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Genetic Characterization of Joubert Syndrome with COACH Features and in Silico Prediction of *TMEM67* Gene Variants Based on Iranome Database

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Abstract

Background: Joubert syndrome (JS) is an uncommon genetic condition presenting with diverse clinical manifestations involving the nervous system, liver, and eyes. A specific form of JS, known as cerebellar vermis hypoplasia, oligophrenia, ataxia, coloboma, and hepatic fibrosis (COACH) syndrome, is primarily associated with variants in the *TMEM67* gene. This study aimed to identify the causative genetic variant in a patient with JS exhibiting the COACH phenotype and to investigate the spectrum and potential founder effects of *TMEM67* gene variants within the Iranian population using the Iranome database

Methods: This study reports an 8-year-old girl with a family history of developmental delay who shows clinical features typical of JS with the COACH phenotype. To verify the disease-causing nature of the genetic variant, whole exome sequencing along with in silico analysis was conducted. The variant's conservation across species highlighted its functional significance, and a co-segregation study confirmed its inheritance pattern. Moreover, we collected all *TMEM67* gene variants identified in the Iranome project.

Results: Our investigation revealed a homozygous missense variant in *TMEM67* (c.725A>G; p.Asn242Ser) in the affected individual. Collective evidence from the Iranome database and previous studies demonstrates that this is a founder variant (c.725A>G) in the Iranian population.

Conclusion: This study highlights the intricate nature of JS and its genetic foundations, emphasizing the significance of founder variants in specific populations and the potential of national databases to enhance the precision of genetic diagnoses.

Keywords: Joubert Syndrome, *TMEM67*, Whole exome sequencing, Iranian population

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Introduction

Joubert syndrome (JS), an uncommon genetic disorder, presents a multifaceted clinical profile (1). Clinically, JS is defined by a characteristic mid-hindbrain malformation known as the "molar tooth sign" on neuroimaging, accompanied by hypotonia, developmental delay, abnormal ocular movements, and, in some cases, multiorgan involvement. JS belongs to a broader spectrum of JS and related disorders (JSRD), which are genetically and phenotypically heterogeneous, caused by defects in genes that affect the structure and function of primary cilia (2).

COACH syndrome is considered a distinct subtype within the JSRD spectrum and is defined by the associa-

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Key messages:

↑What is "already known" in this topic:

The *TMEM67* gene is among the most frequently implicated loci in Joubert syndrome, particularly in patients exhibiting COACH syndrome features (cerebellar vermis hypoplasia, oligophrenia, ataxia, coloboma, and hepatic fibrosis). The c.725A>G (p.Asn242Ser) variant has been documented in several Iranian families, indicating a potential founder effect in this population.

→What this article adds:

This study confirms the pathogenicity and founder nature of *TMEM67* c.725A>G in Iranian patients with COACH features. By integrating case findings with Iranome data, it emphasizes the role of national genomic resources in guiding targeted diagnostics, carrier screening, and genetic counseling in high-consanguinity populations.

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tion of cerebellar vermis hypoplasia, oligophrenia, ataxia, coloboma, and hepatic fibrosis (3). Although the neurological hallmark, the molar tooth sign, is shared with other JSRD subtypes, COACH syndrome is uniquely characterized by the frequent coexistence of ocular coloboma and congenital hepatic fibrosis, which can progress to portal hypertension and liver failure. This specific combination of features makes early recognition essential for prognosis and management (4).

Most of the time, COACH syndrome is caused by a variant in the *TMEM67* gene (5). The *TMEM67* gene is on 8q22.1 and makes a protein that has 955 amino acids and goes through the cell membrane seven times (6). The protein encoded by the *TMEM67* gene plays a crucial role in the proper functioning of cilia, which are essential hair-like structures in many cells. Variants in this gene are linked to several genetic disorders, including JS, Bardet-Biedl syndrome (BBS), and certain forms of Meckel syndrome (MKS) (7).

The genetic variants most frequently implicated in JS occur in genes essential for the formation and function of cellular cilia, the hair-like organelles present on the cell surface. Impairment of ciliary function is a central pathogenic mechanism underlying JSRD (8). Some of the genes frequently implicated in JS and JSRD include *AHI1*, *CC2D2A*, *CEP290*, *TMEM67*, *RPGRIP1L*, *INPP5E*, *TMEM138*, *KIF7*, *TCTN1*, and *TCTN2* (9).

In this study, we described a patient with a familial history of developmental delay who carried a homozygous pathogenic *TMEM67* variant (c.725A>G; p.Asn242Ser). The patient's clinical manifestations—including the molar tooth sign, hypotonia, developmental delay, hepatomegaly, thrombocytopenia, and ocular anomalies—were consistent with a diagnosis of JS exhibiting the COACH phenotype. Furthermore, in silico prediction tools were applied to assess the likely pathogenicity of *TMEM67* variants reported in the Iranome database.

Methods

Patient

In this study, we investigated an 8-year-old female patient born to consanguineous parents (Figure 1A). Before participation, informed consent was obtained, and peripheral blood samples were collected for genetic analysis. For this purpose, 5 to 10 mL of blood was drawn into ethylenediaminetetraacetic acid-containing tubes.

DNA Extraction

Genomic deoxyribonucleic acid (DNA) was extracted from peripheral blood mononuclear cells utilizing the Kowsar extraction kit. The quantity and quality of the extracted DNA were measured using a Nanodrop spectrophotometer. Sequencing studies were performed on DNA derived from whole blood specimens.

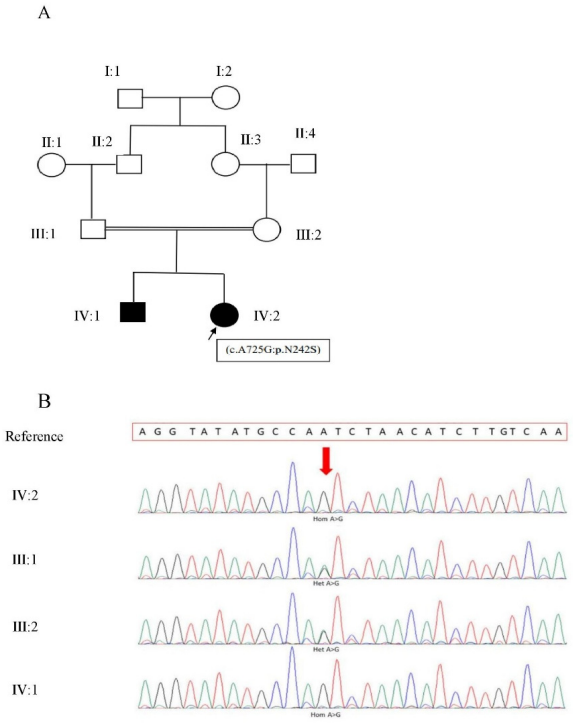

Figure 1. A) A family pedigree analysis of Joubert syndrome identified a homozygous TMEM67 variant in the proband and her brother, whereas both parents were confirmed to be heterozygous carriers. *B)* Sanger sequencing further demonstrated that the proband and her brother carried the TMEM67 c.725A>G (p.Asn242Ser) variant in the homozygous state. At the same time, both parents possessed the same variant in the heterozygous form.

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Whole Exome Sequencing

High-quality genomic DNA was randomly fragmented into 150 to 200 bp pieces using Covaris technology. These fragments were ligated to sequencing adapters, purified, and then amplified using ligation-mediated polymerase chain reaction (LM-PCR). Target enrichment was performed by hybridizing adapter-ligated DNA to SureSelect biotinylated RNA probes, followed by capture with streptavidin-coated beads and washing to remove nontarget sequences. LM-PCR products were assessed for quality using an Agilent Bioanalyzer. Enriched libraries were sequenced on an Illumina HiSeq 2000 platform to generate paired-end reads, with base calling performed by Illumina software. Adapter sequences and low-quality reads were removed from the raw data to produce clean reads for subsequent bioinformatics processing. The sequencing reads were mapped to the human reference genome (GRCh38) using the Burrows–Wheeler Aligner (BWA). Aligned reads were then sorted, assigned read groups, and marked for duplicates using Picard tools, producing final BAM files for downstream variant calling with the Genome Analysis Toolkit (GATK). This step enabled the identification of both single-nucleotide variants and small insertions or deletions (indels). Variant filtering was performed according to GATK best practices and further processed through the PalinVar workflow to retain variants of potential clinical relevance. Variant filtering was applied to keep only rare exonic or splice-site variants. Specifically, we selected those with a minor allele frequency (MAF) of <1% in databases and excluded any previously documented as benign. The selected variants were subsequently annotated and assessed for pathogenic potential in accordance with the American College of Medical Genetics and Genomics (ACMG) guidelines (10).

In Silico Analysis of Variants

To validate variant pathogenicity, multiple tools were employed, including SIFT, CADD, Mutation Taster, Polyphen-2, MetalR, and FATHMM (11-16).

Conservation Analysis

The evolutionary conservation of the *TMEM67* protein sequence was examined using ClustalX software and the MetaDome online tool. *TMEM67* amino acid sequences were obtained from the UniProt database and aligned with ClustalX to conduct multiple sequence comparisons. The alignment included sequences from several species. This analysis aimed to determine conserved residues within the *TMEM67* protein across species. Additionally, MetaDome was employed to identify regions of the *TMEM67* protein that are intolerant to variation (17).

Sequencing and Co-segregation Study

Sanger sequencing was employed to confirm the presence of the variant in the parents. The regions containing the variants were amplified using forward and reverse primers designed with Oligo 7 software. Following this, the sequence chromatograms were examined utilizing the Codon Code Aligner to assess the outcomes.

In Silico Prediction of TMEM67 Gene Variants in the Iranian Population

The Iranome database has documented genetic variations from 800 healthy individuals representing 8 primary ethnic groups in Iran (http://www.iranome.ir) (18). Each ethnic group comprises 100 individuals. All Iranian *TMEM67* gene variations were extracted using the Iranome project. Six prediction instruments were employed, namely, MetalR and SIFT (both accessible at: http://prove an.jcvi.org/index.php), Polyphen-2 (http://genetics.bwh. harvard.edu/pph2/), CADD (https://cadd.gs.washington.edu/), Mutation Taster (http://www.mutationtaster.org/), FATHMM (https://fathmm.biocompute.org.uk/), and Polyphen-2 (http://genetics.bwh. harvard.edu/pph2/). The final classification of variants would be as follows, based on the ACMG.

Results

Clinical Finding

A healthy Iranian couple who are consanguineous had a second affected child, the 8-year-old proband. The proband's developmental impairments began at 2 months of age when she refused to use her eyes to follow her toys. Later observations included balance issues, learning impairments, motor developmental delay, and seizures. The patient presented with hepatic symptoms, altered eyesight, and delayed psychomotor development. The symptoms are the same in the proband brother. After being referred to genetics, the proband underwent a comprehensive genetic evaluation, which confirmed the diagnosis of JS. Although *TMEM67* variants are also associated with BBS and MKS, our patient exhibited no clinical features characteristic of either disorder. Based on the clinical presentation, neuroimaging findings, and hepatic involvement, the phenotype was most consistent with JS with COACH features.

Genetic Testing

A pediatric neurologist made the initial diagnosis, and whole exome sequencing (WES) was used to identify genetic variations. Four steps were involved in the WES data analysis: Removal of benign variants (19). Removal of synonymous variants, elimination of variants with minor allele frequency below 0.001, and retention of homozygous variants are the first 4 steps in the process. Ultimately, a homozygous variant associated with the variant causing JS was identified in *TMEM67*: c.725 A>G (p.Asn242Ser).

In Silico Analysis of Pathogenicity

The MAF of variation c.725 A > G is <0.01. It was previously documented in patients with JS, and in silico prediction indicated that it might be harmful. According to ACMG, this variation is classified as pathogenic. The findings of in silico tools are shown in Table 1.

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Table 1. Genetic Landscape of the TMEM67 Gene Within the Iranome Database

Protein Consequence	Transcript Consequence	Annotation	Exon Number	Allele Count	Allele Number	Number of Homozygotes	Number of Heterozygotes	Allele Frequency
p.Val749Argfs	c.2229_2230insGGAATTATACAGGTAA	frameshift	21	1	1600	0	1	0.0006
p.Ala10Val	c.29C>T	missense	1	1	1598	0	1	0.0006
p.Gly75Val	c.224G>T	missense	2	1	1448	0	1	0.0006
p.Pro93Ser	c.277C>T	missense	2	3	1592	1	1	0.00188
p.Asn158Ser	c.473A>G	missense	4	1	1600	0	1	0.0006
p.Asn242Ser	c.725A>G	missense	8	2	1600	0	2	0.0012
p.Asp261Asn	c.781G>A	missense	8	52	1600	0	52	0.0325
p.Lys331Gln	c.991A>C	missense	10	5	1598	0	5	0.0031
p.Pro476Ser	c.1426C>T	missense	14	2	1600	0	2	0.0012
p.Ala500Val	c.1499C>T	missense	14	1	1600	0	1	0.0006
p.Thr559Arg	c.1676C>G	missense	17	1	1600	0	1	0.0006
p.Ile604Val	c.1810A>G	missense	18	1010	1600	320	370	0.6312
p.Thr670Ile	c.2009C>T	missense	20	5	1600	0	5	0.0031
p.Pro721Ser	c.2161C>T	missense	21	1	1600	0	1	0.0006
p.Arg975Gly	c.2923C>G	missense	28	1	1590	0	1	0.0006
	c.224-1G>T	splice acceptor	2	1	1446	0	1	0.0006
-	c.1066-3C>T	splice region	11	979	1600	301	377	0.6119
-	c.2440-6T>C	splice region	24	1	1600	0	1	0.0006
-	c.2661+3A>G	splice region	25	1	1600	0	1	0.0006

Conservation of Amino Acids

The *TMEM67* protein sequence was subjected to multiple sequence alignments across numerous species using ClustalX. The acquired results showed that the point of variation, amino acid 242 (asparagine; N), was substantially conserved in all other species. Based on this research, the residue is essential to the protein's development and functionality. The results are highlighted in Figures 2 (A and B). Notably, MetaDome has classified the impacted, highly conserved asparagine as limited and marginally intolerant to change (Figure 2C).

Co-segregation Study

The segregation of the identified variant was confirmed by Sanger sequencing of the proband and her family members. The analysis revealed that both parents were heterozygous carriers, whereas the proband and her brother were homozygous carriers of the variant (Figure 1B).

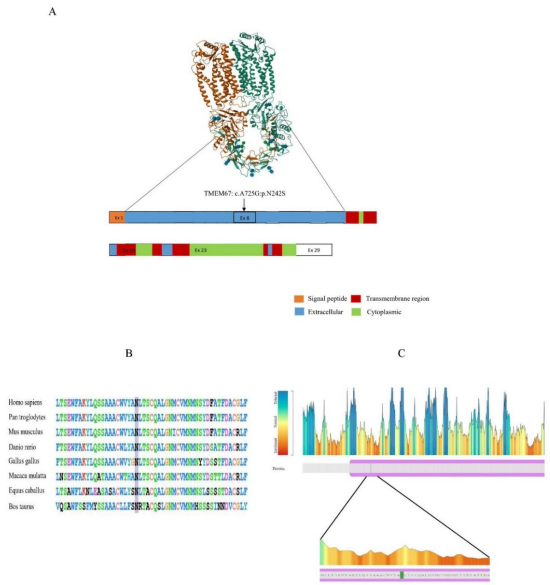

Figure 2. A) Three-dimensional structure and domain organization of the TMEM67 protein. The upper panel shows a ribbon diagram of TMEM67 with its multi-pass transmembrane topology, illustrating the protein's extracellular (blue), cytoplasmic (green), and transmembrane (red) regions, as well as the signal peptide (orange). The lower schematic highlights the exon structure (Ex 1–Ex 29) and indicates the position of the c.725A>G (p.Asn242Ser) variant in exon 8 (arrow). *B)* Evolutionary conservation analysis of p.Asn242Ser variant on TMEM67 using ClustalX. C) MetaDome analysis for the TMEM67 gene. The tolerance landscape illustrates the areas of the TMEM67 genes. The blue bars represent regions of tolerance, whereas the red bars indicate regions of intolerance.

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Table 2. Results of In Silico Analysis

Protein Consequence	Transcript Consequence	SIFT	Polyphen2	MutationTaster	FATHMM	MetalR	CADD score	ACMG
p.Val749Argfs	c.2229_2230insGGAATTATACAGGTAA	-	-	-	-	-	35	VUS
p.Ala10Val	c.29C>T	Tolerated	Benign	Tolerated	Damaging	Damaging	6.8	VUS
p.Gly75Val	c.224G>T	Damaging	Probably damaging	Damaging	Damaging	Damaging	26.7	VUS
p.Pro93Ser	c.277C>T	Tolerated	Benign	Damaging	Damaging	Tolerated	8.12	VUS
p.Asn158Ser	c.473A>G	Tolerated	Benign	Tolerated	Damaging	Damaging	0.001	VUS
p.Asn242Ser	c.725A>G	Damaging	Probably damaging	Damaging	Damaging	Damaging	26.1	Pathogenic
p.Asp261Asn	c.781G>A	Tolerated	Benign	Tolerated	Damaging	Tolerated	9.599	Benign
p.Lys331Gln	c.991A>C	Tolerated	Benign	Damaging	Damaging	Damaging	10.98	VUS
p.Pro476Ser	c.1426C>T	Tolerated	Benign	Damaging	Damaging	Tolerated	20.2	VUS
p.Ala500Val	c.1499C>T	Tolerated	Benign	Tolerated	Damaging	Damaging	5.69	VUS
p.Thr559Arg	c.1676C>G	Damaging	Probably damaging	Damaging	Damaging	Damaging	31	Likely Pathogenic
p.Ile604Val	c.1810A>G	Tolerated	Benign	Tolerated	Damaging	Tolerated	1.8	Benign
p.Thr670Ile	c.2009C>T	Damaging	Probably damaging	Damaging	Damaging	Damaging	28.3	VUS
p.Pro721Ser	c.2161C>T	Tolerated	Benign	Tolerated	Damaging	Tolerated	0.001	Benign
p.Arg975Gly	c.2923C>G	Damaging	Probably damaging	Damaging	Damaging	Damaging	34	VUS
-	c.224-1G>T	-	-	-	Damaging	-	25.3	VUS
-	c.1066-3C>T	-	-	-	-	-	8.06	Benign
-	c.2440-6T>C	-	-	-	-	-	9.67	Benign
-	c.2661+3A>G	-	-	-	-	-	16.21	VUS

Identifying and Validating TMEM67 Genetic Variants Through In Silico Approaches in the Iranian Population

The distribution of known variants may help predict when variants associated with specific clinical diseases are likely to arise. It is reasonable to suppose that the variants described in Iranome may also be present in related patients. Although it is a complex relationship, this one may be significant in predicting harmful variants. Identifying variations that may cause disease was the primary objective of our work. Through the analysis of these variants, targeted clinical validation studies can be directed toward exons exhibiting a heightened propensity for variants in the Iranian demographic population.

An analysis of the Iranome database revealed 14 missense variants, 4 splicing variants, and 1 frameshift variant in the *TMEM67* gene. A total of 14 missense variants were identified; 5 of them (c.224G>T; c.725A>G; c.1676C>G; c.2009C>T; c.2923C>G) had deleterious effects in 6 predictive tools (Table 1). Table 2 lists the ACMG criteria assigned to each variant. Pathogenicity was evaluated using 6 computational tools (SIFT, PolyPhen-2, MutationTaster, FATHMM, MetaLR, and CADD) that predict the likelihood that each variant disrupts protein structure or function. As a result, all variants were classified as benign or VUS, except c.725A>G and c.1676C>G, which were classified as pathogenic and potentially pathogenic, respectively. The 2 most common variations among the 5 that demonstrated harmful effects were c.2009C>T (0.003125) and c.725A>G (0.00125).

Discussion

The study employed advanced genetic analysis techniques, including WES, in silico analysis, and conservation studies, to pinpoint the pathogenic variant responsible for JS in the patient. The homozygous *TMEM67* variant c.725A>G (p.Asn242Ser) was identified as the likely causative variant. In silico tools further supported the pathogenicity of this variant, corroborating its association with JSRD. Additionally, the conservation analysis highlighted the importance of the affected amino acid in the *TMEM67* protein across various species, underscoring its functional significance.

JS, classified under JSRD, encompasses various subtypes based on associated organ-specific complications, each influenced by different genetic factors (20). The presented case highlights the complex nature of JS with COACH features, a rare genetic disorder impacting brain

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development and various organs (21). The patient exhibited a distinct combination of symptoms, including developmental delays, low blood platelets, liver enlargement, and eye defects, and was ultimately diagnosed with JS related to the *TMEM67* gene (22).

The genetic underpinnings of JS with COACH features are primarily associated with variants in the *TMEM67* gene (20). This gene encodes a protein crucial for the proper functioning of cilia, tiny hair-like structures in cells (23). Dysfunctional cilia lead to the diverse clinical manifestations observed in JSRD, including neurological, hepatic, and ocular issues (24). The complexity of the genetic landscape of JSRD is evident from the involvement of numerous genes, including *AHI1*, *CC2D2A*, *CEP290*, and others (25).

The c.725A>G variant was identified as a founder variant in the Iranian population, suggesting it may be a common cause of JS in this population. According to the study, genetic testing for JS in Iranian patients should consider this variant. To develop specific genetic tests for a given population, identifying founder variants is crucial (26, 27). The study highlights the viability of population-specific community genetics programs and the importance of population history in medical genetics. A total of 22 of the affected members have the *TMEM67* (c.725A>G) variant in Iran. Neurodevelopmental delay, aberrant eye movements, and the "molar tooth" sign on brain magnetic resonance imaging were the most frequently observed characteristics in affected individuals. Furthermore, certain patients had varying factors, such as kidney illness, seizures, liver disease, aberrant behavior, and failure to thrive.

Moreover, the study analyzes *TMEM67* gene variants in the Iranian population using the Iranome database. This approach facilitates the prediction of potential disease-causing variants in the Iranian context. By identifying these variants, further clinical validation studies can be tailored to investigate the exons with a higher likelihood of variants. This demonstrates the importance of population-specific genetic research in enhancing the precision of genetic diagnostics and developing healthcare that considers local genetic variations. Recognition of founder variants is crucial for improving the efficiency of genetic testing, particularly in populations with a high prevalence of consanguinity, where targeted variant screening can reduce both diagnostic time and costs (28).

Our in silico evaluation of 19 *TMEM67* variants in the Iranome dataset identified five with predicted deleterious effects, 2 of which, c.725A>G and c.1676C>G, were classified as pathogenic or likely pathogenic. To prevent misdiagnosing JS in Iranian clinical laboratories, consideration should be given to the potential co-inheritance of *TMEM67* gene variations (27).

Overall, our results confirm and extend previous observations regarding the pathogenicity of p.Asn242Ser and its significance as a recurrent, likely founder variant in the Iranian population. For JS in Iran, the recurrent c.725A>G variant should be considered a primary diagnostic target, with implications for carrier screening, genetic counseling, and public health policy in communities with high rates of consanguinity.

Conclusion

This study illustrates the intricate genetic and clinical landscape of JS with COACH features. The discovery of a pathogenic *TMEM67* variant in the patient sheds light on the genetic basis of the disease. The availability of national databases should be viewed as a valuable opportunity, considering the high cost of molecular diagnostics and its critical necessity for many patients. Health policymakers creating community genetic programs and physicians working on uncommon genetic disorders, especially in Iranian populations, should pay particular attention to the c.725A>G variant since it is a founder effect in Iran. Therefore, the c.725A>G variant in TMEM67 represents a primary diagnostic target for JS in Iran. Incorporation of this variant into clinical genetic testing strategies may improve diagnostic yield, shorten turnaround time, reduce costs, and facilitate more effective genetic counseling and family management.

Acknowledgment

N/A.

Conflict of Interests

The authors declare that they have no competing interests.

Authors' Contributions

S.S.H., M.A.B.H., V.T., P.H., S.E.D., and S.Z. were responsible for the study's conception and design. Data acquisition was carried out by M.A.B.H., S.S., M.S., M.S.K., and R.R. The analysis and interpretation of data were performed by V.T., M.H., A.T.N., H.A., A.A., S.Z., and K.N.K. S.S.H., M.A.B.H., and V.T. drafted the manuscript. S.Z. and K.N.K. critically revised it for important intellectual content. All authors read and approved the final manuscript.

Ethical Considerations

This research received approval from the local ethics committee at Mashhad University of Medical Sciences. Written informed consent was secured from all participants involved in the study.

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Data Availability

The datasets used in this study can be obtained from the corresponding author upon reasonable request.

AI Use Statement

The authors declare that no generative artificial intelligence (AI) tools were used for data analysis or interpretation. AI-assisted language editing tools were used only to improve grammar and readability.

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