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ORIGINAL INVESTIGATION

Pentraxin 3, a serum biomarker in human T-cell lymphotropic virus type-1-associated myelopathy patients and asymptomatic carriers

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Abstract

Human T-cell lymphotropic virus type 1 (HTLV-1) can induce a neuroinflammatory condition that leads to myelopathy. Pentraxin 3 (PTX3) is an acute-phase protein that its plasma concentration increases during inflammation. We aimed to determine whether PTX3 serum level is elevated in HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) patients and HTLV-1 asymptomatic carriers (ACs) and evaluate its association with proviral load and clinical features. The serum level of PTX3 was measured using an enzyme-linked immunosorbent assay in 30 HAM patients, 30 HTLV-1 ACs, and 30 healthy controls. Also, the HTLV-1 proviral load was determined via real-time PCR technique. The findings showed that PTX3 serum level was significantly higher in HAM patients than in both asymptomatic carriers and healthy controls (p values <0.0001). No correlation between PTX3 and the proviral load was observed in HAM patients and asymptomatic carriers ($r=-0.238$, $p=0.205$ and $r=-0.078$, $p=0.681$, respectively). The findings showed that there was no significant correlation between PTX3 and motor disability grading (MDG) ($r=-0.155$, $p=0.41$) nor urinary disturbance score (UDS) ($r=-0.238$, $p=0.20$). Higher levels of PTX3 are associated with HTLV-1-associated myelopathy compared to asymptomatic carriers. This finding may support the idea that PTX3 has the potential as a diagnostic biomarker.

Keywords Human T-lymphotropic virus 1 · Pentraxin 3 · HTLV-1-associated myelopathy · Asymptomatic infection carrier

Introduction

Human T-cell lymphotropic virus type 1 (HTLV-1) is a human retrovirus that affects 5–10 million people worldwide [1]. Razavi Khorasan province, in the northeast of Iran has been considered an endemic region [2]. HTLV-1 causes two major diseases, including malignancy of mature $CD4^+$ T-cells named adult T-cell leukemia/lymphoma (ATLL) and HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) [3]. Although most individuals infected by HTLV-1 remain asymptomatic carriers (ACs) lifelong, almost 2–3% of the infected individuals develop HAM/TSP [4]. HAM/TSP is an inflammatory disorder affecting the central nervous system (CNS), in which demyelination of the thoracic cord has been observed, resulting in progressive loss of motor function [5]. HAM/TSP manifests with lower limbs weakness, lumbar pain, neuropathic pain, paresthesia, erectile dysfunction, and constipation [6, 7]. The precise mechanism by which HAM/TSP damages the CNS is still not fully elucidated [6]. However, some studies reported that the development of neuroinflammation in HAM/TSP patients is associated with a higher proviral load (PVL), increased infiltration of $CD8^+$ T-cells and more secretion of proinflammatory cytokines such as interleukin (IL)-6, interferon (IFN)-γ, and tumor necrosis factor (TNF)-α along with a decrease in Th2 cytokines such as IL-4 and IL-10 [8, 9]. It has been demonstrated that inflammation biomarkers provide more substantial evidence of HAM/TSP progression

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than neuronal injury markers, including Tau proteins and neurofilament [10].

Pentraxin 3 (PTX3), a member of the long pentraxin subfamily [11], is an acute-phase protein after trauma, injury, and infections [12]. PTX3 highly binds to various bacteria, fungi, and viruses [13], and activates the complement component C1q to enhance the destruction and clearance of these pathogens [14]. Upregulation of PTX3 expression has been observed in the CNS following inflammatory cytokine release, ischemia, and seizure-induced neurodegeneration [15–17]. Also, PTX3 serum level has been suggested as a new marker in Parkinson's disease [18]. Furthermore, growing evidence points to the involvement of PTX3 in CNS infections [19, 20]. However, whether PTX3 levels are elevated in HAM/TSP patients has remained uncertain. We measured plasma levels of PTX3 protein in HAM/TSP patients, HTLV-1 asymptomatic carriers, and healthy control individuals to evaluate the correlation between PTX3 serum level and HTLV-1 proviral load as well as major clinical features of HTLV-1-associated myelopathy patients and whether PTX3 could be used as a useful biochemical marker to determine the infection progression and disease severity.

Method

Study design

The study protocol was approved by the ethics committee of Mashhad University of Medical Sciences with approval code IR.MUMS.MEDICAL.REC.1399.44.7. All the participants were informed about the study procedure and provided written consent before they participated in the study.

Population study

This study included, 90 participants divided into three groups: 30 HTLV-1 associated myelopathy (HAM) patients, 30 HTLV-1 asymptomatic carriers (ACs), and 30 healthy controls (HCs) who were admitted to the HTLV-1 clinic of Ghaem Hospital affiliated with Mashhad University of Medical Sciences (MUMS), Mashhad, Iran in 2021. It should be noted that the subjects in this study have been recruited from the first national HTLV-1 registry in Iran (Code: 941637).

The inclusion criteria for HAM patients included HTLV-1 positive serology confirmed by polymerase chain reaction (PCR) or Western blot, spastic paraparesis symptoms, and the presence of anti-HTLV-1 antibody in cerebrospinal fluid (CSF). The inclusion criteria for HTLV-1 AC cases were as follows: HTLV-1 positive serology confirmed by PCR or Western blot without any myelopathy-related symptoms and signs. On the other hand, a history of cardiovascular diseases, surgery during the last three months, acute cerebral infarction, rheumatoid arthritis, and Parkinson's disease, as well as the use of immunomodulatory drugs, were defined as exclusion criteria for all three groups.

Data measurements

The individuals were asked to complete a checklist on the demographic data (age, sex, duration of HTLV-1 disease, drug history as well as a history of blood transfusion, breastfeeding in infancy, surgery, dialysis, dental procedures, tattooing, cupping, and unsafe intercourse). All patients underwent neurological evaluation by a neurologist, including muscle strength examination using the Medical Research Council (MRC) scale [21], deep tendon reflexes examination, spasticity evaluation based on the modified Ashworth scale [22], and motor disability based on motor disability grading (MDG) ranging from normal walking and running (score 0) to complete bedridden (score 13), and urinary complaint evaluation using Urinary Disturbance Score (UDS) ranging from being normal (score 0) to severe disturbance based on a feeling of residual urine, incontinence and frequency (score 3) [23].

Blood collection

Plasma samples were obtained from all participants between 9:00 AM and noon and put in heparin tubes. The samples were centrifuged at 2000*g* for 15 min to eliminate cells and other insoluble materials and then were aliquoted in polypropylene tubes.

PTX3 measurement by plasma by enzyme-linked immunosorbent assay (ELISA)

PTX3 plasma levels were measured using a commercially available sandwich ELISA kit (ZellBio, GmbH, Germany) according to the manufacturer's instructions in all three studied groups. According to the manufacturer, the kit sensitivity was 0.096 ng/mL, and the standard curve range was 0.312–20 ng/mL.

HTLV-1 proviral load

HTLV-1 Proviral load was quantified in HAM patients and ACs, using a Real-time PCR commercial Kit (Novin Gene, Iran) on extracted DNA from peripheral blood mononuclear cells (PBMCs), using Rotor-Gene Q 6000 machine (Qiagen, Germany) that was reported in details elsewhere [24].

Statistical analyses

The Statistical Package for Social Sciences version 16 was used for data analysis. Descriptive analysis was performed

using mean ± standard deviation and median (first quartile-third quartile). Inferential analysis regarding differences in the PTX3 concentration between different study groups was performed using one-way ANOVA and post hoc test (LSD). Proviral load values were analysis between HAM and AC groups was performed with Mann–Whitney *U* test. The correlation between quantitative variables was reported based on the spearman correlation coefficient. Chi-squared test was used to compare the frequency of qualitative variables in three study groups. All tests were two-tailed, and p value < 0.05 was considered statistically significant.

Table 1 Demographic characteristics of three study groups

	HAM	AC	HC	*p* value
Gender				
Male	10 (33.3%)	15 (50.0%)	4 (13.3%)	0.01
Female	20 (66.7%)	15 (50.0%)	26 (86.7%)	
Age (years) mean ± SD	47.1 ± 12.2	46.7 ± 12.4	49.0 ± 9.9	0.717

Results

This study was carried out on 90 individuals. The study population was divided into three groups, and each group consisted of 30 participants. The demographic characteristics are shown in Table 1.

Serum level of PTX3

Serum levels of PTX3 mean ± SD, in HAM patients, ACs and HCs were 12.40 ± 4.85 ng/ml, 9.19 ± 2.46 ng/ml, and 8.95 ± 0.95 ng/ml, respectively (Fig. 1). PTX3 serum level was the highest in the HAM patients group and the lowest in the HC group ($p < 0.0001$). It was found that PTX3 serum level in the HAM patients was significantly higher than in AC and HC groups (p values < 0.0001), but no statistically significant difference was observed between AC and HC groups ($p = 0.76$).

Correlation between PTX3 plasma level and proviral load

Quantitative real-time PCR was performed on the DNA extract from PBMCs, as previously described. The mean ± SD (median, 1st quartile–3rd quartile) of proviral

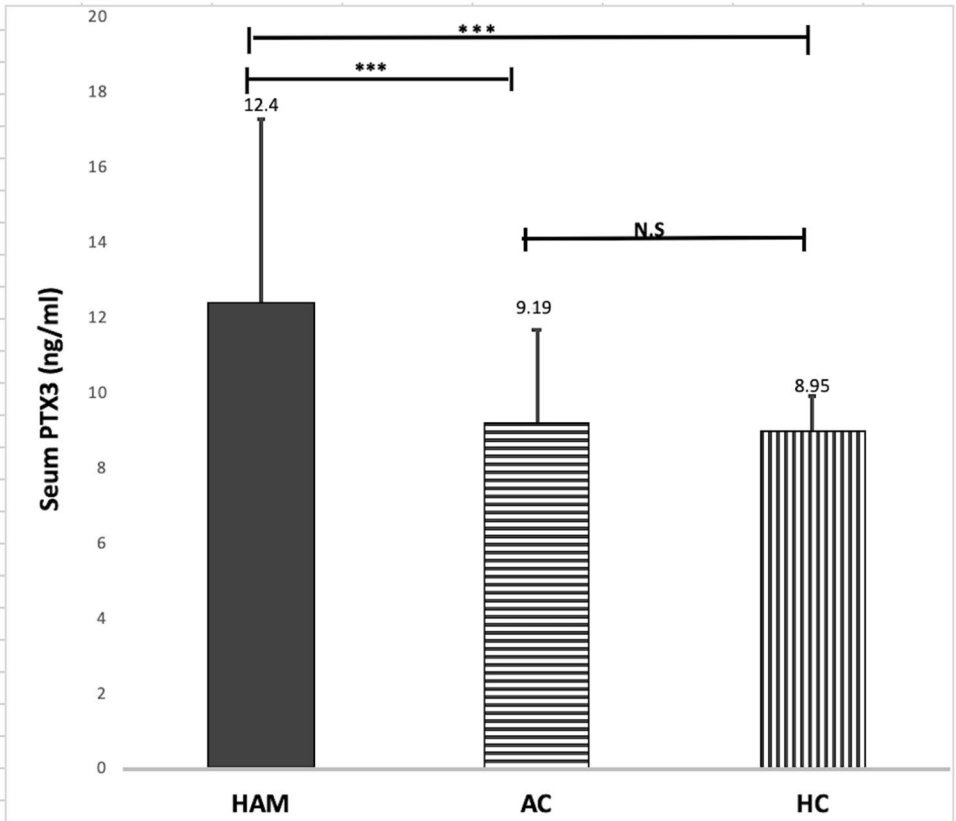

Fig. 1 Serum levels of PTX3 in HAM patients, asymptomatic carriers (ACs), and healthy controls (HCs). Serum PTX3 was higher in the HAM patients compared to AC and HC groups (p-values < 0.0001). No significant difference was observed between AC and HC groups ($p = 0.76$). Error bars show standard deviation. *** denotes p values < 0.0001 and N.S denotes non significant

load (PVL) was 273.2 ± 302.3 (199.9, 102.5–287.4) copies/10^4 PBMCs in HAM patients and 57.18 ± 111.14 (20.7, 12.3–68.8) copies/10^4 PBMCs in ACs, respectively. The difference in PVL between HAM patients and ACs was statistically significant ($p < 0.001$). There was no statistically significant correlation between PTX3 plasma level and PVL in HAM patients ($r = -0.238$, $p = 0.205$) and ACs ($r = -0.078$, $p = 0.681$) (Fig. 2).

Clinical features of HAM patients

The correlation between PTX3 plasma level and clinical features of the HAM/TSP patients, including motor disability and urinary disturbance, were assessed. Motor disability and urinary disturbance were evaluated by motor disability grading (MDG) and Urinary Disturbance Score (UDS), respectively. The findings showed that there was no significant correlation between PTX3 serum level and MDG ($r = -0.155$, $p = 0.41$) nor UDS ($r = -0.238$, $p = 0.20$) (Figs. 3, 4).

Discussion

We assessed the serum level of PTX3 in HTLV-1-associated myelopathy (HAM) patients, HTLV-1 asymptomatic carriers (AC), and healthy controls (HC), as well as its association with proviral load and clinical symptoms. There was a statistically significant gender preference in

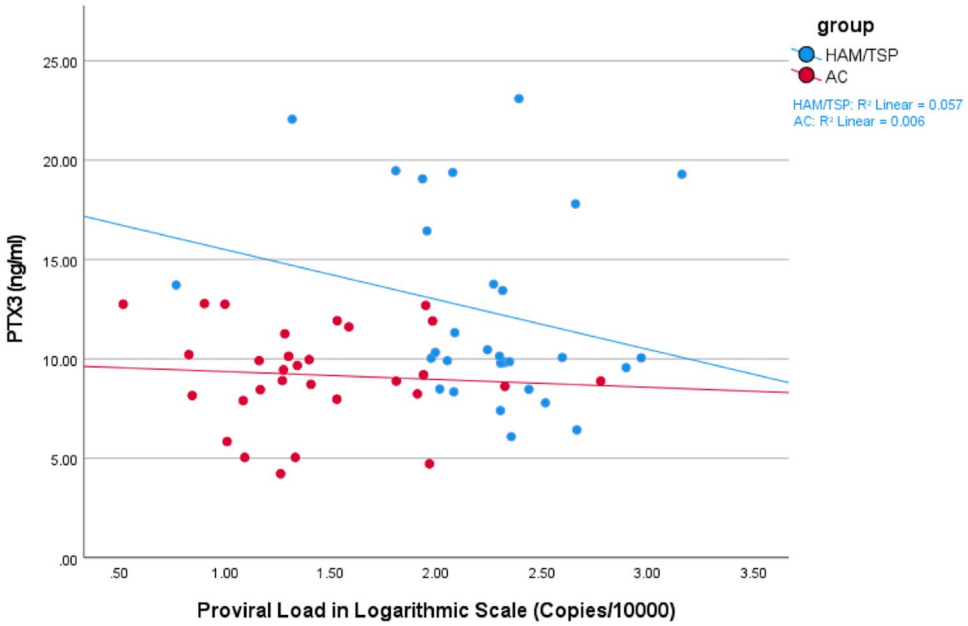

Fig. 2 Scatter-plot of PTX3 serum level and HTLV-1 proviral load in HAM patients, asymptomatic carriers (ACs). No significant correlation between PTX3 plasma level and proviral load in HAM patients ($r = -0.238$, $p = 0.205$) and ACs ($r = -0.078$, $p = 0.681$)

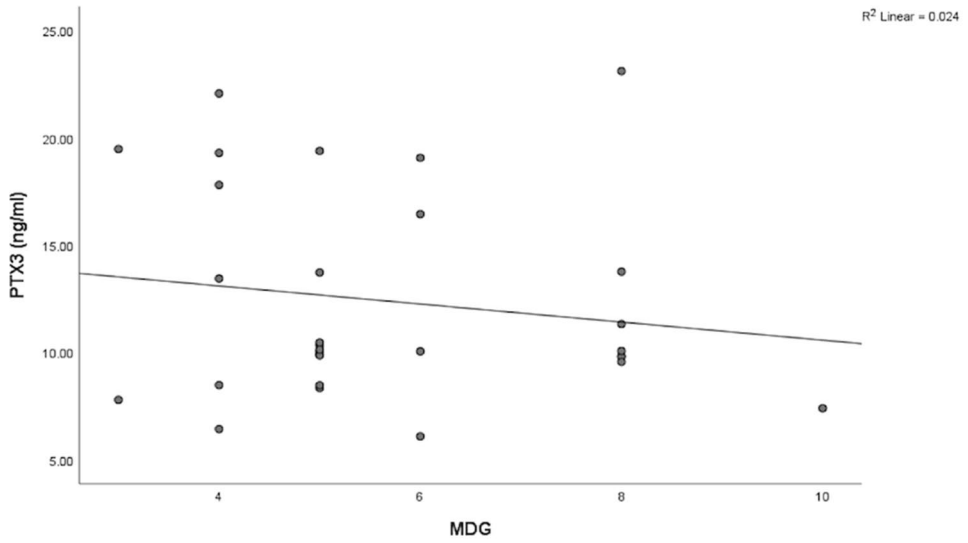

Fig. 3 Scatter-plot of PTX3 serum level and motor disability grading (MDG) in HAM patients. No significant correlation between PTX3 and MDG ($r = -0.155$, $p = 0.41$)

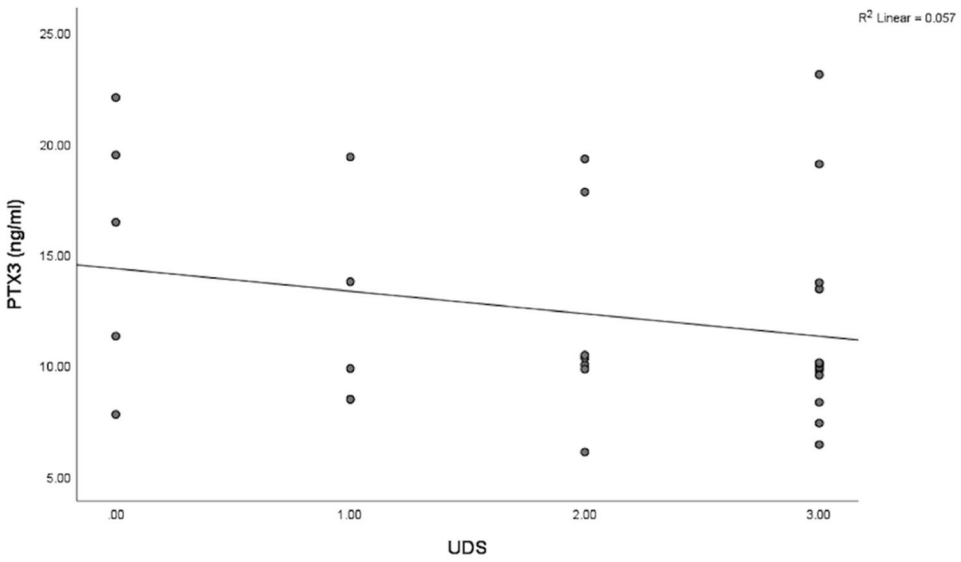

Fig. 4 Scatter-plot of PTX3 serum level and urinary disturbance score (UDS) in HAM patients. No significant correlation between PTX3 and MDG ($r = -0.238$, $p = 0.20$)

HAM/TSP group, which also was reported by Shoeibi et al. in the HTLV-1 data registry in northeast of Iran [26]. It showed that the plasma level of PTX3 in HAM patients was significantly higher than ACs and HCs, whereas no significant difference was observed between AC and HC groups. Pentraxin 3 (PTX3) is recently discovered as an acute-phase protein belonging to the same family as C-reactive protein (CRP) [25]. PTX3 is stored in neutrophils and rapidly released upon pathogen challenge or tissue injury [27]. PTX3 has a vital role in the early stage of inflammation by recognizing microorganisms, enhancing the identification of the pathogen by phagocytes, and activating the classical and lectin complement pathway [28, 29].

PTX3 expression can be induced in neurons, microglia, and, or astrocytes following cytokine release or neuroinflammation. PTX3 upregulation has been revealed in other animal studies under different experimental neuroinflammatory models, such as limbic seizure [17], autoimmune encephalomyelitis [13], neurotrauma [30], globoid cell leukodystrophy [13], and ischemia [15]. Additionally, high serum level of PTX3 has been shown in patients with neurodegenerative conditions, including multiple sclerosis [31], Parkinson's disease [18], and ischemic stroke [32]. An experimental study showed that PTX3 has a role in facilitating myelin phagocytosis during neuroinflammation, whereas it does not affect controlling the autoimmune neuroinflammation development [13]. However, only a few studies evaluated the correlation between PTX3 and CNS infections.

According to the literature, high serum PTX3 level was correlated with the prognosis and severity of infectious diseases [33]. Patients with dengue virus infection, pulmonary aspergillosis, tuberculosis, shigellosis, meningococcal disease, and leptospirosis have elevated PTX3 serum levels, which associated with disease severity and could serve as predictors of adverse outcomes [34–40].

In addition to the application of serum PTX3 level as a biomarker for detecting infections, it has also been used to monitor the response to therapy. In a study consisting of 220 lately diagnosed patients with mycobacterium tuberculosis, PTX3 serum level was remarkedly reduced in people who responded to treatment compared to patients with therapy failure [35]. Moreover, patients with community-acquired pneumonia [41] or pyelonephritis [42] showed a decreased level of PTX3 after antibiotic treatment. To the best of our knowledge, this study is the first one to evaluate the role of PTX3 levels in blood in the setting of CNS involvement with HTLV-1.

Proviral load is an essential factor in determining the outcomes of chronic viral infections, such as hepatitis B virus, hepatitis C virus, and HIV-1 and 2 [43]. Further, a recent study has emphasized the importance of PVL in the outcome of HTLV-1 infection [44]. Consistent with the literature [43], the current study showed that PVL was markedly higher in HAM/TSP patients than that of HTLV-1 HCs, indicating that active HTLV-I viral replication might have significant impact on the disease development.

To interpret the correlation between the serum levels of PTX3 and HTLV-1 proviral load in HAM/TSP and AC groups, we applied a non-parametric statistical technique, since the serum PTX3 levels and viral load values did not follow the normal distribution. However the correlation between serum levels of PTX3 and proviral load was not statistically significant in those groups. Regarding previous studies, PTX3 decreased the viral load of influenza [45] and Human cytomegalovirus [27] but increased the viral load of chikungunya and Ross River virus [46]. Although further studies might elucidate whether these

types of results could be affected by experimental conditions or whether the findings remain true for various pathogen infections, the fact is that PTX3 has a complex role in immunoregulation.

This study has not demonstrated the association between PTX3 plasma level and HTLV-1 proviral load or the clinical features of HAM patients, such as motor disability nor urinary disturbance assessed by MDG and UDS scales. However, in one study that evaluated the PTX3 plasma levels in multiple sclerosis (MS) and Neuromyelitis Optica (NMO) patients, plasma levels of PTX3 were significantly increased in the relapse phase of both groups, and it also had a correlation with EDSS scores of the patients. In addition, the PTX3 plasma levels were decreased and did not correlate with EDSS scores in the remission phase [32]. The inconsistency between our study and the mentioned study in MS and NMO patients might be due to different inflammatory mechanisms involved in the pathophysiology of the diseases and also different disease courses of HTLV-1 associated myelopathy as a chronic evolving myelopathy and MS/NMO myelopathy as an acute or subacute evolving myelopathy.

Future longitudinal studies of HTLV-1 associate myelopathy patients and asymptomatic carriers seem to be needed to evaluate the exact role of PTX3 in the pathophysiology of HTLV-1 infection and disease progression and to define its diagnostic and prognostic value in HTLV-1infected individuals. This study demonstrated that plasma PTX3 level was higher in HAM patients than in both HTLV1 asymptomatic carriers and healthy controls. This finding may support the idea that PTX3 has the potential as a diagnostic biomarker in HAM patients. Further investigation to clarify the exact role of PTX3 in HTLV-1 infection may provide insights, enabling the recognition of possible drug targets for treatment.

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Author contributions MM, ZV, HR and FZ performed research; MKR Analyzed data; ZV and FZ conceived and designed research; RB supervised and coordinated the study; MM wrote the paper draft; FZ contributed to manuscript editing. The manuscript was approved by all the authors.

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Data availability statement The data generated or analyzed during this study are available from corresponding author on reasonable request.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval and consent to participate The study protocol was approved by the ethics committee of Mashhad University of Medical Sciences with approval code IR.MUMS.MEDICAL.REC.1399.44.7. All the participants were informed about the study procedure and provided written consent before they participated in the study.

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