.265	0.618	0.272/1.404	0.251

OR: Odds Ratio; CI: Confidence Interval; P: P-value

P-value < 0.1 are bolded

*P-value < 0.05

Table 4 thoroughly illustrates the statistical significance testing results regarding the alterations of the BDI score with demographics. Using linear regression models, BDI score was solely associated with past medical history of patients (p-value = 0.045).

Table 4
Association between BDI score and demographics

Demographics	BDI Score		
	B	CI	P
Age	-0.141	-0.513/0.097	0.179
Gender	-0.076	-7.343/3.394	0.467
Past Medical History	-0.209	-10.089/-0.111	**0.045**
Alcohol Consumption	0.171	1.680/18.508	0.101
Smoking	-0.031	-6.921/5.112	0.766
Family History	-0.108	-8.269/2.911	0.302
Hoehn and Yahr	0.113	-1.908/6.484	0.282
Parkinson's Disease Duration	0.147	-0.152/0.904	0.161
Depression Duration	0.039	-0.556/0.815	0.708
Parkinson's Disease Drug	0.058	-1.977/3.525	0.578
Depression Drug	-0.144	-8.463/1.505	0.169
B: Beta RatCoefficient; CI: Confidence Interval; P: P-value			
P-value < 0.1 are bolded			

The only significant differences regarding the BDI and NMS were the hyposexuality, MoCA scores, and PSQ scores. The univariate regression analysis indicated that depression was significantly more severe in those with hyposexuality compared to those without this symptom (p-value = 0.016). Moreover, significant correlations were also revealed between the MoCA score and the BDI score (p-value = 0.010), and also between the BDI score and the PSQ score (p-value = 0.011). However, after adjusting for age, gender, Parkinson's disease duration, and Hoehn and Yahr classification considering multivariate regression analysis, BDI score was only associated with the MoCA score and hyposexuality (p-value = 0.011 and p-value = 0.015, respectively) (Table 5).

Table 5
Prognostic value of BDI for prediction of non-motor symptoms in depressed patients with Parkinson's disease.

Clinical outcomes	Unadjusted			Adjusted*		
	B	95% CI	P	B	95% CI	P
ESS Score	0.036	-0.070/0.100	0.731	0.011	-0.081/0.090	0.917
PSQ Score	0.263	0.017/0.131	**0.011**	0.183	-0.004/0.107	0.067
RBDSQ	0.007	-0.040/0.043	0.944	0.029	-0.037/0.048	0.788
MoCA	-0.266	-0.143/-0.020	**0.010**	-0.262	-0.142/-0.019	**0.011**
	Unadjusted			Adjusted*		
	OR	95% CI	P	OR	95% CI	P*
Hyposmia	1.008	0.972/1.046	0.671	1.007	0.969/1.047	0.716
Orthostatic hypotension	1.027	0.992/1.064	0.134	1.025	0.988/1.063	0.193
Constipation	1.010	0.976/1.044	0.577	1.004	0.968/1.041	0.844
Hyposexual	1.045	1.008/1.083	**0.016**	1.050	1.009/1.092	**0.015**
Abbreviations: ESS: Epworth Sleepiness Scale; PSQ: Pain and Sleep Questionnaire; RBSQ: REM Sleep Behavior Disorder Screening Questionnaire; MoCA: Montreal Cognitive Assessment; B: Beta Coefficient; OR: Odds Ratio; CI: Confidence Interval; P: P-value						
*Multivariate logistic regression adjusted for age, gender, Parkinson's disease duration, and Hoehn and Yahr classification.						

Discussion

This study was conducted to explore the association between depression in patients with PD with other NMSs, including sleep disorders, cognitive impairment, autonomic dysfunction, hyposexuality, constipation, and hyposmia.

In the past few years, NMS have been thoroughly scrutinized regarding their potential utility as diagnostic and prognostic tools for PD (19). Some recent studies indicate that non-motor dysfunction has a more significant impact on health-related quality of life rather than motor abnormalities due to their high prevalence of more than 20% of patients diagnosed with PD. Also, recent studies reported that almost all PD patients experienced at least one NMS during the disease, showing a pattern of fluctuation. The importance of early diagnosis through NMSs is that by the time patient shows motor symptoms, more than 50% of striatal dopaminergic capacity is diminished (20).

Although the primary pathology in PD is progressive dopaminergic denervation in substantia nigra, other regions and neurotransmitters are also affected. NMSs are associated with neurotransmitters disturbance alongside dopamine deficiency in PD. Therefore, NMSs and their severity might be associated with depression degree in PD patients. The high prevalence of depressive disorders in the early stages of the disease also confirms this hypothesis (21). Depression has also been indicated as a potential essential risk factor for developing PD in the future (22). Different pathophysiologies could lead to depression as a prodromal symptom for PD, such as loss of dopamine and noradrenaline innervation in the limbic system (23), disruption in serotonergic raphe nuclei in sporadic PD, and atrophic regions in cortical gyri and emotion recognition centers in depression-PD patients (24, 25). However, the exact etiology is yet not well understood.

The majority of patients studied in this research were classified as severely depressed, while merely 11.8% of them were mildly depressed and the rest belonged to the moderately depressed group. Our result showed a strong statistical relationship between cognitive impairment in PD patients with their depression severity. Cognitive deficit in PD patients ranges from mild cognitive impairment (MCI) to dementia in the late stages (26) and is suggested to be related to the accumulation of Lewi bodies in cortical regions and cholinergic dysfunction in the cortex (27). Also, one of the early responses to the loss of dopamine in striae is rising the dopamine levels in the prefrontal cortex that could harm cognitive function (28). Other extranigral pathways such as dorsal serotonergic raphe, amygdala, hippocampal formation, limbic thalamic nuclei with prefrontal projections are also simultaneously impaired in cognitive impairment and depression (29). Based on recent studies, the cognitive deficit can also lead to increased depression in patients through deteriorating the quality of life (QOL) (30).

Our work found a significant correlation between depression score (BDI) with sleep quality (PSQ), cognitive performance (MoCA score), and hyposexuality. This is aligned with the above-mentioned former works in this regard. Although longitudinal studies are required to provide further etiological insights. One of the earliest symptoms in PD patients is REM sleep disorders (90%) that can manifest by insomnia, excessive daytime sleep (EDS), REM sleep without atonia, sleep-related breathing disorders such as obstructive sleep apnea, restless leg syndrome, and nocturia (31). Some studies showed that neuronal damage and dysregulation of circadian molecules might lead to these symptoms (32). Also, some works have suggested that interruptions in a-synuclein clearance by the glymphatic system might lead to sleep disorders and therefore fasten the progression of PD. Sleep also plays a significant role in cognitive and memorial functions and might therefore affect QOL in patients (33). Other studies found a significant association between fatigue and EDS with motor symptoms, disease duration, depression, and dopaminergic treatment (34).

The most prevalent NMSs in our research were constipation and hyposexuality, respectively. A statistically significant correlation was found between hyposexuality and patient's depression severity, but this statistical significance was not found regarding any other NMSs in our research. Autonomic dysfunctions in PD patients consist of a vast spectrum, including cardiovascular, gastrointestinal, and sexual symptoms. Among these symptoms, hyposexuality and constipation are seen in patients frequently (30–50%). Hyposexuality and orgasmic dysfunction are seen in both genders and often neglected because of patients' embarrassment and clinicians' focus on more apparent motor symptoms (35). Hyposexuality and sexual disorders are particularly underdiagnosed in societies where sexual tendencies are not openly discussed like Iran (36). The high rates of constipation among depression-PD patients is also concerning since gastroparesis and small intestine bacterial overgrowth can lead to malabsorption of PD medication in patients and, therefore, exacerbate motor symptoms (37). This finding is also in line with the current literature, suggesting an association between severe constipation and depression (38).

As stated above, NMSs are detected earlier in the course of PD. Still, late-stage NMSs such as depression are not proper measures in differentiating stages and phenotypes of disease. This is particularly notable since some studies have suggested that patients with distinct patterns of motor symptoms are prone to more severe NMSs and poorer prognosis (39). Lastly, among all NMSs investigated in this research, BDI was merely found to predict the PSQ score, MoCA, and hyposexuality significantly. In the multivariate regression analysis, MoCA and hyposexuality were the only significant predictors. Therefore, depression is indeed a significant predictor of hyposexuality and cognitive impairment in PD.

Since depression is easier to detect clinically, our findings are significant in regards to the early detection of other NMSs in patients to start and modify their treatment. This could make a considerable difference in QOL in patients. Also, one of the most critical areas in neurodegenerative disease like PD is early diagnosis, since by the time of recognizable motor symptoms, the disease is already advanced. Eventually, NMSs significantly impact the pace of deterioration of symptoms and QOL in PD patients, and their potential utility to diagnose PD earlier (like developing biochemical tests) could be a subject of future related works.

Declarations

Ethics approval and consent to participate

The study proposal was evaluated ethically at the ethics committee of Tehran University of Medical Sciences and was approved with the ethics code of IR.TUMS.MEDICINE.REC.1398.455. The protocol of this study corresponded to the 2013 Helsinki declaration. All participants gave written informed consent and were considered anonymous and all data registered confidentially with no personal information.

Consent for publication

All participants gave written informed consent.

Availability of data

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare no conflict of interest.

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Author Contributions

M.M.: Conception and design of the study; analysis of data; drafting the manuscript and figures. Mah.S.: Conception and design of the study; analysis of data; drafting the manuscript and figures. Mar.S.: Conceptualization, Resources. Z.M.: Conceptualization, supervision, Review and editing. F.R.: Conceptualization, supervision. R.S.: Writing Original Draft. V.A.: Conceptualization, Supervision, Project Administration.

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