Research Article

The Effects of two TP53 Polymorphisms on Its Expression and Folding and Association with the Pathogenesis of Polycystic Ovary Syndrome: in-silico analysis

Mahboobeh Sabeti Akbar-Abad[1,2], Hossein Shahriari[3,*], Mahdi Majidpour[2,], Razieh Akhtar[4], Ramin Saravani[2,5], Mehdi Zandhaghighi[6,7], Khodadad Sheikhzadeh[8]**

[1] *Cellular and Molecular Research Centre, Birjand University of Medical Sciences, Birjand, Iran.*
[2] *Department of Clinical Biochemistry, School of Medicine, Zahedan University of Medical Sciences, Zahedan, Iran.*
[3] *Clinical Immunology Research Centre, Zahedan University of Medical Sciences, Zahedan, Iran.*
[4] *Student Research Committee, Zahedan University of Medical Sciences, Zahedan, Iran.*
[5] *Cellular and Molecular Research Centre, Research Institute of Cellular and Molecular Sciences in Infectious Diseases, Zahedan University of Medical Sciences, Zahedan, Iran.*
[6] *Department of Medical Microbiology, School of Medicine, Zahedan University of Medical Sciences, Zahedan, Iran.*
[7] *Infectious Diseases and Tropical Medicine Research Centre, Resistant Tuberculosis Institute, Zahedan University of Medical Sciences, Zahedan, Iran.*
[8] *Department of Epidemiology and Biostatistics, Health Promotion Research Centre, Zahedan University of Medical Sciences, Zahedan, Iran.*

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[*] **Corresponding Author:**

Hossein Shahriari
Clinical Immunology Research Centre, Zahedan University of Medical Sciences, Zahedan, Iran
Email: hosseinshahriari1971@gmail.com

Mahdi Majidpour
Department of Clinical Biochemistry, School of Medicine, Zahedan University of Medical Sciences, Zahedan, Iran
Email: mahdimajidpour@gmail.com

ABSTRACT

Objectives: Polycystic ovary syndrome (PCOS) is a multifactorial endocrinopathy characterized by various reproductive and metabolic abnormalities. The tumor suppressor p53 (*TP53*) plays a crucial role in cellular stress responses. Alterations in its structure or expression can influence *PCOS* pathogenesis. We aim to use in-silico analyses to predict the effects of the rs2287499 and rs1042522 genetic variants on the expression and structural stability of the *TP53* protein.

Methods: This study investigated the association of two genetic variants, rs2287499 and rs1042522, with the expression levels and folding stability of *TP53* protein through in-silico analyses. Utilizing bioinformatics tools (*VMD, WebLogo* and *PROMO*), we examined the potential impacts of these variants on *TP53* transcriptional activity, protein structure, and functional integrity.

Results: Our findings indicate that the rs2287499 variant significantly influences *TP53* expression level, while rs1042522 is associated with altered protein folding dynamics. These changes may disrupt *TP53* normal regulatory functions, contributing to *PCOS* etiology. Furthermore, our study establishes a framework for integrating genetic variants into the understanding of *TP53*-mediated mechanisms in *PCOS*, which could pave the way for developing targeted therapeutic strategies.

Conclusion: These results underscore the importance of genetic variants in *PCOS* hormonal and metabolic dysregulation.

Keywords: TP53, PCOS, Bioinformatics, rs1042522, rs2287499.

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Introduction

Polycystic ovarian syndrome (PCOS) is a hormonal disorder characterized by multiple symptoms, including irregular menstrual cycles, hirsutism, acne, and polycystic ovaries. *PCOS* mechanisms are not fully understood (1, 2). Its pathophysiology involves genetic, environmental, and hormonal factors (3). It has been shown that variations in certain genes may be associated with the development of this syndrome.

Tumor suppressor p53 (TP53*)*, also known as tumor protein 53 or p53, is a gene that encodes a protein involved in cell cycle regulation, apoptosis, DNA repair, and other essential cellular processes (4, 5). While *TP53* is recognized for its role in cancer biology, emerging research suggests it may also be involved in *PCOS* pathophysiology. *TP53* may be involved in *PCOS* through cell cycle regulation, apoptosis and follicle development, insulin resistance, oxidative stress and inflammation. *TP53* is a critical cell cycle regulator (6). Dysregulation of the cell cycle has been implicated in various reproductive disorders, including *PCOS* (7). In abnormal ovarian follicles, *TP53* may influence ovarian follicle growth and maturation and affect oocyte quality (6). *TP53* plays a critical role in apoptosis, especially in cellular stress and DNA damage (8). In the ovaries, dysfunction in apoptosis may contribute to follicle accumulation and the characteristic polycystic appearance. Apoptosis regulation could lead to non-functional follicles instead of normal ovulation (3). *TP53* has also been linked to metabolic processes. Insulin resistance is a common feature of *PCOS* and associated with metabolic syndrome. *TP53* may influence adipose tissue function and insulin signaling, impacting metabolic health in *PCOS* women (1). *TP53* is also involved in oxidative stress response. Increased oxidative stress has been suggested as a factor in *PCOS* pathogenesis, particularly in relation to oocyte quality and follicular health (9). Chronic low-grade inflammation is often seen in *PCOS*, and some studies suggest that *TP53* may play a role in inflammatory pathways (10) (11).

The *TP53* gene is polymorphic. In DNA, single nucleotide polymorphisms (SNPs) occur when one nucleotide is replaced with another. Cancer risk, progression, or response to treatment have been reported to be associated with these changes of the *TP53* protein (12). In this regard, prior studies have suggested an association between the rs2287499 and rs1042522 SNPs and various diseases (13, 14). Importantly, the association between these two variants of the P53 gene with PCOS has been previously reported (1, 15).

The in-silico approach provides a powerful tool for predicting how SNPs may influence the expression of genes and folding of proteins. In this study, we aim to study the impact of the variants of TP53 gene on its expression and folding. In particular, we in this study investigated the effects of the rs2287499 and rs1042522 variants of the TP53 gene on the expression and folding. By analyzing these variants' potential impacts using computational modeling, we can gain insights into their functional consequences, which would be challenging to assess experimentally in a clinical setting.

Methods

Analysis of protein dynamics

We predicted whether allele substitution in the *TP53* rs1042522 would change its visual molecular dynamics (*VMD*). PDB information for the TP53 protein with 393 amino acids (ID: P04637) was retrieved from *UniProt* (https://www.uniprot.org) and displayed in *VMD* software (16) to analyze the *TP53* protein structure under the influence of the rs1042522 variant.

Analysis of Conservation

WebLogo v.2.8.2 was used to identify preserved regions of polymorphisms. Sequence logos are generated by *WebLogo* to represent the patterns in multiple sequence alignments. Sequence logos provide a richer and more precise characterization of the sequence identity than consensus sequences. By using them, alignment features that would otherwise be difficult to detect can be discovered. Each letter in an individual logo is represented by a stack of letters. Stack heights (as measured by bits) indicate sequence conservation at each position, and nucleic acid abundance is determined by symbol heights (17). Schneider and Stephens describe sequence conservation as the symbol distribution's observed entropy minus its maximum potential entropy. Multiple sequence alignments are available at https://weblogo.threeplusone.com/create.cgi). Based on their frequency, SNPs were scaled.

Variations' effect on the transcription factor binding sites

The current study used *PROMO v.3.0.2* to identify transcription factor binding sites (TFBS) in DNA sequences (18). With the *TRANSFAC v.8.3* database, we made unique binding site weight matrices to find the transcription factor binding site in the *TP53*-rs2287499 C>G promoter polymorphism. We selected homo sapiens factors and their corresponding sites of recognition accordingly. We observed a 5% discrepancy between the actual binding site of the transcription factor and the anticipated site, based on predictions made under a dissimilarity threshold of less than 5%. We then included the gene sequence from the NCBI database associated with the promoter location.

Results

Functional Impact of the rs1042522 Missense Variant

Our analysis of the *TP53* gene revealed (Table 1) that the rs1042522 polymorphism (a G-to-C substitution)

Table 1. Specifications of studied variants

GENOMIC [a]										PROTEIN [b]
Chr. [c]	Cytoband	Coordinate [d]	SNP ID [e]	Ref. [f]	Alt. [g]	Gene [h]	Codon (strand) [i]	AA pos. [j]	AA change [k]	Consequence(s) [l]
17	p13.1	7676154	rs1042522	C	G	TP53	cCc/cGc	72	Pro/Arg	Missense
17	p13.1	7688850	rs2287499	C	G	TP53	-	-	-	2KB Upstream Variant

[a] Gene and nucleotide level annotations; [b] Amino acid/protein level annotations; [c] Chromosome; [d] Genomic coordinate; [e] User entered variant identifier; [f] Reference allele; [g] Alternative allele; [h] HGNC short gene name; [i] Change of the codon containing the variant nucleotide the position of which is capitalized; [j] Position of the amino acid containing the variant in the displayed isoform; [k] Three letter amino acid code for the reference and alternative alleles; [l] A description of the consequence of the variant.

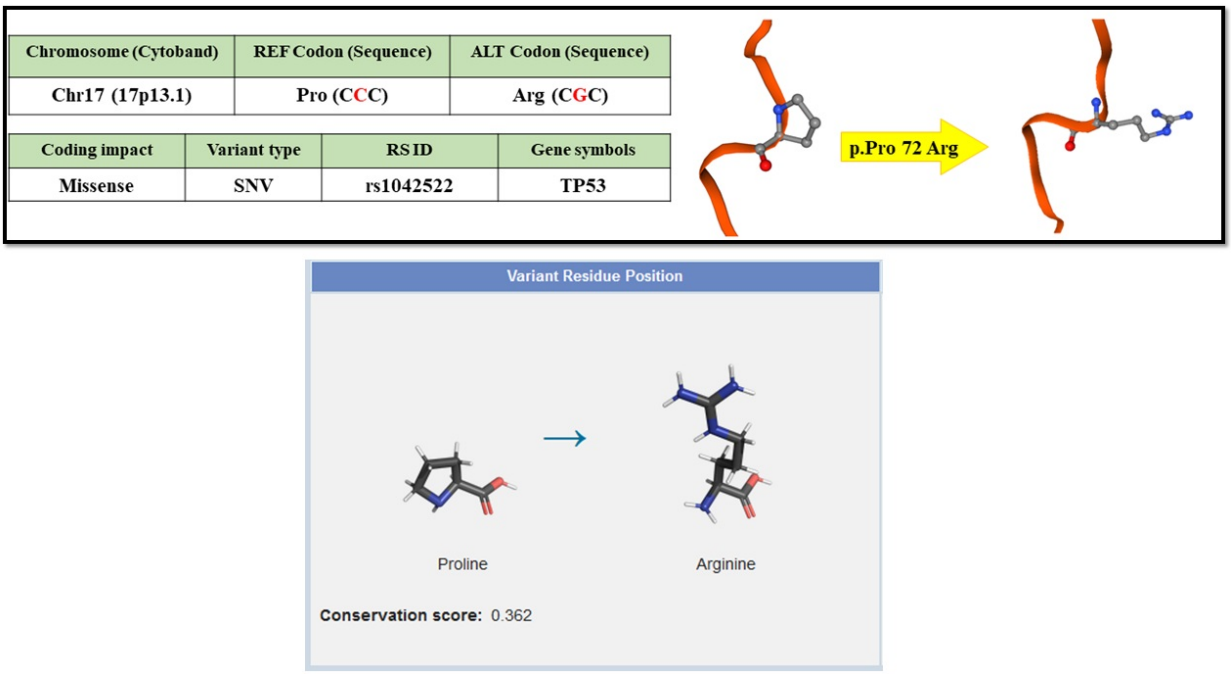

Figure 1. The TP53 visual molecular dynamics (VMD) images, shown by a new cartoon, the model presents the effect of Arginine residue on Turn structure of the protein in position 72.

results in a non-synonymous change at the protein level, changing the amino acid from proline (Pro) to arginine (Arg) in the DNA-binding domain of *TPp53* (Figure 1). Given that proline is a rigid, structure-disrupting residue while arginine is positively charged and often involved in protein-DNA interactions, this substitution could significantly alter p53's DNA-binding affinity or protein stability. Previous studies have reported the association of this variant (commonly known as the *P72R* polymorphism) with differences in cancer susceptibility and apoptosis efficiency, supporting the notion that this variant has functional consequence (15, 19).

Evolutionary Conservation Analysis Using *WebLogo*

To evaluate whether the identified variants reside in evolutionarily constrained regions, we performed a sequence conservation analysis using the *WebLogo* server. The results indicated that none of the variant positions were located within highly conserved regions across mammalian species (Figure 2). This suggests that these loci may be under relaxed selective pressure, allowing for genetic variation without severely disrupting essential protein functions. However, the lack of conservation does not necessarily rule out functional significance, as some regulatory or structural variants may still influence phenotype in a species-specific manner.

Transcriptional Regulation Alteration at rs2287499

A particularly intriguing finding emerged from the analysis of the rs2287499 variant, located in the promoter region of *TP53*. Using the *PROMO* transcription factor binding prediction tool, we discovered that the alternative allele (G) creates a stronger binding site for the glucocorticoid receptor-α (GR-α, T00337), a key regulator of stress response and cell proliferation (Figure 3). Since GR-α is known to modulate gene expression in response to hormonal signals, this allelic variation

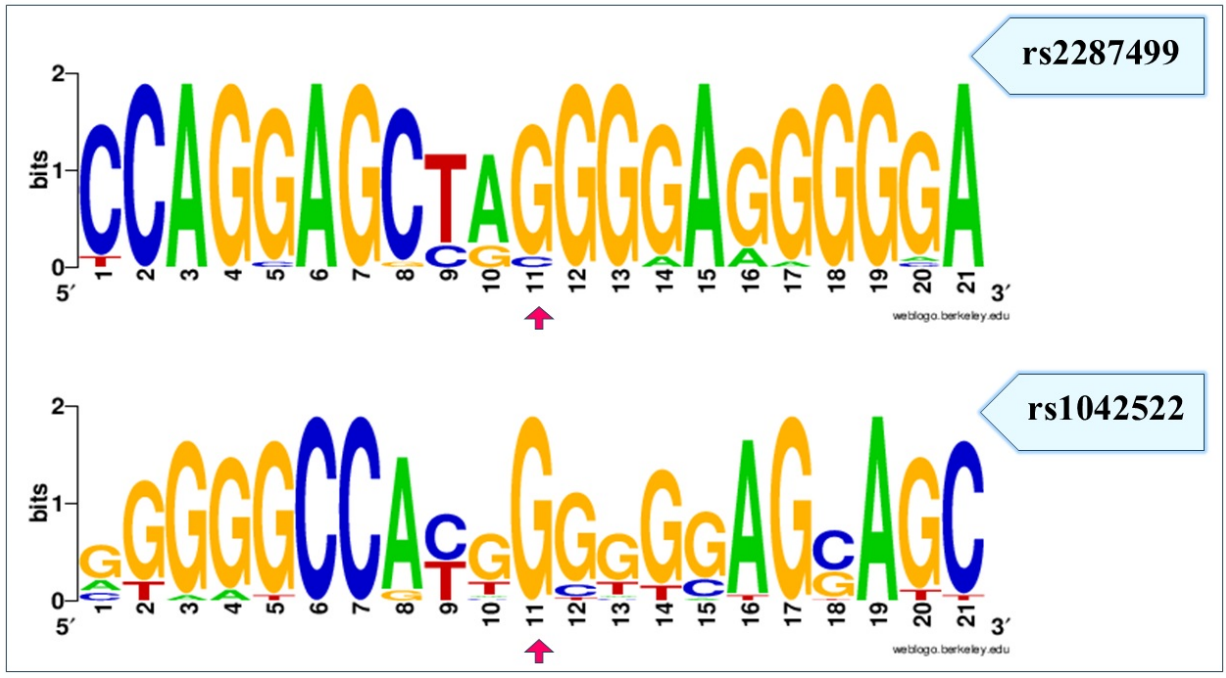

Figure 2. Schematic representation of DNA sequence conservation using the WebLogo tool around rs1042522 and rs2287499 TP53 SNPs locus. Pink arrow shows the position of locus variations in humans and wild allele conservation among mammalian species. Smaller and more varied nucleotides have less conservation.

Input sequence: CAGGAGCTACGGGAGGGGG

Reference allele : C

PROMO predictions detail:

Color	Factor name	Start position	End position	Dissimilarity	String	RE equally	RE query
1	GR-alpha [T00337]	11	15	8.281568	GGAGG	0.07422	0.39189
2	TFII-I [T00824]	11	16	11.337888	GGAGGG	0.02319	0.19712
3	MAZ [T00490]	6	18	11.158034	CTACGGGAGGGGG	0.00005	0.00027

Input sequence: CAGGAGCTAGGGGAGGGGG

Alternative allele : G

PROMO predictions detail:

Color	Factor name	Start position	End position	Dissimilarity	String	RE equally	RE query
1	GR-alpha [T00337]	6	10	8.073878	CTAGG	0.07422	0.09625
	GR-alpha [T00337]	11	15	8.281568	GGAGG	0.07422	0.49567
2	TFII-I [T00824]	11	16	11.337888	GGAGGG	0.02319	0.26947
3	MAZ [T00490]	6	18	5.568003	CTAGGGGAGGGGG	0.00004	0.00786

Figure 3. TFBS prediction at rs2287499 in the *TP53* gene promoter. The Random Expectation (RE) gives the number of expected occurrences of the match in a random sequence of the same length as the query sequence based on the dissimilarity index. Data is achievable through http://factor.genexplain.com/cgi-bin/transfac_factor/search.cgi *via* inserting the transcription factor ID. TFBS, transcription factor binding site; GR-α, glucocorticoid receptor α; TFII-I, Transcription factor II-I; MAZ, MYC associated zinc finger protein.

suggests that individuals carrying the G allele may exhibit enhanced *TP53* transcriptional activity under conditions where GR-α is activated (e.g., glucocorticoid exposure). Given that *p53* is a critical tumor suppressor, this regulatory change could influence cancer risk, therapy response, or stress-induced apoptosis.

Discussion

The rs1042522, also known as *TP53* codon 72 polymorphism, is a SNP found within the *TP53* gene. It plays a critical role in tumor suppression (19). This polymorphism occurs where a guanine (G) or cytosine (C) is present at codon 72, leading to amino acid substitutions: arginine (Arg) for G and proline (Pro) for C. This SNP has been extensively studied for its associations with various cancers and other diseases (20, 21). The different amino acids produced by rs1042522 (Arg vs. Pro) may influence the protein's interaction with other cellular proteins, its stability, and its ability to induce apoptosis. Studies indicate that the Arg variant might enhance the apoptotic response and DNA damage repair, suggesting a more effective tumor suppression role than the Pro variant (22). In this study, we found that the substitution from proline to arginine at position 72 in the *TP53* protein resulted in a relatively noticeable structural change. This missense mutation occurs in rare cases but alters protein interactions when it occurs. The polypeptide backbone is not affected, but the side chains of the two amino acids are distinct. Hydrophobicity and charge are unique to each amino acid. Mutated and wild-type proteins exhibit differences in these characteristics. The wild amino acid is smaller than the altered residue, influencing its interaction with other molecules. It is found in the turn structure that the amino acid number 72 appears (Figure 1). The study found that it can naturally engage with proteins that regulate the expression of protein arginine methyltransferase 1 (*PRMT1*) (23) and cell cycle and apoptosis regulator 2 (*CCAR2*) (24) genes. The *VMD* study showed that the 17p13.1 missense change could change the secondary structure and characteristics of the *TP53* protein. This change affects *PRMT1* and *CCAR2*, which regulate cell proliferation (25). Restelli et al. claim that knocking out *CCAR2* directly affects the activation of serine/threonine kinase Akt (26); however, normal human cells do not support these findings. Recent research found that negative Akt signaling pathway modulation enhances *PCOS* granulosa cell death risk (27). Another investigation by Song et al. revealed that reduced Akt-mTOR signaling may cause *PCOS* (28). Asymmetric dimethylarginine (ADMA) affects PCOS women's metabolic and endocrine systems. Oxidative stress can increase ADMA levels by decreasing dimethylaminohydrolase (DDAH) activity and raising PRMT1 activity, which play a role in ADMA synthesis. The same methyltransferase that operates on meiotic recombination 11 (MRE11) is PRMT1, which methylates arginine at the glycine arginine-rich (GAR) motif of TP53BP1. Due to 53BP1 recruitment to double-strand DNA breaks and the creation of unique nuclear foci, oxidative stress-exposed cells identify and repair these damages early (29). In vitro studies of the DDAH and PRMT1 enzymes have shown that redox-sensitive mechanisms regulate ADMA levels (30). Changing ADMA levels in ovarian cells is a notion that needs more research.

Our *in-silico* analysis showed that the promoter allele polymorphism (in alternative allele G) enhances the gene's factor site for GR-α. Thus, the *TP53* gene is likely more regulated. This means that the presence of the G allele could provide the basis for GR-α effect. We believe that this variant of the *TP53* gene can potentially change *PCOS* symptoms. TP53 is involved in the regulation of ovarian follicular development and atresia (the process of degeneration of ovarian follicles) (31). Overexpression of TP53 could lead to increased apoptosis of ovarian follicles, potentially contributing to the formation of cysts and affecting ovulatory function (32). Corticosteroid resistance is heavily influenced by the glucocorticoid receptor α isoform. Through modifying corticosteroid signaling pathway protein expression and activity, inflammatory cytokines reduce steroid sensitivity. Steroid-mediated anti-inflammatory effect depends on GR expression and activation. GR requires HSP90 to prevent protein degradation. HSP90 is released when GR binds to the corticosteroid to mature and bind to the glucocorticoid response element (GRE) (33). GR-α is prevalent in the cytoplasm and up-regulates IKB-α and directly binds to NF-kappaB to prevent its activation. The upregulation of histone acetyltransferase (HAT) and creation of NF-kB/HAT complexes cause inflammation. After activation by ligand hormones, GR-α increases HDAC2 recruitment to the protein complex to decrease NF-kB/HAT complex formation and deacetylate histones in the promoter area of important pro-inflammatory cytokines (33). The relationship between GR-α and *PCOS* involves several complex biological mechanisms, as both hormones and transcription factors play significant roles in the regulation of ovarian function and metabolic pathways (34). Glucocorticoids influence ovarian function, affecting steroidogenesis and ovarian follicle development (35). Disruption of normal glucocorticoid signaling may contribute to *PCOS*'s abnormal hormonal profiles, such as elevated androgens. Many women with *PCOS* exhibit insulin resistance, which is associated with dysregulation of GR-α. Insulin can influence glucocorticoid signaling, leading to altered GR activity and further contributing to the hormonal imbalance's characteristic of the syndrome (36).

PCOS women often experience inflammation and stress (9). The GR-α pathway modulates inflammatory responses, and aberrations in this signaling may contribute to *PCOS* pathology. Understanding the role of GR-α in *PCOS* might open new avenues for targeted therapies. Modulating glucocorticoid activity or improving insulin sensitivity could alleviate some *PCOS* symptoms. Some studies suggest that alterations in GR-α expression or function may be associated with *PCOS* symptoms severity (36). Further research is ongoing to delineate the exact molecular mechanisms linking GR-α to *PCOS* pathophysiology. In summary,

GR-α likely plays a role in the etiology and symptoms of PCOS through its influence on ovarian steroidogenesis, insulin action, and inflammatory processes.

Although research is ongoing to better understand the precise role of *TP53* in *PCOS*, it's critical to note that it is likely just one piece of the larger puzzle. The interplay between various genes, hormones, environmental factors, and lifestyle issues complicates *PCOS* understanding, and further studies are needed to clarify how *TP53* and other molecular pathways contribute to this condition. Considering the high importance of *TP53*'s role in many diseases, it especially requires a comprehensive investigation from molecular and bioinformatics angles. This investigation should also include its effect on signaling processes and cell cycle.

In summary, the *in-silico* analysis of the association effects of the rs2287499 and rs1042522 variants on the expression and folding of the *TP53* protein enhances our understanding of the molecular mechanisms underlying *PCOS*. The findings suggest that these genetic variants may significantly influence the stability and functionality of *TP53* protein. This protein is a key regulator of cellular stress responses and reproductive functions. By elucidating the relationship between these variants and *TP53* dysregulation, this study provides valuable insights into how genetic predispositions can contribute to the pathogenic mechanisms of *PCOS*. Future research, integrating in vitro and clinical studies, will be essential to validate these *in-silico* observations and to further explore the therapeutic implications of modulating *TP53* activity in the context of *PCOS*.

Authors Contribution

MS-A, HS and **MM** designed the study; **MS-A**, **HS**, **MM**, **RA**, **RS**, **MZ** and **KS** wrote the manuscript; **MM**, **HS** and **RS** revised the manuscript; **HS** and **MM** supervised the project. All authors read and consented to the last version of the article.

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Conflict of Interest

The authors declared that they have no conflict of interest.

Ethical Approval

The ethics committee of Zahedan University of Medical Sciences authorized the study protocol (ethical code: IR.ZAUMS.REC.1402.434).

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