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Original Article

Association of ABCC2 Gene Polymorphism (rs3740066) with Thalidomide-Induced Peripheral Neuropathy in Transfusion-Dependent β-Thalassemia Patients: A Case–Control Study from Pakistan

Shafiq Ahmad[1], Sami Siraj[2], Inayat Ur Rahman[3], Muhammad Shahid[4] Ghazala Shaheen[1] & Umar Aleem[5]

[1]KMU Institute of Dental Sciences, Kohat, Pakistan
[2]Khyber Medical University, Peshawar, Pakistan
[3]Saidu College of Dentistry, Saidu Sharif, Swat, Pakistan
[4]Peshawar Medical College, Peshawar, Pakistan
[5]Saidu Medical College, Saidu Sharif, Swat, Pakistan

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Abstract

Background: Thalidomide has re-emerged as a potential fetal hemoglobin (HbF) inducer for transfusion-dependent β-thalassemia (TDT). However, its clinical use is limited by thalidomide-induced peripheral neuropathy (TIPN), a frequent and sometimes irreversible adverse effect. Genetic variations in the ABCC2 gene may influence susceptibility to TIPN, yet evidence in thalassemia patients is scarce.

Objective: To assess the frequency and severity of TIPN and explore its association with ABCC2 single-nucleotide polymorphism (SNP) rs3740066 among Pakistani TDT patients.

Methodology: A case–control study was conducted on 102 TDT patients who received thalidomide (1.5 mg/kg/day) for at least six months. Patients diagnosed with TIPN per the National Cancer Institute Common Terminology Criteria for Adverse Events (Version 5.0) were classified as cases (n = 51), and those without neuropathy as controls (n = 51). Blood samples were collected for DNA extraction, and genotyping was performed using Sanger sequencing.

Results: Among cases, 72% had Grade 1, 22% Grade 2, and 6% Grade 3 neuropathy. Logistic regression revealed a significant association between TIPN and female gender (β = 1.271, p = 0.008, OR = 3.56, 95% CI: 1.39–9.08). No significant association was found between ABCC2 genotypes and TIPN (p > 0.05).

Conclusion: Female gender was a significant predictor of TIPN, whereas ABCC2 rs3740066 polymorphism showed no significant association. These findings suggest that non-genetic factors, such as gender-related biological differences, may contribute more strongly to TIPN risk than this genetic variant.

Keywords: ABCC2 gene, Peripheral neuropathy, rs3740066, Thalidomide, Transfusion-dependent β-thalassemia.

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Corresponding Author:
Dr. Inayat Ur Rahman
Associate Professor,
Saidu College of Dentistry, Saidu Sharif, Swat, Pakistan
inayaturrehman.kmu@gmail.com

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Introduction

Thalassemia comprises a group of inherited hematologic disorders characterized by defective synthesis of globin chains, resulting in reduced hemoglobin production and chronic anemia. It is broadly classified into α-thalassemia and β-thalassemia, with disease severity ranging from mild to life-threatening. Clinically, thalassemia is now categorized as transfusion-dependent thalassemia (TDT) and non-transfusion-dependent thalassemia (NTDT), based on the requirement for regular blood transfusions [1].

Fetal hemoglobin (HbF = $\alpha_2\gamma_2$) is the predominant hemoglobin at birth but is progressively replaced by adult hemoglobin (HbA = $\alpha_2\beta_2$) during infancy [2]. Several studies have demonstrated that reactivation or induction of HbF synthesis ameliorates disease severity and reduces transfusion needs in β-thalassemia patients [3]. Pharmacological HbF inducers such as erythropoietin, sodium butyrate, hydroxyurea, and 5-azacytidine have shown varying degrees of efficacy [4]. Among them, hydroxyurea remains the most potent HbF inducer and is the only FDA-approved therapy for sickle cell disease [5,6]. Nevertheless, its long-term efficacy may decline over time, emphasizing the need for alternative or adjunctive treatments with sustained benefits.

Thalidomide, initially introduced as a sedative, has been repurposed as a potent HbF inducer and an effective therapeutic option for β-thalassemia [7,8]. Several clinical trials have reported significant increases in total hemoglobin and HbF levels among TDT patients treated with thalidomide [9–11]. Despite these promising outcomes, one of the major limitations of thalidomide therapy is thalidomide-induced peripheral neuropathy (TIPN)—a dose-limiting and potentially irreversible adverse effect that affects 25–83% of treated patients, with up to 15% requiring drug discontinuation [12].

The ABCC2 (ATP Binding Cassette Subfamily C Member 2) gene, located on chromosome 10q24.2, encodes a transporter protein involved in the efflux of various drugs and metabolites [9]. Genetic variations in ABCC2 have been associated with inter-individual differences in drug response and toxicity, including susceptibility to neuropathies induced by thalidomide and other chemotherapeutic agents. Studies conducted among patients with multiple myeloma and inflammatory bowel disease have linked ABCC2 polymorphisms to TIPN, although findings remain inconsistent across populations.

Currently, most available evidence on TIPN arises from adult cohorts treated for multiple myeloma, leaving a significant knowledge gap regarding genetic susceptibility and neuropathy risk in pediatric thalassemia populations. To address this gap, the present study was designed to evaluate the association between ABCC2 rs3740066 polymorphism and the occurrence of thalidomide-induced peripheral neuropathy in Pakistani TDT patients.

Methodology

Study Design:

This was a case–control study designed to investigate the association between ABCC2 gene polymorphism (rs3740066) and thalidomide-induced peripheral neuropathy (TIPN) among transfusion-dependent β-thalassemia (TDT) patients in Pakistan. The study compared two groups of patients who had received thalidomide therapy (1.5 mg/kg/day for at least six months): those who developed TIPN (cases) and those who did not (controls). The case–control design enabled evaluation of both clinical and genetic factors contributing to TIPN while minimizing time and resource constraints relative to prospective cohort designs.

Ethics:

Ethical approval was obtained from the Institutional Research Ethics Board of the Institute of Pharmaceutical Sciences (IPS), Khyber Medical University (KMU), Peshawar, Pakistan (approval no. KMU/IPS/PG/IREB/2nd meeting/2024/1). Written informed consent was obtained from the parents or legal guardians of all participating children prior to enrollment. All study procedures adhered to the ethical principles outlined in the Declaration of Helsinki for human research involving identifiable participants.

Setting:

The study was conducted in collaboration with several tertiary-level medical and dental institutions affiliated with Khyber Medical University, including KMU Institute of Dental Sciences (Kohat), Saidu College of Dentistry (Swat), and Peshawar Medical College (Peshawar). Recruitment, clinical evaluation, and sample collection were performed in thalassemia treatment centers within these institutions, where patients routinely received transfusion and thalidomide therapy. Laboratory-based molecular analysis was carried out at the Department of Pharmacology, Institute of Pharmaceutical Sciences, KMU.

Participants:
A total of 102 TDT patients were recruited using purposive sampling based on defined inclusion and exclusion criteria. Eligible participants included males and females aged ≥3 years who had received thalidomide continuously for at least six months. Patients were excluded if they had preexisting neurological disorders, vitamin B12 deficiency, concurrent use of neurotoxic medications, or pregnancy, given thalidomide's known teratogenic potential. Of these, 51 patients diagnosed with TIPN according to NCI-CTCAE Version 5.0 (2017) were classified as cases, while 51 without neuropathy were categorized as controls.

Variables:
The primary outcome variable was the occurrence and severity of thalidomide-induced peripheral neuropathy (TIPN). The main independent variable was ABCC2 single nucleotide polymorphism (SNP) rs3740066 genotype (CC, CT, TT). Covariates included age, gender, socioeconomic status (SES), height, weight, and body mass index (BMI). SES was categorized as high (>100,000 PKR/month), middle (50,000–90,000 PKR/month), or low (<40,000 PKR/month) income levels.

Data Sources/Measurement:
Clinical data, including demographic characteristics, transfusion history, and anthropometric measurements, were collected through patient records and structured interviews. TIPN was graded based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), where Grade 1 indicated mild symptoms, Grade 2 moderate, and Grade 3 severe neuropathy affecting activities of daily living. Venous blood samples were collected in EDTA tubes for genomic DNA extraction using the standard salting-out method [14]. The extracted DNA was quantified spectrophotometrically and amplified using polymerase chain reaction (PCR) with primers specific for ABCC2 rs3740066. Sanger sequencing was performed using the BigDye Terminator v3.1 kit on a SeqStudio™ Genetic Analyzer (Thermo Fisher Scientific, USA). Sequence chromatograms were analyzed through FinchTV software, and genotypes were confirmed by forward and reverse reads for quality assurance.

Bias:
Potential selection bias was minimized by enrolling consecutive eligible patients from the same treatment facilities. To reduce information bias, neuropathy grading was performed by trained clinicians blinded to genotype results. Laboratory personnel performing genotyping were blinded to the clinical status of participants. Random re-sequencing of 10% of samples ensured genotyping reliability, and any ambiguous chromatograms were re-analyzed.

Study Size:
Sample size was calculated assuming a two-sided α of 0.05, 80% statistical power, a 1:1 case-to-control ratio, a control minor allele frequency of 0.326, and an odds ratio (OR) of 1.97 [13]. The minimum required sample size was 144 subjects per group. Due to the available cohort, 51 participants were included in each group (total n=102). This smaller sample limited the power to detect small effect sizes, and thus findings were interpreted as exploratory.

Quantitative Variables:
Continuous variables such as age, height, weight, and BMI were expressed as means and standard deviations (SD). TIPN grades were treated as ordinal variables, while gender, SES, and genotypes were treated as categorical variables.

Statistical Methods:
Data were analyzed using Statistical Package for Social Sciences (SPSS) version 22. Continuous variables were compared between cases and controls using independent samples t-tests, while categorical variables were analyzed using Chi-square or Fisher's exact tests as appropriate. Allele and genotype frequencies were calculated manually, and Hardy–Weinberg equilibrium was assessed using an online calculator. Multivariable logistic regression analysis was conducted to identify independent predictors of TIPN, adjusting for potential confounders. Odds ratios (ORs) and 95% confidence intervals (CIs) were reported, and a p-value <0.05 was considered statistically significant.

Results

Participants:
A total of 102 transfusion-dependent β-thalassemia (TDT) patients who had received thalidomide therapy were enrolled in this case–control study. Among these, 51 patients developed thalidomide-induced peripheral neuropathy (TIPN) and were classified as cases, while 51 patients without neuropathy served as controls. The mean age of participants was 5.60 ± 4.29 years, indicating that most subjects were children. The recruitment process achieved full data completion with no dropouts or missing variables for clinical or genetic analysis, ensuring consistency and comparability between groups.

Descriptive Data:
The demographic and anthropometric characteristics of the participants are summarized in Table 1. There were statistically significant differences between cases and

controls in mean age, weight, and height (p = 0.006, 0.01, and 0.006, respectively), whereas body mass index (BMI) did not differ significantly (p = 0.35). The mean age of cases (6.76 ± 4.4 years) was higher than that of controls (4.43 ± 3.79 years), suggesting that slightly older patients may be more susceptible to neuropathic manifestations. Similarly, mean weight and height were higher in the case group (20.27 ± 12.4 kg and 106.21 ± 20.1 cm, respectively) than in controls (15.39 ± 6.55 kg and 95.39 ± 18.8 cm, respectively). These findings reflect some degree of heterogeneity in growth parameters, possibly related to disease severity or thalidomide exposure duration.

Gender distribution revealed a greater proportion of females among the cases (58.8%) compared to males (41.2%), while the opposite was true for the control group, where males predominated (64.7%). This gender imbalance was statistically significant (p = 0.01), suggesting a potential sex-related predisposition to TIPN. Socioeconomic status (SES) distribution showed that most participants belonged to the middle-income group, with no significant difference between cases and controls (p = 0.30).

Outcome Data:

Peripheral neuropathy severity was assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, Version 5.0). Among the 51 cases, 37 patients (72%) presented with Grade 1 neuropathy, 11 patients (22%) with Grade 2, and 3 patients (6%) with Grade 3 neuropathy. No participants experienced Grade 4 symptoms. This distribution indicates that the majority of neuropathic events were mild and did not result in severe functional impairment. Figure 1 illustrates the distribution of neuropathy grades among affected patients.

Genotyping analysis of the ABCC2 gene polymorphism (rs3740066) was successfully completed in 100% of samples, with a genotyping call rate above 98%. The most common genotype observed in both groups was CC, accounting for 86.3% of cases and 96.1% of controls, whereas CT and TT variants were infrequent. The overall allele frequencies were 90.2% for C and 9.8% for T among cases, and 96.1% for C and 3.9% for T among controls. Both case and control groups deviated from Hardy–Weinberg equilibrium (p < 0.001), likely due to small sample size and hospital-based recruitment.

Main Results:

The bivariate analysis demonstrated that gender was significantly associated with TIPN (p = 0.01), with females showing a higher prevalence. In contrast, socioeconomic status and ABCC2 genotypes did not show significant associations (p > 0.05). In univariate logistic regression, females had approximately 2.6 times higher odds of developing neuropathy than males (OR = 2.62; 95% CI: 1.18–5.83). Upon adjustment for potential confounders in multivariable logistic regression, gender remained an independent and significant predictor of TIPN (β = 1.271, p = 0.008, OR = 3.56, 95% CI: 1.39–9.08).

The overall regression model was statistically significant ($\chi^2(8) = 25.937$, p = 0.001, Omnibus test), indicating that the combination of demographic and genetic predictors reliably differentiated between patients with and without neuropathy. The model explained approximately 22.5% (Cox & Snell R^2) to 29.9% (Nagelkerke R^2) of the variance in neuropathy status and achieved an overall correct classification rate of 72.5%. The Hosmer–Lemeshow test ($\chi^2 = 8.522$, p = 0.384) confirmed that the model fit was adequate.

Although the ABCC2 rs3740066 genotype did not reach statistical significance (p = 0.07 in multivariable analysis), the direction of association suggested a potential trend where CT/TT genotypes might be associated with higher odds of developing TIPN (OR = 5.67; 95% CI: 0.87–36.84). However, due to limited sample size and low variant frequency, these results should be interpreted with caution.

Table 1: Demographics of study participants

Variables	Overall Mean±SD	Cases Mean±SD	Controls Mean±SD	p-value*	95% CI for Mean Difference (Case-Control)
Age (years)	5.60±4.29	6.76±4.4	4.43±3.79	0.006	0.69-3.96
Weight (kg)	17.83±10.19	20.27±12.4	15.39±6.55	0.01	0.97-8.79
Height (cm)	100.80±20.14	106.21±20.1	95.39±18.8	0.006	3.16-18.4
BMI	15.99±1.81	15.80±1.70	16.18±1.91	0.35	-1.08-0.34

*Independent sample t-test

Table 2: Association between different variables

Variables		Cases n (%)	Controls n (%)	p-value
Gender	Male	21 (41.2)	33 (64.7)	0.01a
	Female	30 (58.8)	18 (35.3)	
Socioeconomic status	High	4 (7.8)	1 (2.0)	0.30b
	Middle	25 (49.0)	30 (58.8)	
	Low	22 (43.1)	20 (39.2)	
Genotypes	CC	44 (86.3)	49 (96.1)	0.16b
	CT+TT	7 (13.7)	2 (3.9)	

a. Chi square test, b. Fisher exact test

Table 3: Multivariate analyses for association of demographic and genetic factor with peripheral neuropathy

Predictor variable	Univariate OR (95% CI)	p value	Multivariate OR (95% CI)	p value
ABCCCT genotypes				
CC (ref)				
CT+TT	3.90 (0.77–19.76)	0.10	5.67 (0.87 to 36.84)	0.07
Gender				
Male (ref)				
Female	2.62 (1.18–5.83)	0.018	3.56 (1.39 to 9.08)	0.008
Socioeconomic status				
High (ref)				
Middle	0.21 (0.02–1.99)	0.17	0.13 (0.01 to 1.72)	0.12
low	0.27 (0.03–2.67)	0.27	0.21 (0.01 to 2.68)	0.23
Weight	1.08 (1.01 to 1.14)	0.01	1.01 (0.92 to 1.11)	0.71
Height	1.03 (1.01 to 1.05)	0.008	1.02 (0.97 to 1.07)	0.33
BMI	0.89 (0.70 to 1.11)	0.305	0.87 (0.66 to 1.15)	0.34
Age	1.15 (1.04-1.28)	0.008	1.08 (0.91 to 1.29)	0.36

Table 4: Distribution of Genotypes and Allele Frequencies at rs3740066

Genotypes	Cases (n=51)	Controls (n=51)	Expected count	HWE p-value (Cases/Controls
CC	44	49	41.49/47.08	<0.001/<0.001
CT	4	0	9.02/3.84	
TT	3	2	0.49/0.08	
Allele C	92 (90.2%	98(96.1%)	-	-
Allele T	10(9.8%)	4(3.9%)	-	-

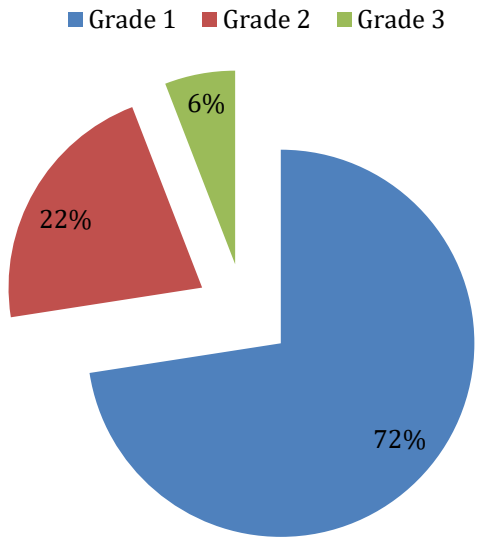


Figure 1: Distribution of different grades of peripheral neuropathy among cases

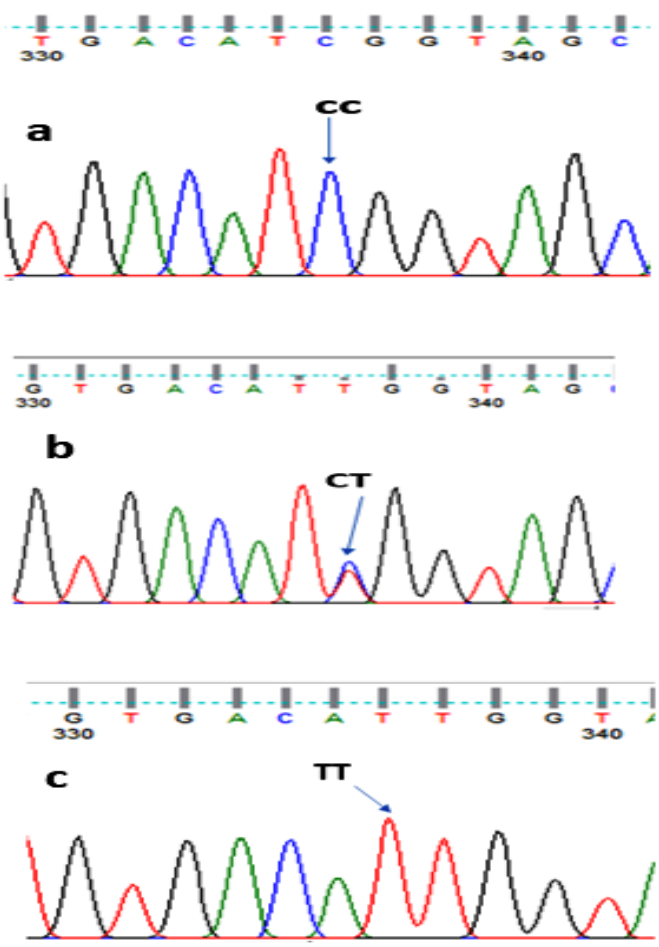


Figure 2: Chromatogram showing SNP (rs3740066) genotyping results (a) Homozygous CC (b) Heterozygous CT (c) Homozygous TT

Discussion

Thalidomide has been re-established as a potent inducer of fetal hemoglobin (HbF) and is increasingly used as an adjunct therapy for transfusion-dependent β-thalassemia (TDT) [8]. Its clinical benefit lies in the reduction of transfusion frequency and the improvement of total hemoglobin levels, as observed in several recent studies [9–11]. However, the major concern limiting its long-term use is thalidomide-induced peripheral neuropathy (TIPN)—a dose-dependent and potentially irreversible adverse event that can severely affect quality of life and treatment adherence. Previous reports indicate that the incidence of TIPN may range from 25% to 83%, and approximately 15% of patients require discontinuation of therapy because of neurotoxicity [12].

In the present study, the majority of patients with TIPN exhibited mild symptoms (Grade 1, 72%), while moderate (Grade 2) and severe (Grade 3) cases comprised 22% and 6% respectively. This pattern mirrors the findings of Kocer et al. (2009), who also reported that most thalidomide-related neuropathies were mild and predominantly sensory in nature [15]. Similarly, Yang et al. (2020) observed a comparable distribution of neuropathy grades among β-thalassemia patients treated with thalidomide [16]. The evidence suggests that TIPN typically emerges early during therapy and may stabilize or decline with dose reduction or treatment interruption [17,18]. These findings underscore the need for early neurological screening and periodic monitoring in TDT patients receiving thalidomide.

Genetic factors have been postulated to modulate susceptibility to thalidomide toxicity, particularly variants within drug-metabolizing and transporter genes such as ABCC2. In this cohort, the CC genotype of rs3740066 was predominant (91.2%), consistent with previous studies in Asian populations, including those by Chen et al. (2019) and Qu et al. (2012) [19,20]. However, the present study did not demonstrate a statistically significant association between rs3740066 genotypes and the risk of TIPN, although a non-significant trend was noted where CT/TT carriers appeared to have higher odds of neuropathy.

The lack of statistical significance may be attributed to the relatively small sample size and the low minor allele frequency in this population, limiting the power to detect small genetic effects. Nonetheless, these results align with previous contradictory findings. Johnson et al. [13] reported a significant association of rs3740066 with TIPN in multiple myeloma patients, whereas Lopez-Lopez et al. [21] found a similar relationship between ABCC2 rs3740066 and vincristine-induced peripheral neuropathy in pediatric leukemia patients. In contrast, Zgheib et al. [22] observed no such association in a comparable cohort. Such inconsistencies highlight the importance of considering disease context, cumulative dose, age, and polygenic interactions when evaluating pharmacogenetic predictors of neuropathy.

A key finding of this study was the gender-based susceptibility, with females exhibiting a significantly higher risk of developing TIPN (OR = 3.56, p = 0.008). This observation corroborates earlier work by Morino et al. (2004) and Martin et al. (2013), both of whom reported that female patients were more prone to thalidomide-related neurotoxicity [23,24]. The underlying mechanisms remain speculative but may involve differences in body composition, hormonal regulation, and drug metabolism between males and females, influencing thalidomide's pharmacokinetic and neurotoxic profiles. In contrast, Xue et al. (2015) reported no association of gender with neuropathy risk [25], suggesting that the relationship may be influenced by ethnic, pharmacogenetic, and therapeutic factors.

Collectively, these findings suggest that TIPN in thalassemia patients is multifactorial, arising from a complex interplay between drug exposure, host susceptibility, and genetic background. While ABCC2 polymorphism (rs3740066) alone may not be a major determinant, its interaction with other transporter or oxidative-stress genes (such as ABCB1, GSTM1, or CYP2C19) warrants further exploration. Expanding sample sizes and integrating multi-gene analyses may help clarify the genomic contribution to thalidomide neurotoxicity.

Study Limitation & Future Recommendation

Given the small sample size and limited representation of rare genotypes, the results should be interpreted as preliminary. Future large-scale, multicenter studies using comprehensive pharmacogenomic profiling and longitudinal follow-up are recommended to confirm these findings and to develop predictive models for neuropathy risk. Early identification of susceptible individuals could enable dose adjustments, personalized monitoring, and improved safety in thalidomide-based therapy for β-thalassemia.

Conclusion

This study identified a significant association between female gender and thalidomide-induced peripheral neuropathy (TIPN) among transfusion-dependent β-

thalassemia patients, whereas no statistically significant relationship was observed between ABCC2 rs3740066 polymorphism and neuropathy risk. The predominance of the CC genotype in this Pakistani cohort suggests population-specific allelic distribution patterns.

Authors' Contributions

All authors meet the ICMJE criteria for authorship. They have reviewed and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Author 1: Substantial contribution to conception and design, drafting the manuscript, final approval, agreed to be accountable for all the work.
Author 2: Substantial contribution to conception and design, data acquisition, drafting the manuscript, final approval, agreed to be accountable for all the work.
Author 3: Analysis and interpretation of data, drafting the manuscript, final approval, agreed to be accountable for all the work.
Author 4: Analysis and interpretation of data, critical revision, final approval, agreed to be accountable for all the work.
Author 5: Substantial contribution to conception and design, drafting the manuscript, final approval, agreed to be accountable for all the work.
Author 6: Substantial contribution to conception and design, data acquisition, drafting the manuscript, final approval, agreed to be accountable for all the work

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