RESEARCH ARTICLE

Editorial Process: Submission:07/14/2025 Acceptance:01/28/2026 Published:02/06/2026

MALAT1 Gene Variants rs619586, rs664589, and rs3200401 and Their Association with Non-Hodgkin Lymphoma Risk: Evidence from a Case- Control Study in Southeast Iran

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Abstract

Introduction: Non-Hodgkin lymphoma (NHL) represents a diverse spectrum of lymphoid malignancies, which are defined by abnormal proliferation of lymphocytes and the absence of Reed–Sternberg cells. Both genetic and epigenetic mechanisms play critical roles in the etiology of this group of cancers. In this context, the present study aimed to assess the potential relationship between three specific single nucleotide polymorphisms (SNPs) in the *MALAT1* gene namely rs619586 A>G, rs664589 C>G, and rs3200401 C>T and their association with susceptibility to NHL in a population sample from Zahedan, Iran. **Materials and Methods:** A case-control study design was utilized, comprising 185 individuals diagnosed with NHL (118 men and 67 women; mean age: 45.46 ± 15.44 years) and an equal number of age- and sex-matched healthy controls (106 men and 79 women; mean age: 43.26 ± 12.27 years). Genomic DNA was isolated from peripheral blood leukocytes using the conventional salting-out method. Genotyping for the selected *MALAT1* polymorphisms was performed using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) and amplification refractory mutation system PCR (ARMS-PCR) methodologies. Statistical evaluations were performed using chi-square tests, independent sample t-tests, and logistic regression models to analyze the data. **Results:** The rs3200401 C>T polymorphism of the *MALAT1* gene was significantly associated with a reduced risk of NHL, suggesting a protective effect (P<0.05). Similarly, the rs619586 A>G variant showed a significant protective association with NHL. In contrast, the rs664589 C>G polymorphism did not show any significant differences in genotype or allele frequencies between NHL patients and healthy subjects (P>0.05). **Conclusion:** The findings suggest that *MALAT1* gene polymorphisms, particularly rs3200401 and rs619586, as well as the TCG haplotype, may influence susceptibility to non-Hodgkin lymphoma and serve as potential genetic biomarkers. However, further studies involving larger and ethnically diverse cohorts are required to validate these associations.

Keywords: Non-Hodgkin lymphoma, *MALAT1*, polymorphism, gene association, lncRNA

Asian Pac J Cancer Prev, **27 (2)**, 629-635

Introduction

Non-Hodgkin lymphoma (NHL) is a type of hematological cancer that affects people of all ages and contributes significantly to cancer mortality. The need for early diagnosis, combined with the use of complex and expensive treatments, places a significant financial burden on patients, their families, and the healthcare system [1]. Lymphoma is a type of lymphatic cancer that originates in lymphocytes and spreads to lymph nodes, the spleen, the thymus, and the bone marrow. This disease causes uncontrolled cell growth and tumor formation in the lymphatic system due to genetic and biochemical changes [2].

A meta-analysis study in Iran showed that the prevalence of leukemia and lymphoma is 3.26% and 7.15%, respectively, which is influenced by demographic, environmental, and genetic factors [3].

Lymphomas are generally divided into Hodgkin lymphoma (HL), representing around 10% of cases, and NHL, which represents about 90%. The primary distinction between the two types is the presence of Reed-Sternberg cells in Hodgkin lymphoma, which are found in tissue samples with specific histopathological characteristics, whereas these cells are absent in non-Hodgkin lymphoma [4]. The global incidence of NHL

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in 2020, with approximately 545,000 new diagnosed and 260,000 deaths, ranks it as the 11th most common and deadly cancer [5].

Long non-coding RNAs (lncRNAs) have emerged as key regulatory molecules in oncogenesis and tumor progression, drawing increasing scientific interest in recent years. These molecules, which are more than 200 nucleotides long, regulate gene expression, chromatin organization, and epigenetic control [6]. According to studies, changes in lncRNA expression can be linked to DNA damage, cancer cell immune evasion, and disruption of cellular metabolism. Furthermore, lncRNAs play a role in epithelial-to-mesenchymal transition (EMT) and metastasis. As a result, targeting them in novel cancer therapies is a promising and evolving strategy [7].

MALAT1 (Metastasis Associated Lung Adenocarcinoma Transcript1) is one of the most prominent lncRNAs that plays a role in the regulation of the expression of key transcriptional and post-transcriptional genes. This lncRNA, approximately 8.7 kilobases in length, is highly expressed in various tissues, and its level is significantly increased in many cancers, particularly in tumor tissues (13, 58–62). *MALAT1* facilitates tumor growth, metastasis, and chromosomal instability through mechanisms such as regulating mRNA alternative splicing, binding to active chromatin, and recruiting SR proteins [8, 9].

Studies have shown that inhibition of *MALAT1* can reduce invasion, migration, and EMT, arrest the cell cycle, and induce apoptosis [10]. High levels of *MALAT1* in colorectal, gastric, lung, glioma, and other cancers are associated with poor prognosis [11-15]. Additionally, its presence in serum exosomes has garnered attention as a potential noninvasive diagnostic marker [16]. However, the precise mechanism of action of *MALAT1* remains under investigation.

Single-nucleotide polymorphisms (SNPs) in *MALAT1*, such as rs619586, rs664589, and rs3200401, have been associated with susceptibility to various cancers, including lung, breast, thyroid, prostate, cervical, and esophageal cancers [17-22]. Functional studies have also shown that carriers of the G allele at rs619586 reduce *MALAT1* expression and limit proliferation in thyroid cancer (PTC) [20].

Given the known role of lncRNAs in carcinogenesis, the key role of *MALAT1*, and the potential consequences of its SNPs in various cancers, this study aimed to evaluate the potential association between specific polymorphic variants of the *MALAT1* gene (including rs3200401, rs619586, and rs664589) and susceptibility to NHL within an Iranian population, to evaluate the possible role of these variants in genetic susceptibility to cancer.

Materials and Methods

Subjects

A total of 185 patients diagnosed with non-Hodgkin lymphoma (118 males and 67 females; mean age 45.46 ± 15.44 years) alongside 185 healthy control subjects (106 males and 79 females; mean age 43.26 ± 12.27 years) were enrolled in this study. Exclusion criteria for both groups included a history of other malignancies, autoimmune disorders, chronic infectious diseases, and previous chemotherapy or radiotherapy. Controls were additionally screened to ensure no family history of hematological malignancies. No statistically significant differences were observed between the two groups regarding age and gender distribution (P = 0.130 and P = 0.242, respectively). The study protocol received ethical approval from the Local Ethics Committee of Zahedan University of Medical Sciences (IR.ZAUMS.REC.1402.410), and informed consent was obtained from all participants prior to sample collection. Peripheral venous blood samples were drawn into tubes containing ethylenediaminetetraacetic acid (EDTA). Genomic DNA was subsequently isolated using the salting-out technique and stored at -20°C until further analysis.

Genotyping

Genotyping of the *MALAT1* polymorphisms rs3200401 and rs619586 was performed using the tetra-primer amplification refractory mutation system PCR (T-ARMS-PCR), whereas rs664589 was genotyped via polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) assay. The primer sequences used are listed in Table 1. For rs3200401 and rs619586, PCR reactions were prepared in a total volume of 20 µL, consisting of 1 µL genomic DNA (~100 ng/µL), 1 µL of each primer, 10 µL master mix, and 5 µL of double-distilled water (ddH_2O). For rs664589, each 20 µL reaction contained 1 µL genomic DNA, 1 µL of each primer, 10 µL master mix, and 7 µL ddH_2O.

Thermal cycling conditions for rs3200401 included an initial denaturation at 95°C for 5 minutes, followed by 35 cycles of denaturation at 95°C for 30 seconds, annealing at 59°C for 35 seconds, extension at 72°C for 50 seconds, and a final extension step at 72°C for 5 minutes. The PCR conditions for rs664589 were an initial denaturation at 95°C for 6 minutes, followed by 40 cycles of 95°C for 35 seconds, 62°C for 38 seconds, 72°C for 38 seconds, and a final extension at 72°C for 10 minutes. Subsequently, 10 µL of the PCR product for rs664589 was digested with the corresponding restriction enzyme (HaeIII). For rs619586, PCR cycling consisted of an initial denaturation at 95°C for 5 minutes, 35 cycles at 95°C for 30 seconds, 61°C for 35 seconds, 72°C for 50 seconds, and a final extension at 72°C for 5 minutes.

Amplification products were separated by electrophoresis on agarose gels containing 0.5 µg/mL ethidium bromide and visualized under ultraviolet (UV) illumination (Figures 1, 2, and 3). To ensure accuracy, approximately 20% of the samples were randomly re-genotyped, and the results were 100% concordant.

Statistical analysis

All statistical analyses were conducted using SPSS version 22. Comparisons between groups were carried out using the independent samples t-test and chi-square (χ^2) test. Logistic regression analysis was utilized to estimate odds ratios (ORs) along with their 95% confidence intervals (CIs). A P-value of less than 0.05 was considered indicative of statistical significance. Haplotype analyses were performed using the SNPStats online tool (https://

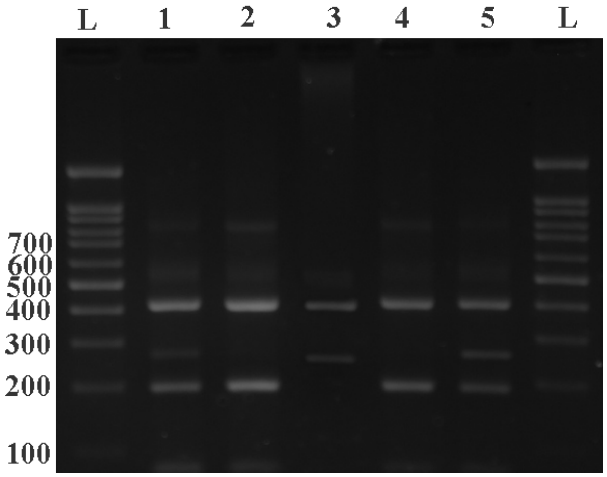

Figure 1. Electrophoresis Pattern of *MALAT1* rs3200401 polymorphism. L, DNA Ladder; lanes 1 and 5, C/T; lanes 2 and 4, C/C; lane 3: T/T

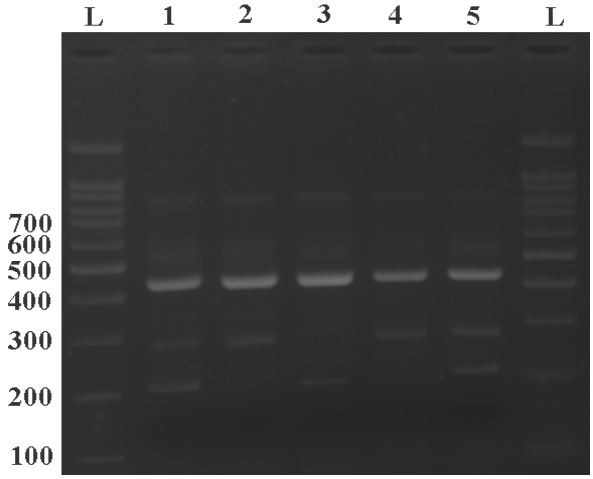

Figure 3. Electrophoresis Pattern of MALAT1 rs619586 polymorphism. L, DNA Ladder; lanes 1 and 5, A/G; lanes 2 and 4, A/A ; and lane 3, G/G

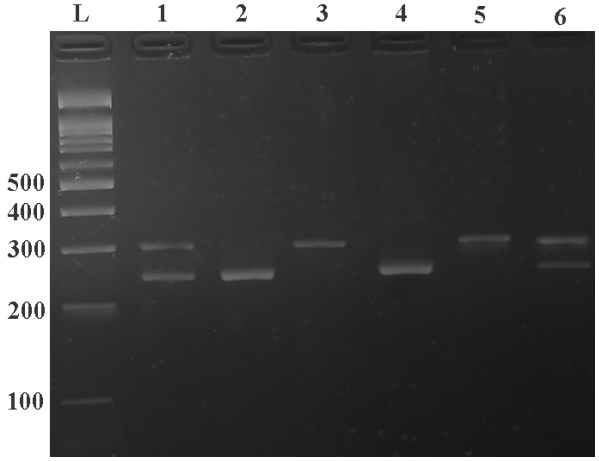

Figure 2. Electrophoresis Pattern of *MALAT1* rs664589 polymorphism. L, DNA Ladder; lanes 1 and 6, C/G; lanes 2 and 4, C/C; and lane 3 and 5, G/G

www.snpstats.net/).

Results

The subjects enrolled in this study are 185 pathologically confirmed Non-Hodgkin Lymphoma patients and 185 unrelated healthy persons. No significant difference was found between the groups regarding sex and age ($p > 0.05$). The genotype frequencies of all three SNPs in the control group were consistent with Hardy-Weinberg equilibrium (rs3200401: P = 0.095; rs619586: P = 0.409; rs664589: P = 0.462), indicating no significant deviation from expected distributions.

Genotypic and allelic frequencies of *MALAT1* rs3200401, rs664589 and rs619586 variants in Non-Hodgkin Lymphoma patients and controls are shown in Table 2. The results showed that rs3200401 C>T variant of *MALAT1* gene significantly decreased the

Table 1. The Primers Used for Detection of *MALAT1* rs3200401, rs664589, rs619586 Polymorphisms

MALAT1 SNPs	PCR primers (5'→3')	Restriction Enzyme	Fragment, bp
	rs3200401		
Forward Inner (C allele)	AGAGAATGCAGTTGTCTTGACTTCAGTTC		C allele=201
Reverse inner (T allele)	GCATTTACTTGCCAACAGAACAGAAAA		T allele=277
Forward outer	TTTAAAGAATTTTCCTTTGCAGAGGCAT		Control=422
Reverse outer	AAATTTCCTCAACACTCAGCCTTTATCA		
	rs664589		
Forward	CTTAGAAGTTTTATTAAAGGGGAGGGG	HaeIII	G allele=305 C allele=251+54
Reverse	CTAATTATGACACTTTCCTTGCCC		
	rs619586		
Forward Inner (G allele)	CTTCCTTCAAAAGGTGGTAAACTATACATG		G allele=213
Reverse inner (A allele)	TTCTTGTGTTCTCTTGAGGGACCGT		A allele= 279
Forward outer	CAAGAGTGGGTTTTCACGTTTCTAAGAT		Control=436
Reverse outer	TGAATGCAAACTACACATGCAGAAATAC		

Table 2. Association of *MALAT1* (rs3200401, rs664589, rs619586), Polymorphisms and the Risk of NHL

SNP	Model	Genotype / Allele	Case n (%)	Control n (%)	OR (95% CI)	P-value
rs3200401	Codominant	C/C	107 (57.8)	83 (44.9)	Ref	-
		C/T	73 (39.5)	89 (48.1)	0.636 (0.417–0.970)	0.035
		T/T	5 (2.7)	13 (7.0)	0.298 (0.102–0.870)	0.021
	Dominant	C/T + T/T	78 (42.2)	102 (55.1)	0.593 (0.393–0.895)	0.013
	Recessive	T/T	5 (2.7)	13 (7.0)	0.368 (0.128–1.053)	0.054
	Allele	C	287 (77.6)	255 (68.9)	Ref	-
		T	83 (22.4)	115 (31.1)	0.641 (0.462–0.891)	0.008
rs664589	Codominant	C/C	113 (61.1)	120 (64.9)	Ref	-
		C/G	66 (35.7)	56 (30.3)	1.252 (0.807–1.942)	0.317
		G/G	6 (3.2)	9 (4.8)	0.708 (0.244–2.053)	0.524
	Dominant	C/G + G/G	72 (38.9)	65 (35.1)	1.176 (0.771–1.795)	0.452
	Recessive	G/G	6 (3.2)	9 (4.8)	0.656 (0.228–1.880)	0.43
	Allele	C	292 (78.9)	296 (80.0)	Ref	-
		G	78 (21.1)	74 (20.0)	1.069 (0.748–1.527)	0.716
rs619586	Codominant	A/A	111 (60.0)	82 (44.3)	Ref	-
		A/G	65 (35.1)	86 (46.5)	0.558 (0.363–0.859)	0.008
		G/G	9 (4.9)	17 (9.2)	0.391 (0.166–0.921)	0.028
	Dominant	A/G + G/G	74 (40.0)	103 (55.7)	0.531 (0.351–0.802)	0.003
	Recessive	G/G	9 (4.9)	17 (9.2)	0.505 (0.219–1.165)	0.104
	Allele	A	287 (77.6)	250 (67.6)	Ref	-
		G	83 (22.4)	120 (32.4)	0.603 (0.434–0.836)	0.002

risk of lymphoma; codominant (OR = 0.636, 95% CI = 0.417–0.970, P=0.035, C/T vs C/C; OR = 0.298, 95% CI = 0.102–0.870, p = 0. 021, T/T vs C/C), dominant (OR = 0.593, 95% CI = 0.393–0.895, P=0.013, C/T + T/T vs C/C) and allelic (OR = 0.641, 95% CI = 0.462–0.891, p =0.008, T vs C) inheritance models were utilized. Findings showed that rs619586 A>G variant significantly decreased the risk of NHL; codominant (OR = 0.558, 95% CI = 0.363–0.859, P=0.008, A/G vs A/A; OR = 0.391, 95% CI = 0.166–0.921, p = 0. 028, G/G vs A/A), dominant (OR = 0.531, 95% CI = 0.351–0.802, P=0.003, A/G + G/G vs A/A) and allelic (OR = 0.603, 95% CI = 0.434–0.836, p =0.002, G vs A) inheritance models were utilized. There are no significant differences between cases and controls in rs664589 variants and alleles.

Haplotype analysis between NHL patients and healthy controls are summarized in Table 3. The haplotype analysis result revealed that TCG haplotype was significantly associated with the risk of NHL. The TCG haplotype was significantly lower in NHL patients and associated with a 0.09-fold lower risk of NHL (OR=0.09, 95%CI=0.01-0.66, p=0.018)

Discussion

The results of this study indicated that the rs3200401 C>T and rs619586 A>G polymorphisms in the *MALAT1* gene are significantly linked to a decreased susceptibility to NHL in the Iranian population. In particular, the T allele in rs3200401 and the G allele in rs619586 were identified as protective factors against NHL.

The association between single-nucleotide polymorphisms and a wide range of diseases and complex disorders has been extensively studied. Numerous investigations have also established strong links between genetic variants and lymphoma risk [23-

Table 3. Association of *MALAT1* Haplotypes and Risk of NHL

rs3200401	rs664589	rs619586	Case (frequency)	control (frequency)	OR (95%CI)	P-value
C	C	A	0.4189	0.3857	1	-
C	C	G	0.1867	0.1697	0.99(0.59- 1.67)	0.97
T	C	A	0.175	0.1744	0.89 (0.50 - 1.60)	0.7
C	G	A	0.1526	0.0733	1.87 (0.91 - 3.82)	0.088
T	C	G	0.0085	0.0703	0.09 (0.01 - 0.66)	0.018
C	G	G	0.0174	0.0605	0.27 (0.06 - 1.12)	0.072
T	G	A	0.0291	0.0423	0.60 (0.18 - 1.97)	0.4
T	G	G	0.0117	0.0239	0.53 (0.11 - 2.69)	0.45

25]. A large meta-analysis investigating the rs619586 A>G polymorphism in the *MALAT1* gene across various cancers (including approximately 13,000 individuals from 9 studies) demonstrated that the G allele is associated with a reduced overall cancer risk, particularly in Asian populations [26]. However, to date, no published study has specifically explored the association between *MALAT1* gene polymorphisms and the risk of NHL. Therefore, our study provides the first evidence suggesting a potential role for *MALAT1* SNPs in NHL susceptibility.

Moreover, previous studies have shown the oncogenic role of *MALAT1* in various hematological malignancies through its altered expression patterns. In a mechanistic study conducted on mantle cell lymphoma (MCL), *MALAT1* was shown to promote disease progression by interacting with EZH2, a key epigenetic regulator involved in gene silencing and tumor progression [27]. This finding highlights the importance of *MALAT1* at the functional and transcriptomic level, rather than focusing on its genetic variation. Additionally, a recent preprint study reported that elevated expression of *MALAT1* is associated with poorer clinical outcomes in patients with follicular lymphoma, further supporting its potential role as a biomarker of disease aggressiveness and prognosis in lymphoid malignancies [28]. Although these studies did not examine polymorphisms within the *MALAT1* gene, they provide a biological rationale suggesting that dysregulation of *MALAT1*, whether at the expression or genomic level, may influence lymphoma development and progression. Our findings, which reveal an association between *MALAT1* polymorphisms and NHL susceptibility, therefore extend this understanding by introducing a novel genetic dimension to the pathogenic role of *MALAT1* in lymphomas.

Consistent with our findings, Qu et al. (2019) demonstrated that the rs3200401 C>T polymorphism is associated with an elevated risk of esophageal squamous cell carcinoma (ESCC). In contrast, the association between rs619586 A>G and ESCC susceptibility did not remain statistically significant following false discovery rate (FDR) correction, suggesting that this variant may have a protective effect [22]. These findings suggest that the effect of SNPs may depend on the target tissue and cancer type.

Wang et al. (2019) also reported that rs619586 in the *MALAT1* gene acts as a protective factor against papillary thyroid cancer, with the presence of the G allele leading to decreased *MALAT1* expression, reduced cell proliferation, and increased apoptosis [20]. These results are consistent with our findings that the G allele has a protective role in NHL.

In contrast to the above results, Hu et al. [19] reported that rs619586 and rs1194338 are associated with prostate cancer progression, including higher Gleason and lymph node metastasis . In our study, rs619586 A>G was associated with a reduced risk of NHL. This difference in effects may be due to differences in tissue type, epigenetic contexts, or gene–environment interactions in different cancer types.

In another study, Yao et al. [18] demonstrated that the C allele at rs3200401 may serve as a protective factor for the development of stage I cervical cancer These findings are consistent with our results, which showed that rs3200401 C>T was associated with a reduced risk of NHL. Similarly, Tong et al.[17] found that this polymorphism was associated with a lower risk of both non-small cell lung cancer (NSCLC) and lung squamous cell carcinoma (LUSC). However, no statistically significant association was identified between rs619586 and these cancer types . In the present study, both rs3200401 and rs619586 variants exhibited a protective effect against NHL, which may be attributed to differences in the prevalence of genotypes, the target population, or specific disease mechanisms.

From a functional perspective, the *MALAT1* gene, as a long non-coding RNA (lncRNA), is involved in transcriptional regulation, mRNA stability, RNA processing, and the regulation of oncogenic pathways, such as the PI3K/AKT and Wnt/β-catenin pathways. Polymorphisms such as rs3200401 and rs619586 are thought to lead to modify *MALAT1* expression or activity by altering RNA secondary structure, reducing SR protein binding, or altering interactions with miRNAs. These changes can inhibit processes related to cell proliferation, invasion, and metastasis [29].

In contrast, the rs664589 C>G polymorphism in this study did not show a significant association with the risk of NHL. Previous studies in other cancers, such as endometrial cancer, have shown an association between this variant and increased disease risk; however, its role in NHL appears to be limited [21]. The absence of a significant association between rs664589 and NHL risk in our study may be due to several possible reasons. First, this SNP may have limited functional relevance in lymphomagenesis pathways. Second, the effect size of this variant may be small and undetectable in our sample size. Third, population-specific genetic backgrounds or environmental interactions may influence the role of rs664589 differently compared to other cancers in which it has shown significance.

Although the study yielded valuable findings, it is subject to certain limitations, including a relatively small sample size, its single-center nature, and the absence of functional analyses to support the observed genetic associations. Therefore, studies with larger sample sizes, multicenter designs, and investigation of the biological function of SNPs, including *MALAT1* expression in tumor tissue or blood, could be useful in confirming the present findings.

In conclusion, to the best of our knowledge, this is the first study to investigate the association between *MALAT1* gene polymorphisms and non-Hodgkin lymphoma risk, offering new insight into lncRNA-related genetic susceptibility in hematologic cancers. Our findings suggest that the rs3200401 and rs619586 variants in the *MALAT1* gene may contribute to a reduced susceptibility to non-Hodgkin lymphoma. Nevertheless, further biomolecular investigations and validation studies in larger, ethnically diverse cohorts are required to clarify the functional significance of these variants.

Author Contribution Statement

SMH and MT recruited the subjects, collected clinical data. HM, MS and MB collected clinical data. HM and MB prepared materials, performed experiments, and drafted the manuscript. GB designed the study, analyzed the data, interpreted data, and approved the final version and proofread the manuscript. All authors approved the final manuscript.

Acknowledgements

The authors extend their sincere appreciation to all the participants involved in this study, as well as to the Research Council of Zahedan University of Medical Sciences for their valuable support. This manuscript is based on a thesis approved as part of an MSc program at Zahedan University of Medical Sciences (Zahedan, Iran). All relevant supporting data are included within the manuscript.

Data availability

The datasets generated during and/or analyzed dur¬ing the current study are available from the corresponding author on reasonable request.

Ethical Approval

The project was approved by the Local Ethics Committee of Zahedan University of Medical Sciences (IR.ZAUMS.REC.1402.410), and written informed consent was obtained from all participants.

Funding

This study was supported by a research grant (No. 11124) from Zahedan University of Medical Sciences.

Conflicting Interest

The authors declare that they have no conflicting interests.

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