Original Article

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Identification of a Pathogenic Mutation in *GMPPB* Gene Through Whole Exome Sequencing in Two Consanguineous Families with Limb-Girdle Muscular Dystrophy

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ABSTRACT

Background & Objective: Dystroglycanopathies represent heterogeneous clinical and genetic disorders typically characterized by weakness of the limb muscle. Pathogenic mutations in the *GMPPB* gene (OMIM # 615320) have been identified in various syndromes, including CMD, LGMD, and CMS. In this present study, our aim is to elucidate the presence of pathogenic mutation in two consanguineous Iranian families affected by LGMD2T.

Materials & Methods: Two families with affected children diagnosed with LGMD2T were recruited in the study. Comprehensive clinical examinations were performed by an expert neurologist on the proband and their respective families. Whole-exome sequencing (WES) was performed on genomic DNA extracted from peripheral blood mononuclear cells. Subsequently, candidate variants were identified using a bioinformatics pipeline, and familial co-segregation was confirmed through sanger sequencing.

Results: The present study is focused on two families whose identified variants are confirmed. Our findings revealed a heterozygous missense mutation in the GMPPB gene (NM_021971.4, c.308C>T (p. Pro103Leu) that entirely segregated from the observed phenotypes within his family. This variant was not identified in either the Exome Aggregation Consortium or the 1000 Genomes Project.

Conclusion: The present findings contribute to the expansion of genetic data for Iranian individuals affected by LGMD2T. This data can be instrumental in enhancing screening, diagnosis, and interpretation within families with a history of this disease.

Keywords: Dystroglycanopathy, Guanosine diphosphate-mannose pyrophosphorylase-B coding, Limb-girdle muscular dystrophy, Muscular Dystrophies, Whole exome sequencing

Introduction

Dystroglycanopathy encompasses a set of muscular dystrophies resulting from abnormal glycosylation of alpha-dystroglycan, structural membrane protein located in the sarcolemma. Consequently, the protein loses its capacity to bind to laminin **(1–3)**. Dystroglycanopathies span a spectrum of disorders, ranging from severe congenital muscular dystrophy (CMD) with associated brain and eye abnormalities to milder phenotypes, including muscular limb-girdle dystrophy **(4,5)**. Dystroglycopathies are classified into

three groups; the first directly impacts the dystroglycan gene, known as primary dystroglycanopathies; the second modifies dystroglycan through glycosyltransferases, essential for effective glycosylation of α-DG termed secondary dystroglycanopathies; and tertiary dystroglycanopathies indirectly influence dystroglycan function through gene mutations **(6).** Secondary dystroglycanopathies manifest in various forms. Limb-Girdle muscular dystrophy, for instance, tends to be mild, whereas Walker-Warburg syndrome is characterized by a more severe presentation **(7,8)**. Limb-Girdle Muscular Dystrophy (LGMD) represents a diverse set of muscular disorders marked progressive weakness, dysfunction, and atrophy in the shoulder and pelvic girdles. **(9)**. In 2013, new mutations associated with LGMD were detected in guanosine diphosphate-mannose pyrophosphorylase-B (GMPPB) coding gene (*GMPPB*). Consequently, the LGMDT2 subtype was characterized **(10)**. The *GMPPB* gene is mapped on chromosome 3p21, encoding GMPPB protein, and plays a crucial role in the glycosylation of proteins, including alpha-dystroglycan as well as lipids **(11).** Mutations in the *GMPPB* gene result in a-DG hypoglycosylation, leading to cerebral and ocular CMD phenotypes. This can be associated with severe mental disabilities, epilepsy, or mild cognitive impairment **(4,10,12–14).** To date, studies have documented mutations in the *GMPPB* gene in at least 72 patients **(15)**. The most common *GMPPB* gene variants, c.79G>C p.(Asp27His) and c.860G>A p.(Arg287Gln), are prevalent in the Caucasian population and are linked to various phenotypes, including CMD, LGMD, congenital myasthenic syndrome (CMS), muscular dystrophy-dystroglycanopathy (MDDG), rhabdomyolysis, and epilepsy **(4,10,12,16–18)** . In this context, the comprehensive screening of the entire coding region can be efficiently achieved through whole-exome sequencing (WES), particularly in families and genetically heterogeneous populations. One advantage of WES compared to panel sequencing and whole genome sequencing is its cost-effectiveness. Another benefit is the identification of novel mutations for diagnosing complex diseases, particularly those ruling out differential diagnoses. Last but not least, the annotation of exome sequencing is more feasible compared to other sequencing methods. Therefore, the present study aims to investigate the existence of genetic variants and mutations in two consanguineous Iranian families affected by LGMD2T within the South Khorasan province.

Materials and Methods

Clinical evaluation

Expert neurologists conducted examinations on the three patients (with II.2, III.7 and III.8) who had medical and family histories of LGMD. Electromyography (EMG) data were collected as part of the evaluation. Additionally, biochemical analyses, including the measurement of serum levels of creatine kinase (CK) and liver enzymes include LDH (Lactate dehydrogenase), AST(Aspartate aminotransferase), and ALT(Alanine transaminase) were performed for all patients.

Sample preparation and data analysis

Blood samples were collected from the proband and other family members. Genomic DNA was extracted from peripheral blood mononuclear cells (PBMCs) using standard procedures. DNA quality was assessed through qualitative methods (gel electrophoresis) and quantitative method (Nano drop). In family I, the entire genome of the proband (Patient II.2) was sequenced using the Illumina sequencing machine which handled sample clustering and sequencing. Then, raw data were processed into FASTQ files and aligned to the reference genome. variant call format and binary alignment map (BAM) files were generated for variant identification. Functional annotation and frequency analysis of variations were conducted using the online tool wANNOVAR **(1)**. Variants with allele frequencies less than 1% in the dbSNP, 1000 Genomes Project, Exome Sequencing Project (ESP), ExAC and gnomAD data set were excluded **(2)**. Non-functional variants among intronic mutations were excluded. Various bioinformatics tools and genomic databases, including Franklin (), VarSome (https://varsome.com), and ClinVar (www.ncbi.nlm.nih.gov/ClinVar), were utilized to predict the deleterious effects of the identified sequence. According information from OMIM, Human Phenotype Ontology (HPO), Orphanet, GeneCards, and PubMed databases, the variant was deemed consistent with the probable pathogenicity and hereditary pattern of this disease and it was considered autosomal recessive.

Sanger sequencing and family segregation analysis

The National Center for Biotechnology Information (NCBI) data bank was utilized to obtain candidate-related sequencing data for the *GMPPB* gene. Subsequently, using Primer3 software, specific forward (5′- CCCATCCTGGTAGAACCTGAC -3′) and reverse (5′- CTGCACAGCTCTGTATCCATAAC -3′) primers were designed, and validated through OLIGO version 7 software. Following primer design, a polymerase chain reaction was performed, and agarose gel electrophoresis was employed to visualize the targeted DNA band. To validate the WES results, sanger sequencing was carried out on both the proband and family members.

Results

Clinical tests

Family I-Patient II.2

The proband, a 45-year-old man, had experienced progressive muscle weakness and atrophy over the past 15 years, resulting in paralysis of both legs. The muscle weakness was so severe that he required assistance for sitting, standing and walking. Cognitive evaluation of the proband indicated normal intellectual function. He experiences weakness and hypotonia throughout his entire body. Electromyography revealed myogenic damage in the proband. No skeletal abnormalities were detected in the examination. Additionally, the proband (II.2) appeared have a slight spine curvature or scoliosis. He had five children (three girls and two boys) who did not exhibit any issues with their appearance or walking (**Figure 1)**.

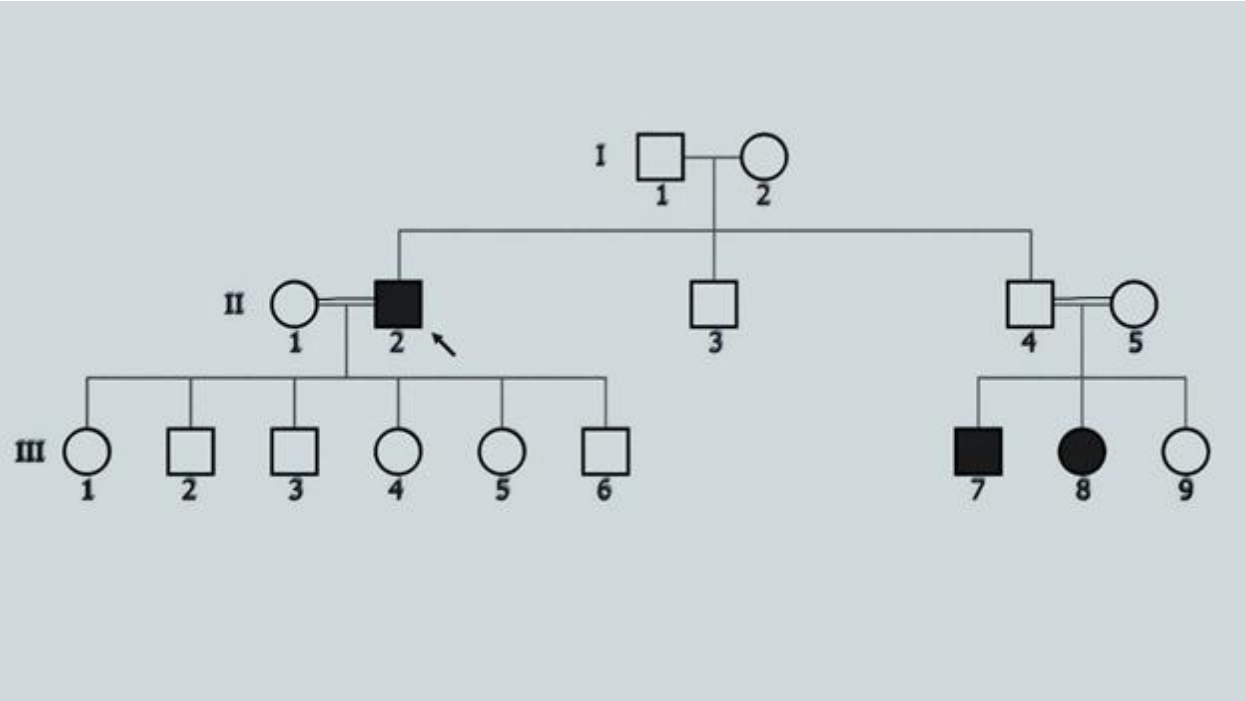

Figure 1. Pedigree of the family with Limb-girdle muscular dystrophy. Squares defined a man, and circles defined a woman. An arrow indicates the proband. The patients are shown with II.2, III.7 and III.8. A dot within the symbol illustrates carrier status for *GMPPB* mutations.

Family II- Patient III.7

Patient III.7, a thirty-year-old male, started experiencing symptoms after the age of 16. He reported difficulty swallowing, mild slight eye pain and exhibited an abnormal spinal curvature. the individual is currently dealing with generalized hypotonia and weakness.

Family II- Patient III.8

Patient III.8, a thirty-eight-year-old female, exhibited motor development retardation, weakness when climbing stairs, and symptoms of respiratory insufficiency that started two years ago. While able to sit without assistance, she was unable to walk independently.

Biochemical analysis

In Family I, Patient II.2 , the white blood cells rate (WBC) and red blood cells rate (RBC) counts were within normal ranges. However, the concentration of creatinine phosphokinase (CPK) was elevated. Other abnormal test results included LDH, AST, and ALT.

In Family II, Patient III.7, blood element tests were normal. However, the CPK was elevated beyond the reference. Other tests, including LDH, AST, and ALT were within the standard range.

In Family II, Patient III.8, Blood element tests were normal. The CPK and ALT tests were abnormal, respectively. However, the results of the AST and LDH tests were within the normal range. The results of biochemical tests of affected people are shown in Table 1.

Table 1. List of routine Biochemical tests of patients

Biochemistry test	II.2	III.7	III.8	Normal reference rang
S.G.O.T(AST)	78	28.5	33.7	Men: up to 37 IU/L Women: up to 31 IU/L
S.G.P.T(ALT)	50	27.9	53.3	Men: up to 41 IU/L Women: up to 31 IU/L
ALP	162	71	36	29-170 U/L
LDH	505	239	241	Men: 105-225 U/L Women: 105-214 U/L
CPK Total	1230	770	960	Men: 24-195 IU/L Women: 24-170 IU/L

AST alanine transaminase, ALT aspartate aminotransferase, ALP alkaline phosphatase, LDH lactate dehydrogenase, CPK creatine phosphokinase, U/L units per liter, IU/L International Units Per Liter.

Pathogenic mutations identified by WES

A missense mutation was identified in exon 4 of the *GMPPB* gene at positions 49 of 143 (coding), "*GMPPB* (NM _013334.3): c.308C>T (p. Pro103Leu)", located on chromosome 3p21. 31. This sequence variant resulted in substitution of prolin with lusin at position 103 (p. Pro103Leu) in the *GMPPB* gene. To enhance confirmation, the above variant was sequenced by the Sanger method for his wife and all six children in the family. The Sanger sequencing further validated this genomic variation in one male and one female among the affected subjects. Patients II.2, III.7, and III.8 were identified as homozygous for this sequencing variation. The genotype of the mother was wild-type, while the children exhibited a heterozygous genotype **(Figure 2).**

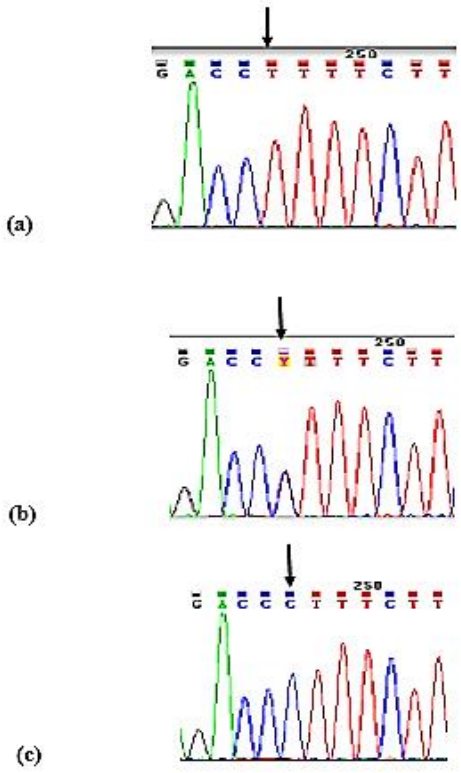

Figure 2. The presence of the c.308C>T (p. Pro103Leu) variant" in the homozygous form in the proband and two other patients, (b) the heterozygous form in parents, and, (c) wild type in healthy.

Identification of pathogenic variations in silico studies

The pathogenicity of the identified missense sequence variant was assessed and determined to have a deleterious impact as indicated in Table 2. This assessment aligns with the American College of Medical Genetics (ACMG) guideline**(19)**. The variant c.308C>T in *GMPPB* gene was consequently categorized as "Pathogenic," in accordance with its characteristics.

Table 2. Summary of the gene Candidate

		Prediction	Database	Frequency
Gene	**Variant**	**Mutation Taster** **PROVEAN** **CADD**	**ClinVar**	**Genome AD** **ExAC** **1000 Genomes** **Iranome**
GMPPB	c.308C>T (p.Pro103Leu)	Disease-causing Damaging Damaging	pathogenic	No Observation

Discussion

Currently, studies have reported several mutations in the *GMPPB* gene in dystroglycanopathies **(15)**. The present study investigated two consanguineous Iranian families affected by LGMD2T. The outcomes of WES

revealed a missense mutation in the *GMPPB* gene (NM_021971.4, c.308C>T (p. Pro103Leu)). Up to the current time, this identified variation has not been documented in the 1000 Genomes Project, ExAC, gnomAD, or Iranome database. Mutations in *GMPPB* gene are associated with a wide range of phenotypes, exhibiting extreme variability. These phenotypes appears in LGMD2T, CMD, isolated rhabdomyolysis, and congenital myasthenic syndrome (CMS) with or without elevated serum CK levels(10,18,20). Additionally, individuals with *GMPPB* gene mutations may present features including, mental retardation, epilepsy, vision impairments, and abnormalities in the heart and brain systems **(10,16,18)**. In our study, the patient, a 40-year-old male, exhibited severe mobility issues include paralysis of both legs and severe muscle weakness, hindering independent sitting, standing, or walking with no accompanying cognitive impairment. Notably, his children were observed to be normal, displaying no motor or cognitive problems. To date, more than 45 pathogenic mutations in GMPPB have been reported in patients with LGMD phenotype **(Table 3)**.This findings aligns with documented cases of the same syndrome in the existing literature **(18,20)**. Furthermore, our patient exhibited onset at the age of 25, without any concurrent eye or mental retardation complications. However, consistence with previous findings, the serum CK level was elevated **(10,21)**. In agreement with our findings, Cruz and colleagues found no cognitive impairment(20). Previous studies have demonstrated that LGMD patients homozygous for the c.308C>T mutation exhibit overlap syndromes with CMS phenotypes, accompanied by elevated serum CK levels **(20)**. In 2015, Belaya et al. reported three adult siblings born to consanguineous Iranian parents with muscular dystrophy-dystroglycanopathy type C14 (MDDGC14; 615352) exhibiting features indicative of CMS. They identified a homozygous c.308C-T transition (c.308C-T, NM_021971) in the *GMPPB* gene, leading to a Pro103Leu (P103L) substitution at conserved residue in the nucleotidyltransferase domains (18). GMPPB is a novel protein that plays a role in both N-glycosylation and O-mannosylation **(22)**. It catalysis the synthesis of GDP-mannose from GTP and mannose-1-phosphate. GDP-mannose is crucial for cytosolic mannosyltransferases, facilitating the production of the core N-glycan structure and Dol-P-Man in the endoplasmic reticulum **(22,23)**. Moreover, GMPPB is essential for the glycosylation of dystroglycan, proteins, and lipids **(23)**. The dystroglycan protein complex, particularly α-dystroglycan, provides a crucial connection between the contractile components of muscles and the extracellular matrix contributing to membrane integrity and cellular stability **(24)**. Mutations in the O-mannosylation process were first identified in individuals with muscular dystrophy as part of dystroglycanopathies **(3)**. Therefore, even minor defects in the function of GMPPB protein can result in the clinical manifestation observed in affected individuals, notably in the context of LGMD. Other studies showed that mutations in *GMPPB* gene can disturb the proper functioning of α-DG and the neurotransmission process **(18)**. In 2013, Keren et al, showed that individuals with *GMPPB* gene mutations demonstrated reduced glycosylation of α-Dystroglycan in both muscle biopsies and fibroblasts. Restoring wild-type GMPPB levels partially improved a-Dystroglycan glycosylation. The study also emphasized the impact of GMPPB mutations on its subcellular localization and formation of protein aggregates, potentially disrupting its enzymatic activity. The wild-type GMPPB enzyme was primarily located in the cytoplasm, aligning with its role in synthesizing nucleotide sugars within the cell. However, certain mutations in GMPPB led to the formation of protein aggregates in the cytoplasm or close to cell membrane extensions, potentially disrupting its normal enzymatic function. This study shed light on how these mutations impact the cellular localization and activity of GMPPB. Knocking down the GMPPB ortholog in zebrafish led to muscle abnormalities, reduced mobility, eye defects, and diminished a-Dystroglycan glycosylation, further underlining the importance of GMPPB in these biological processes **(10)**. Further study identifies the molecular pathway involves in mutant GMPPB, specifically the mutations c.803T>C and c.1060G>A, localizing with auto phagosomes at a subcellular level. Mutant GMPPB forms cytoplasmic aggregates that completely localize with microtubule-associated protein 1 light chain 3-II (LC3-II), markers of autophagosomes . The degradation of GMPPB is accompanied by an upregulation of LC3-II, indicating activation of the autophagy-lysosome pathway. Therefore, these missense mutations in the *GMPPB* gene activated autophagy-lysosome pathway in LGMD2T**(10)**. Other study showed that the same mutation with our study, c.308C>T (p.Pro103Leu), in GMPPB alters the enzymatic activity of the GMPPB protein, potentially resulting in a more severe phenotype in individuals with limb-girdle muscular dystrophy (LGMD). This mutation likely disrupts the normal function of GMPPB in the glycosylation pathway, contributing to the development of GMPPB-related disorders**(25).** The significance of our study is that whole-exome sequencing emerged as a successful method in patients facing challenges with diagnosing LGMD**(26)**. The study highlights the importance of precise clinical evaluation and established diagnostic protocols to complement and validate the findings obtained through WES**(27,28).**

Table 3. Reported GMPPB mutations in patients LGMD

References	Onset age	Sex	Mutation, Protein	Mutation, DNA	NO
–4,10,15)15 (35–18,20,29	Variable	F/M	p.Asp27His	c.79G>C c.79G>A	1
(15)	48	M	p.Cys29*	c.87C>A	2
(10,15,16,34)	15,20,26,43	M	p.Pro32Leu	c.95C>T	3
(18,20)4	15	F	Splicing	c.130-3C>G	4
(18,20)	Variable	F/M	p.Pro103Leu	c.308C>T	5
(15)	49	M	p.Cys113Tyr	c.338G>A	6
(36)	29	M	p.Pro116Ser	c.346C>T	7
(37)	-	-	p.Gly131Cys	c.391G>T	8
(17,32)	23,-	M	Splicing	c.402+1G>A	9
(38)	9	M	p.Thr153Ile	c.458C>T	10
(29)	12	F	p.Arg155His	c.464G>A	11
(34)	13	F	p.Ser168Phe	c.503C>T	12
(36)	29	M	p.Arg185Cys	c.553C>T	13
(34)	25	F	p.Gly220Arg	c.658G>C	14
(34)	13	M	p.Gln234*	c.700C>T	15
(17)	5	F	p.Pro241Ser	c.721C>T	16
(15,34)	20,17	M	p.Arg243Trp	c.727C>T	17
(15)	17	M	p.Gly252Cys	c.754G>T	18
(17,29,32)	15,18	M/F	p.Val254Met	c.760G>A	19
(18,20)	15	F	p.Arg261Cys	c.781C>T	20
(4)	2,5,-	M/F	p.Gln264*	c.790C>T	21
(16)	Late 20s, 35	F/M	p.Cys266Tyr	c.797G>A	22
(25)	22	F	p.Ile268Thr	c.803T>C	23

(15)	1	F	p.Glu281Gln	c.841G>A	24
(34)	7	F	p.Cys285Tyrfs*19	c.854_855delGT	25
(31–15,29)	20,8,15,30,5,37	F/M	p.Arg287Trp	c.859C>T	26
(15)	1,49	F/M	p.Arg287Gln	c.860G>A	27
(34)	7	F	p.Arg288Gln	c.863G>A	28
(39)	14	F	p.Arg293Trp	c. 877C>T	29
(29)	25	M	p.Ser301Cys	c.902C>G	30
(15,18,20)	25-35	F	p.Leu303Phe	c.907C>T	31
(34)	6	F	p.Gly315Ser	c.943G>A	32
(39)	Variable	F/M	p.Asn322Lys	c.966C>A	33
(10,15,34)	Variable	M	p.Val330Ile	c.988G>A	34
(15,24)	Variable	F/M	p.Asp334Asn	c.1000G>A	35
(39)	26	F	p.Gly340Arg	c. 1018G>A	36
(17)	5	F	p.Val345Ala	c.1034T>C	37
(16)	Early 20s	F/M	p.Arg346Ser	c.1036C>A	38
(29)	12	F	p.Ile349Serfs	c.1039_1043dup	39
(25)	22	F	p.Gly354Ser	c.1060G>A	40
(17,29)	17-25	M	p.Val357Ile	c.1069G>A	41
(39)	Variable	F/M	p.Arg357His	c.1070G>A	42
(37)	-	-	p.Tyr364Asn	c.1090T>A	43
(15)	43	F	p.Val370Leu	c.1108G>C	44
(40)	22-1	M	p.Arg384His	c.1151G>A	45

Conclusion

According to this study, LGMD patients process a pathogenic homozygous missense mutation at codon Pro103Leu of the GMPPB gene, known as the p. Pro103Leu variant, following an autosomal recessive pattern. This mutation may be prevalent among Iranian populations affected by LGMD2T disease. These findings offer new insights into the diagnostic capability of WES. Additionally, the identified mutation may serve as a potential marker in consanguineous Iranian families, paving the way for more personalized and effective treatment approaches in the future.

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Authors' Contribution

HD and MA designed the paper. MA, AA, MD, ZSH, and HD were responsible for data collection or acquiring the data in south Khorasan. MA, MM, and HD carried out the analysis. MA and MM wrote the first draft of the manuscript. All authors critically reviewed and modified the manuscript, and have approved the final version of the manuscript.

Conflict of Interest

The authors declare that they have no conflict of interest.

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Ethics Approval and consent to participate

The Declaration of Helsinki was used as a guideline for this study. Prior to enrollment in the trial\, obtaining informed consent from patients was a mandatory prerequisite. This study was approved by the Birjand University of Medical Sciences Research Committee (IR.BUMS.REC.1399.418).

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