Original Article

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The rs739837 Polymorphism of Vitamin D Receptor Gene and Its Relationship with Type 2 Diabetes Mellitus in the Eastern Population of Mazandaran Province

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ABSTRACT

Background & Objective: The relationship between vitamin D receptor (VDR). Polymorphisms, and diabetes remain uncertain. This study aimed to examine the potential correlation between type 2 diabetes mellitus (T2DM) and rs739837 single nucleotide polymorphism (SNP) in the Mazandaran province population.

Materials & Methods: A case-control study was conducted, involving 100 individuals diagnosed with T2DM and 100 healthy controls, all residents of Mazandaran province. The extraction of genomic DNA and rs739837 polymorphism was genotyped using the Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP) method.

Results: The data indicated a significant association between GT genotype and a decreased risk of T2DM (OR= 0.5135, 95%CI= 0.2759 to 0.9559, P=0.0355). Moreover, individuals carrying T allele showed a reduced likelihood of progressing T2DM (OR= 0.4657, 95%CI= 0.2564 to 0.8461, P=0.0121).

Conclusion: The findings suggested that rs739837 polymorphism in the VDR gene may serve as a protective factor against T2DM in the studied population. Further research with larger samples is needed to confirm these results across different populations.

Keywords: VDR gene, rs739837, Genetic polymorphism, T2DM

Introduction

Diabetes mellitus (DM) is one of the most pressing global health challenges, with its prevalence growing rapidly. It is predicted that by 2025, over 300 million people will be affected by the condition **(1)**. In Iran alone, approximately 1.5 million individuals currently suffer from DM, a number expected to increase dramatically, contributing to a rise in cardiovascular diseases **(2)**. While T2DM is more prevalent than type 1 diabetes, its exact causes remain incompletely understood **(1)**. T2DM epidemic is a significant public health issue that elevates the likelihood of peripheral circulatory disease, neuropathy, cardiovascular disorders, renal failure, and blindness. The most significant prediction is that the prevalence of this condition will increase significantly over the next decade as a result of the growing obesity epidemic in numerous countries **(3, 4)**. T2DM is a complex, chronic, lifelong disorder with a robust genetic background that has a main effect on life quality and results to increase the mortality and morbidity of other disorders **(5)**. The rise in obesity rates globally exacerbated T2DM epidemic, making the identification of genetic and environmental risk factors increasingly important **(6, 7)**. Among genetic factors associated with T2DM is the vitamin D receptor (VDR) gene **(8, 9)**.

This gene, located on chromosome 12, was implicated in numerous metabolic processes, including insulin secretion and sensitivity, and has long been a

key gene involved in T2DM pathogenesis. By forming a heterodimer with the retinoid X receptor (RXR), the VDR gene functionally mediates the majority of the effects of vitamin D on the regulation of gene expression and the binding to promoter sequences, as well as the regulation of multiple target genes **(10)**. Numerous studies have reported correlations between VDR gene variations and T2DM, calcitriol levels, insulin secretion, insulin sensitivity, glucose intolerance, and fasting glucose **(11)**. These results obviously indicate that VDR is an innovative candidate gene for diabetes type I and II, where VDR variations might be involved in T2DM pathogenesis by affecting the secretory capability of β-cells. There are many polymorphisms in VDR gene, including *TaqI* (rs731236), *BsmI* (rs1544410), *ApaI* (rs7975232), *Fok1* (rs2228570), and *BglI* (rs739837) polymorphisms **(8, 12)**. Meanwhile, rs739837 polymorphism is a 3_prime_UTR_variant that causes a G>T substitution in this position. In 2022, Zeng et al. conducted a meta-analysis study that demonstrated the correlation between this polymorphism and the risk of developing T2DM **(13)**. Nevertheless, the rs739837 polymorphism was the subject of limited research in Iranian populations. This study investigated the potential association between rs739837 polymorphism and T2DM risk in a population from Mazandaran province. By understanding these genetic variations, we hope to contribute to the growing body of knowledge on the genetic determinants of T2DM.

Materials and Methods

Study participants

This case-control study included 200 participants, comprising 100 individuals diagnosed with type 2 diabetes mellitus (T2DM) and 100 healthy controls, all recruited from hospitals in Neka and Behshahr, Mazandaran province. T2DM was diagnosed using World Health Organization criteria, and all individuals gave informed permission. Each participant provided 2 ml of blood, which was drawn into EDTA-coated tubes and kept at -20°C. The study received approval from Ethical Committee under protocol **(14)**, and all participants provided informed consent. Blood samples were collected from each participant, with 2 ml of blood drawn into EDTA-coated tubes and stored at -20°C until further analysis. The study was approved by the Ethical Committee under protocol (IR.IAU.SARI.REC.1402.326).

Genome extraction and genotyping of samples

Genomic DNA was extracted from the blood samples using the phenol-chloroform extraction method. The quality and concentration of extracted DNA were assessed using spectrophotometry and agarose gel electrophoresis. The rs739837 polymorphism in the VDR gene was genotyped using the Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP) method. Specific primers were designed to amplify the polymorphic region of the VDR gene. The primer sequences are as follows: forward primer 5'-GCAGGGCCTTGCCCA-3' and reverse primer 5'-CACTAGGCGCTGGACAAGC-3'. PCR amplification was conducted in a 20 µl reaction mixture containing 250 ng of DNA template, 1.5 µl of each primer, and 10 µl of 2X PCR Master Mix. PCR cycling conditions consisted of an initial denaturation at 95°C for 5 minutes, followed by 35 cycles of denaturation at 95°C for 35 seconds, annealing at 57°C for 35 seconds, extension at 72°C for 35 seconds, and a final 5-minute extension. PCR products were verified on a 1% agarose gel. For RFLP analysis, using *BglI* enzyme the PCR product was digested (Fermentas, Germany) at 37°C for 16 hours. The resulting fragments were then separated on a 1.5% agarose gel. The genotype was determined based on the fragment sizes: samples with the GG genotype displayed two bands (110-bp and 39-bp), the GT genotype showed three bands (149-bp, 110-bp, and 39-bp), and the TT genotype produced a single 149-bp band.

Statistical Analysis

The chi-square test was employed to assess Hardy-Weinberg equilibrium in both case and control groups. The chi-square test was used to evaluate the differences in genotype and allele frequencies between the two groups. Odds ratios (OR) and 95% confidence intervals (CI) were computed using binary logistic regression to assess the relationship between the rs739837 polymorphism and the risk of T2DM. All statistical analyses were performed using SPSS software (version 19), with a significance threshold set at $P < 0.05$.

Results

Genotype of samples

Genomic DNA was checked on agarose gel and formed a band with low mobility on the agarose gel. PCR-amplified fragments containing the rs739837 polymorphism formed a 149-bp band on a 1% agarose gel. Subsequently, enzyme mixtures containing distinct fragments were electrophoresed on a 1.5% agarose gel. Samples with varying genotypes exhibited distinct patterns on the gel. The genotypic distribution of rs739837 polymorphism in the case and control groups was analyzed. In the control group, GG, GT, and TT

genotypes were 57%, 36%, and 7%. In the patient group, the frequencies were 74%, 24%, and 2%, respectively. The genotype frequencies in both groups were in Hardy-Weinberg equilibrium (control: χ^2 = 0.16, P = 0.689; case: χ^2 = 0.001, P = 0.973). The results of PCR as well as enzymatic digestion on agarose gel are shown in **Figure 1.**

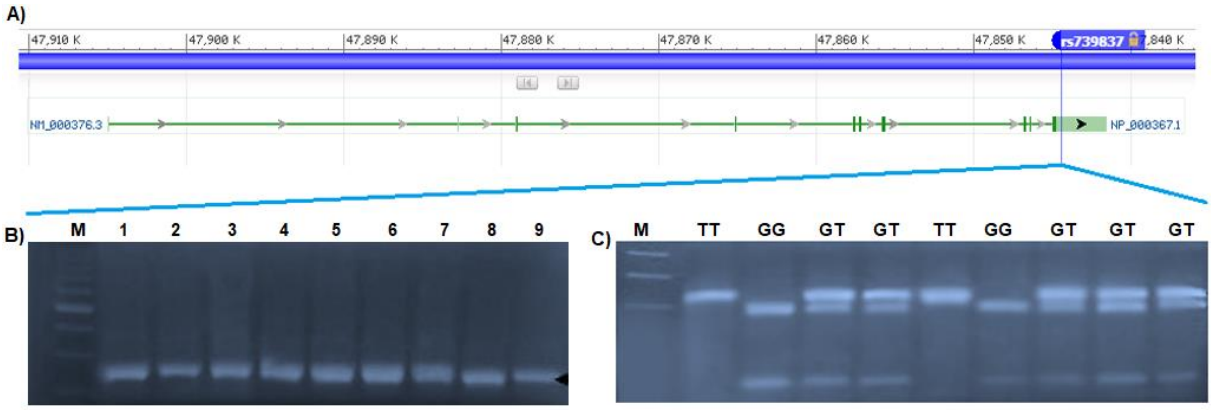

Figure 1. Gene map and genotyping of rs739837 polymorphism. VDR gene, which contains 12 exons, and rs739837 polymorphism, which is located downstream of this gene (A). Amplification results of the VDR gene containing rs739837 polymorphism, which forms a 149-bp band on agarose gel (B). RFLP results that TT, GG, and GT samples have 1, 2, and 3 bands respectively on agarose gel (C).

Association of rs739837 polymorphism with type 2 diabetes risk

Logistic regression analysis showed a significant association between the GT genotype and a lower risk of developing type 2 diabetes (illustrated **in Tables 1 and 2)**. Individuals with the GT genotype had a lower risk of T2DM (OR = 0.5135, 95% CI = 0.2759 to 0.9559, P = 0.0355) related to those with the GG genotype. Additionally, GT and TT genotypes were found to have a protective effect against T2DM when combined (OR = 0.4657, 95% CI = 0.2564 to 0.8461, P = 0.0121). The G allele was more prevalent in the case and control groups in terms of allele frequencies **(Table 2)**. G allele frequency was 86% in the T2DM group and 75% in the control group. Conversely, the T allele was found at a frequency of 14% in the T2DM group and 25% in the control group based on Figure 2. Allele analysis indicated a statistically significant association between the T allele and a decreased risk of progressing T2DM (OR = 0.4709, 95% CI = 0.2809 to 0.7896, P = 0.0043).

Table 1. Genotypic frequencies of rs739837 polymorphism for control and patient groups

Genotype	Number and percentage		OR (95% CI)	*P*-value
	Control (n=100)	Patient (n=100)		
GG	57 (57.00%)	74 (74.00 %)	-	-
GT	36 (36.00%)	24 (24.00%)	0.5135 (0.2759 to 0.9559)	0.0355
TT	7 (7.00%)	2 (2.00%)	0.2201 (0.0440 to 1.0999)	0.0652
GT+TT	43 (43.00%)	26 (26.00%)	0.4657 (0.2564 to 0.8461)	0.0121

Table 2. Allele frequencies of rs739837 polymorphism for control and patient groups

Allele	Number and percentage		OR (95% CI)	*P*-value
	Control (n=100)	Patient (n=100)		
G	150 (75.00%)	172 (86.00%)	-	-
T	50 (25.00%)	28 (14.00%)	0.4709 (0.2809 to 0.7896)	0.0043

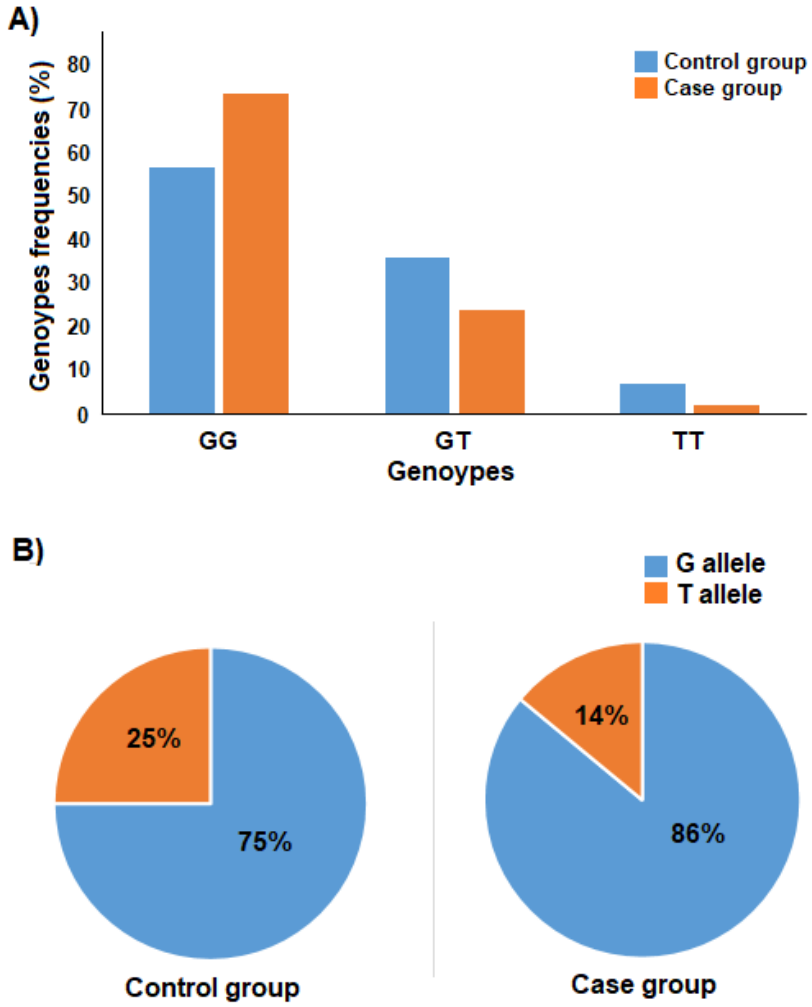

Figure 2. Allelic and genotypic frequency of rs739837 polymorphism. frequencies of GG, GT, and TT genotypes in the control group are 57%, 36%, and 7%, respectively while these ratios for the case group were 74%, 24%, and 2%, respectively (A). The frequencies of G and T alleles in the control group are 75% and 25%, respectively while these ratios are 86% and 14% in the case group (B).

Discussion

Diabetes is a disease that occurs with increased blood sugar due to a lack of insulin secretion (diabetes type 1) or damaged insulin activity (diabetes type 2). Most diabetic subjects have type 2 diabetes. In recent years, the prevalence of T2DM substantially increased, while the age at which this type of diabetes is diagnosed has decreased significantly in comparison to previous decades. In other words, a greater number of youthful individuals are being diagnosed with this type of diabetes **(15)**. Therefore, identifying the risk factors of diabetes will lead to early recognition of this disease and prevention in the early stages, and ultimately prevent the occurrence of diabetes. There are the factors that increase the chance of developing diabetes, which include family history, aging, sedentary lifestyle, unhealthy eating habits, racial or ethnic history, etc. **(16)**. Genetic polymorphisms, especially in key genes, can change the risk of developing this disease. Vitamin D receptor gene or VDR is one of these genes that has key polymorphisms. We studied the relationship between rs739837 polymorphism and the risk of type 2 diabetes in the population of northern Iran, which, according to our knowledge, is the first study in the Iranian population.

The current study explored the association between rs739837 polymorphism in the vitamin D receptor (VDR) gene and the risk of type 2 diabetes mellitus (T2DM) in an Iranian population from Mazandaran province. Our findings indicate that individuals carrying the GT genotype, as well as those with the T

allele, show a reduced risk of developing T2DM. These findings indicate that the rs739837 polymorphism may serve as a protective factor against the disease in this population. The significance of VDR gene polymorphisms in the risk of diabetes has been the subject of conflicting results in previous studies. For instance, Zeng et al. (2022) conducted a meta-analysis and found that rs739837 polymorphism was associated with an increased risk of T2DM in certain populations. The discrepancy between our findings and those of previous studies may be attributed to differences in genetic background, environmental factors, or even sample sizes across populations. This highlighted the importance of conducting region-specific research to better understand the genetic underpinnings of diabetes susceptibility **(13)**. The contradictory results of different studies show that the effect of this polymorphism may be related to environmental, racial, and other factors. In addition to this polymorphism, several studies have been published on other VDR polymorphisms. Ahmed et al. (2019) examined the potential link between vitamin D and VDR single nucleotide polymorphisms in type 1 diabetes (T1DM) among Egyptian youngsters. The results showed that *BsmI* and *ApaI* polymorphisms were correlated with the risk of T1 diabetes in children of Egyptian ethnicity. Low vitamin D status occurs frequently among type 1 diabetics, with significant improvements in glycemic control in such children when vitamin D supplementation is added to standard insulin therapy **(17)**. Furthermore, our findings correspond with earlier research that has shown protective benefits of certain VDR mutations across diverse populations. For example, Malik et al. (2018) found that other polymorphisms in the VDR gene, such as *BsmI* and *TaqI*, were linked to a reduced risk of diabetes in North Indian populations. The role of vitamin D in glucose metabolism, particularly through the VDR pathway, was increasingly recognized. Vitamin D, via its receptor, regulates several genes involved in insulin secretion and sensitivity, which may explain the observed protective effects of rs739837 polymorphism **(18)**. Abd-Allah et al. (2013) investigated the status of vitamin D and VDR gene variations and their association with T1DM in a study. The results showed that 75% of patients had vitamin D insufficiency or deficiency. The mean vitamin D levels in patients were meaningfully lower than in the control group. Their study displayed that the deficiency of vitamin D and BsmI and FokI variations in VDR gene are associated with T1DM in Egyptian children **(19).** Jahanpour et al (2018) conducted a study to investigate the correlation between kidney diseases and various polymorphisms of the vitamin D receptor gene (*TaqI*, *BsmI*, *ApaI*, *FokI*) in patients with type 2 diabetes. The results showed that the genotypic frequency of *BsmI*, *ApaI*, *FokI*, and *TaqI* variations is associated with the occurrence of kidney diseases in type 2 diabetic subjects. Meanwhile, stusying the association of different variations with the occurrence of kidney diseases displays that the ApaI variation has the greatest effect on the occurrence of kidney complications in subjects with type 2 diabetes. Moreover, *BsmI* variation has the most impact on the occurrence of type 2 diabetes **(20)**. Hajimohammadi et al. (2015) studied the relationship between single nucleotide polymorphisms of vitamin D receptor gene with metabolic syndrome and type 2 diabetes. Evidence that VDR gene variations have a role in type 2 diabetes risk and metabolic syndrome in Iranian people was not found **(21).** VDR gene is implicated in the pathobiology of type 2 diabetes, as demonstrated above. Variations in the expression and structure of this gene can alter the likelihood of developing the disease. Consequently, the incidence of T2DM may be either increased or decreased by genetic polymorphisms of this gene. Genetic polymorphisms may cause changes in gene structure and expression based on their location on the gene. Exonic polymorphisms can change protein structure and function, while upstream and downstream polymorphisms can affect gene expression. Vitamin D receptor is encoded by a huge gene that covers 12 exons and is positioned on chromosome 12 **(22)**. This gene interacts with many other genes **(Figure 3)**. Numerous variations were recognized in different exons and introns of VDR sequence, with *FokI*, *BsmI*, and *ApaI* polymorphisms being the most common **(23, 24)**. ApaI (rs7975232) and BsmI (rs1544410) genetic variations are positioned in intron 8 of the VDR gene and are considered silent variations that do not alter the peptide sequence of encoded protein. Nevertheless, these two genetic variations may affect gene regulation by regulating the stability of mRNA **(25, 26)**. The *FokI* (rs2228570) variation in the VDR gene generates an alternative transcription start site, which leads to a protein variant with three additional residues at the amino terminus **(27)**. *BglI* polymorphism, which is positioned in the 3'-UTR of the gene, may affect the expression of this gene.

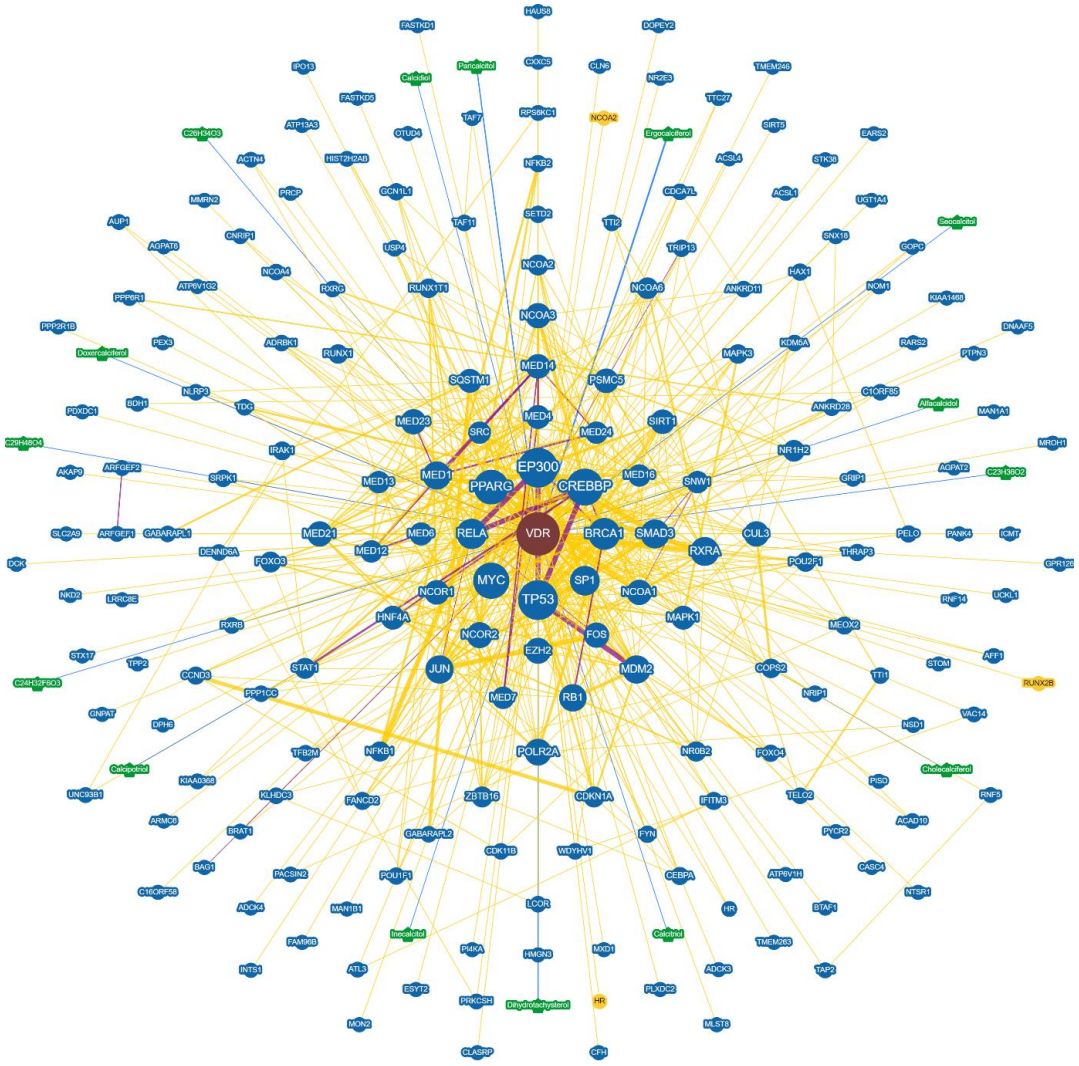

Figure 3. VDR interaction network. There are 340 interactions for the VDR between 213 interactors. The Chemical Interactions were estimated at 43.

Conclusion

The findings of this study suggested that rs739837 polymorphism in the vitamin D receptor (VDR) gene may play a protective role to reduce the risk of type 2 diabetes mellitus (T2DM) in the Mazandaran population. Individuals carrying GT genotype and those with the T allele were found to have a lower likelihood of developing T2DM. These findings underline the need of genetic elements in diabetes susceptibility and the possible relevance of the VDR gene in control of glucose metabolism. However, due to the relatively small sample size and lack of vitamin D level measurements, further research with larger, more diverse populations is necessary to confirm these findings. Future studies should consider including clinical factors, such as vitamin D concentrations to better understand the interaction between genetic predisposition and environmental factors in the development of T2DM.

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Authors' Contribution

NM assisted with sample collection and clinical information of patients, contributed to methodology, and writing—original draft preparation. **EJJ** assisted with sample collection and clinical information of patients, **BE** and **BS** participated in the study conception and design of experiments, data curation,

Validation, statistical analysis, preparation of the manuscript, writing—review, and editing.

Conflict of Interest

The authors declare that they have no conflict of interest.

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Ethics Approval and consent to participate

The study was approved by the Ethical Committee under protocol (IR.IAU.SARI.REC.1402.326)

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