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Original article

Prevalence and risk factors of hearing loss and otological symptoms among Sickle Cell Disease patients in Saudi Arabia: a single center experience

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Abstract. *Background and aim:* Sickle Cell Disease (SCD) is a genetic hematological disorder associated with various complications, including sensorineural hearing loss (SNHL). However, the prevalence and risk factors of SNHL among SCD patients remain unclear. The aim of the study is to determine the prevalence and risk factors of sensorineural hearing loss along with otological manifestations in SCD patients; to compare the findings between mild-moderate versus severe SCD patients. *Research design and methods:* A cross-sectional study was conducted between December 2022 and March 2023 at King Fahd University Hospital in Al Khobar. The study included fifty-four SCD patients (18-45 years old) who were receiving follow-up care. Participants underwent comprehensive audiological assessments; The Otology Questionnaire Amsterdam and clinical parameters were used to assess hearing in the patients. *Results:* Twelve patients (22.2%) had hearing loss on pure tone audiometry. Hearing loss risk factors in SCD patients were not statistically significant in our sample ($P > 0.05$). The Otology Questionnaire Amsterdam impact domain score and most of the complaints apart from ear itching and loss of taste showed a statistically significant correlation with SCD severity ($P < 0.05$). *Conclusions:* Sensorineural hearing loss is not uncommon in patients with sickle cell disease. Our study did not demonstrate any significant risk factors for hearing loss. However, the severity of various otological symptoms correlated significantly with SCD disease severity. Screening for ear-related complaints is therefore encouraged during patient encounters. (www.actabiomedica.it)

Key words: sickle cell disease, hearing, sensorineural, prevalence

Introduction

Sickle cell disease (SCD) is a genetic hematological disorder first identified in 1872 by Dr. James Africanus Beale Horton (1). It is prevalent in Saudi Arabia, with carrier status ranging from 2% to 27% and SCD prevalence reaching 14% in some regions (2). SCD is characterized by a point mutation in the β globin chain of hemoglobin, leading to multiple genetic variants and phenotypic differences in symptom severity (3). The most common genetic variant is sickle cell anemia (SCA), with a homozygous inheritance of HbS (3). Another form of SCD involves the co-inheritance of β-Thalassemia and HbS, resulting in

the genetic variant (HbS/β^0 or HbS/β^+) (3, 4). Patients with heterozygous inheritance of HbS gene are asymptomatic and considered sickle cell trait or carriers (5, 6). In SCD, red blood cells (RBCs) sickle under oxidative stress, leading to occluded capillaries (3). This causes vaso-occlusive crisis (VOC), in which patients experience excruciating pain (4).

Hearing loss is classified as conductive, central, or sensorineural hearing loss (SNHL) (7). SNHL is caused by dysfunction in the cochlea or cochlear nerve in the inner ear (7). Sudden onset hearing impairment can be due to microvascular occlusion and repeated hypoxic stress of the Labyrinthine artery leading to cochlear damage, death of outer hair cells, and permanent hearing loss (8). An association between SNHL and both pediatric and adult HbSS patients has been established (9).

Risk factors for SNHL in SCD patients include high platelet count (>450x10^9/l), poor clinic attendance, noncompliance to medications, and severe sickle cell crises with frequent hospitalizations (10). Literature on the precise relationship between hearing loss and SCD is limited, with most studies relying on questionnaires and lacking a correlation between risk factors and hearing loss.

Our study aimed to determine the prevalence of sensorineural hearing loss and its risk factors among SCD patients and compare hearing function tests between mild-to-moderate and severe cases. We also sought to investigate possible otologic manifestations in SCD patients that may impact their quality of life.

Patients and methods

Study setting and participants

This cross-sectional study was conducted between December 2022 and March 2023 at King Fahd University Hospital in Al Khobar. Participants were selected through convenience sampling. The study included male and female SCD patients (18-45 years old) who were receiving follow-up care at King Fahad University Hospital. All patients had a confirmed diagnosis of SCD (Hb SS) through electrophoresis.

SCD patients with history of meningitis, mumps, tuberculosis, human immunodeficiency virus infection (HIV), tympanic membrane perforation, previous ear surgery, head trauma, head and neck radiation therapy, or Meniere's disease were excluded from the study. Fifty-four subjects met the inclusion criteria for participation in the study (Figure 1).

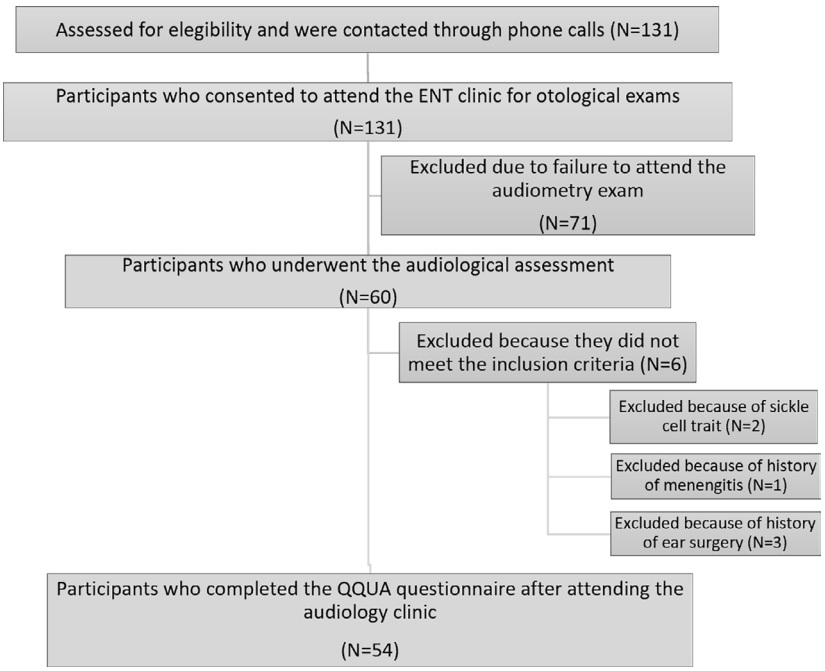

Figure 1. Flow chart of the study recruitment of participants.

Procedure and ethical considerations

Ethical approval was obtained from the research committee (IRB) of Imam Abdulrahman bin Faisal University (letter number: IRB-UGS-2021-01-351, 24/11/2022). Informed consent was acquired from the participants. Data collection took three stages: first, the recruited subjects underwent a comprehensive audiological assessment, which included tympanometry, pure tone audiogram, distortion product otoacoustic emissions (DPOAEs), and transient-evoked otoacoustic emissions (TEOAEs) tests, conducted by a certified audio vestibular consultant. Second, all participants were requested to complete the Otology Questionnaire Amsterdam (OQUA) (Annex 1) (11). Finally, additional details on the patient's medical history were obtained from the hospital's medical records.

Tympanometry and otoscopy

Tympanometry and otoscopy were performed using the Grason-Stadler GSI Tympstar V2 Tympanometer Middle Ear Analyzer, following the recommendations of the British Society of Audiology (2014) (12). Otoscope examination assessed the condition of the external auditory canal, tympanic membrane, and middle ear.

Pure tone audiometry

Subjects underwent pure tone audiometry at standard frequencies ranging from 250 Hz to 8000 Hz. The audiograms were classified into normal hearing, conductive hearing loss (CHL), or sensorineural hearing loss (SNHL). The degree of hearing loss was determined based on the pure tone average and categorized as mild (26-40 decibels), moderate (41-60 decibels), or severe (61-80 decibels) (13). A subject was identified to have hearing loss when their pure tone average (the average of the thresholds at 500 Hz, 1000 Hz, 2000 Hz, and 4000 Hz) exceeded 25 decibels in either ear (13).

DPOAEs and TEOAEs

DPOAEs and TEOAEs were recorded utilizing the ILOv6 Otodynamic Analyzer (Otodynamics Ltd., Hatfield, UK). The former test measures cochlear emissions in response to two tone frequencies, f2 and f1, providing valuable information for hearing function screening and diagnostics (14, 15). The latter test introduced nonlinear clicks at an 80 dB signal pressure level (SPL), and the analyzer averaged the results, displaying the signal-to-noise ratio (SNR) across various frequency bands (1.0-4.0 kHz). A response was considered normal if the SNR reached six or higher for at least three frequencies (16).

Otology Questionnaire Amsterdam (OQUA)

OQUA was employed to evaluate the presence, severity, and impact of ear complaints on the quality of life of sickle cell anemia patients (Annex 1) (11). The questionnaire comprises 34 questions, nine of which pertain to impact and the remaining 25 to the eight most prevalent ear complaints such as earache and itchiness. Each complaint has one question on the visual analog scale to determine its severity. Eighteen questions were scored using a 5-Likert scale answers category (11). The OQUA was translated into Arabic following the World Health Organization (WHO) guidelines (17) through a back-to-back translation process. The translated instrument was then administered to 20 sickle cell patients for a pilot study. Internal consistency Cronbach's alpha for the impact items of the OQUA was 0.903, indicating strong evidence for a good internal consistency, which comes in agreement to Kraak et al. questionnaire validation results (11).

Chart review

A chart review of electronic medical records was performed to retrieve data on SCD severity. The retrieved information included baseline hemoglobin, use of chelation therapy and hydroxyurea, duration of therapy, history of acute chest syndrome (ACS), age at first vaso-occlusive crisis (VOC), and frequency of VOC.

Sickle cell disease severity classification

There is no standardized, widely accepted score in clinical practice for sickle cell disease severity classification. Therefore, we classified the patients

according to their sickle cell genotype and complications. We screened patients for different complications through history taking and chart review of laboratory tests, however, we only included the two most life-threatening complications, stroke and acute chest syndrome. Patients with less than three VOC per year and no history of ICU admission or end-organ damage defined as history of acute chest syndrome or stroke were considered to have mild SCD. Whereas patients with three VOC per year and no history of end-organ damage were considered to have moderate SCD. Severe SCD was characterized by more than three VOC per year, end-organ damage, or a history of ICU admission. For analysis, patients with mild to moderate were combined into a single category (mild-moderate).

Statistical analysis

Descriptive statistics were used to summarize the demographic, clinical, and audiological characteristics of the study participants. Continuous variables are presented as means ± standard deviations (SD), while categorical variables are reported as frequencies and percentages.

Shapiro-Wilk Test was used to measure the normality of data distribution with a p-value less than 0.05 being considered significant.

For comparing means between the right and left ear audiometry, DPOAE, TEOAE, OQUA scores in mild-moderate SCD group vs severe SCD group; independent, unpaired t-tests were conducted. T-statistic and p-values were reported to evaluate the significance of the differences between the two ears. Binary Logistic regression analyses were done to evaluate the risk factors to develop hearing loss among SCD patients. *P* values less than 0.05 were considered significant. Spearman's rank correlation coefficients (rho) were also calculated to assess the correlation between sickle cell disease severity and the OQUA questionnaire. A *P* value of less than 0.05 was considered significant for all the tests.

All statistical analyses were performed using an IBM Statistical Package for the Social Sciences (SPSS) Version 26, with a 95% confidence level adopted for all inferential analyses.

Results

The study sample included 54 participants with a mean age of 31.52 years (SD=6.45), ranging from 20 to 45 years old. Most participants were male (33, 61.1%) and of Saudi nationality (54, 96.3%). Demographic and Clinical Characteristics of the study population are described in Table 1.

Furthermore, SCD-related complications and received treatments are listed in Table 2. All patients received episodic blood transfusions as needed, rather than as part of a regular transfusion program.

Based on clinical manifestations of the participants, 23 were labeled as mild-moderate SCD and 31 participants as severe SCD.

The pure tone audiometry results revealed a total of 12 (22.2%) patients to have hearing loss. Five patients (9.2%) had mild unilateral SNHL. One patient (1.852%) had a bilateral SNHL. Whereas three patients (5.5%) showed mild bilateral high frequency hearing loss and two (3.7%) had unilateral high frequency hearing loss in the left ear with one of them being mild and the other is moderate. Finally, one patient (1.852%) had noise induced hearing loss in the left ear. Further details are presented in Table 3.

Hearing loss risk factors including sex, age, hemoglobin type, baseline hemoglobin, history of stroke, number of VOC, age at first VOC, history of using hydroxyurea, history of using chelation therapy, number of hospital admissions/year, and total number of ICU admissions, do not show significant associations with hearing loss in SCD patients. Although no statistically significant risk factors of hearing loss were identified among SCD patients, ferritin level and history of ACS showed trends that may warrant further investigation. Further details are presented in Table 4.

The prevalence of different ear complaints in the OQUA are reported in Table 5.

The most frequently reported symptom was dizziness. Furthermore, significant positive correlations (P <0.05) are observed between the severity of SCD and the following OQUA scores: Earache (rho = 0.43, P = 0.004), Ear Pressure Sensation (rho = 0.41, P = 0.002), Tinnitus (rho = 0.44, P = 0.002), Hearing loss (rho = 0.36, P = 0.02), and Dizziness (rho = 0.50,

Table 1. Demographic and clinical characteristics of the study population (N=54).

Variable	Category	Values
Age (years)	Mean ± SD	31.30 (±6.68)
	Minimum	20
	Maximum	45
Gender	Female	21 (38.9%)
	Male	33 (61.1%)
Nationality	Saudi	52 (96.3%)
	Non-Saudi	2 (3.7%)
Educational level	Bachelor's degree or higher qualification	33 (61.1%)
	High school	17 (31.5%)
	Middle school	2 (3.7%)
	No formal education	2 (5.7%)
Baseline hemoglobin level (mg/dl)	Mean ±SD	9.84 (±1.55)
Ferritin > 1000 ng/dl (iron overload)	Measured	32 (59.3%)
	Not Measured	22 (40.7%)
Hemoglobin variant	HbSS	48 (88.9%)
	Hb S/β Thal	6 (11.1%)

Abbreviations: SD: standard deviation; mg/dL: Milligrams Per Deciliter; ng/dL: Nanograms Per Deciliter; SCD: sickle cell disease; HbSS: Sickle cell anemia; Hb S/β Thal: Sickle Cell Beta Thalassemia.

Table 2. Sickle Cell Disease-Related Characteristics and Management**.**

Variable	Category	Values
Age at First Vaso-occlusive Crisis	Less than 6 years old	26 (48.1%)
	More than 6 years old	16 (29.6%)
	I don't know	12 (22.2%)
Hospital admissions due to SCD per year Mean (±SD)		3.61 (±6.31)
History of stroke		4 (7.4%)
History of acute chest syndrome		29 (53.7%)
ICU admission history		27 (50%)
History of blood transfusion		35 (64.8%)
Use of chelation therapy		5 (9.3%)

Abbreviations: SD: standard deviation; SCD: sickle cell disease; ICU: intensive care unit.

P = 0.002). The Impact Domain score also shows a strong positive correlation with the severity of sickle cell disease (rho = 0.61, *P* < 0.001). On the other hand, there are no significant correlations between the severity of SCD and Itching (rho = 0.23, *P* = 0.113) or Loss of Taste (rho = 0.21, *P* = 0.289) as illustrated in Table 6.

Discussion

The study aimed to determine the prevalence and risk factors of hearing loss in SCD patients, compare hearing function tests between mild-to-moderate and severe cases, and identify ear-related complaints affecting the patients' quality of life.

Table 3. Hearing status of the study.

Category	Severity	Frequency	Percentage
Right Normal Hearing	Normal Hearing	46	85.2%
Right Sensorineural hearing loss	Mild	5	9.2%
Right High frequency SNHL	Mild	3	5.6%
Total		54	100%
Left Normal hearing	Normal hearing	46	85.1%
Left Sensorineural hearing loss (SNHL)	Mild	2	3.7%
Left High frequency SNHL	Mild	5	9.2%
Left Noise induced hearing loss	Mild	1	1.85%
Total		54	100%

Abbreviation: SNHL: Sensorineural hearing loss.

Table 4. Logistic Regression Model of predictors of hearing loss among sickle cell disease patients.

Covariate	Odds Ratio	95% CI	*P* value
Sex	0.92	(0.30 – 3.12)	0.949
Age	1.32	(0.75 – 1.29)	0.254
Hemoglobin type Hb SS	1.20	(0.31 – 10.12)	0.601
Baseline hemoglobin < 9 mg/dl	1.59	(0.30 – 5.12)	0.798
Ferritin level > 1000 ng/dl	4.91	(1.31 – 40.8)	0.081
History of stroke	1.32	(0.21 – 10.21)	0.891
History of acute chest syndrome	3.39	(0.89 – 16.1)	0.081
Number of Vaso-occlusive crisis More than 3 Less than 3	1.38	(0.41 – 3.96)	0.778
Age at first Vaso-occlusive crisis More than 6 years Less than 6 years Unknown	0.59	(0.21 – 1.63)	0.208
History of using hydroxyurea	0.56	(0.17 – 1.89)	0.354
History of using chelation therapy	0.91	(0.11 – 8.21)	0.899
Number of hospital admissions per year	1.32	(0.88 – 1.89)	0.301
Total number of ICU admissions	0.94	(0.58 – 1.21)	0.380

Abbreviations: CI: confidence interval; HbSS: sickle cell anemia; mg/dL: Milligrams Per Deciliter; ng/dL: Nanograms Per Deciliter; ICU: intensive care unit.

In this study, the prevalence of hearing loss was 22.2%, which is equal to what was reported locally in Saudi Arabia (22.5%), and internationally in Jamaica (22%) and less than that of Oman (36.95%). (18-21). However, our estimates of hearing loss were higher than those reported in Nigeria (4.3%), Brazil (21%) and the United States (12%) (21- 23). Generally, the reported prevalence ranged between 66% and 4.3% (18-21, 24, 25).

This variation in prevalence could be attributed to differences in genotype, age, socioeconomic factors, geographic area, disease severity, received treatments, access to audiological care, and the cutoff values utilized in identifying patients with hearing loss (26, 27).

Table 5. Prevalence of various otological symptoms, and their impact on SCD patients' quality of life.

Symptom	Never	Sometimes	Regularly	Often	Always
Complaint domain					
Earache	55.6%	35.2%	7.4%	1.9%	0.0%
Pressure sensation	57.4%	27.8%	7.4%	3.7%	3.7%
Itch	50%	24.1%	9.3%	11.1%	5.6%
A hum, murmur, beeping noise or buzzing sound	38.9%	37.0%	13.0%	9.3%	1.9%
Ear discharge	88.9%	9.3%	0.0%	0.0%	1.9%
Poor sense of taste	79.6%	14.8%	0.0%	5.6%	0.0%
Balance Issues	55.6%	29.6%	11.1%	1.9%	1.9%
Dizziness	40.7%	29.6%	16.7%	7.4%	5.6%
Impact domain					
Irritation by the ear problems	40.7%	33.3%	14.8%	3.7%	7.4%
feeling upset due to the ear problems	48.1%	25.9%	14.8%	11.1%	0.0%
Impaired concentration due to ear problems	53.7%	20.4%	13.0%	11.1%	1.9%
depressed due to my ear problems	50.0%	27.8%	13.0%	7.4%	1.9%
Tiredness due to ear problems	51.9%	24.1%	11.1%	11.1%	1.9%
Limited participation in social activities due to ear problems	59.3%	27.8%	9.3%	3.7%	0.0%
Modification of daily activities and/or work due to ear problems	68.5%	22.2%	5.6%	3.7%	0.0%
Life difficulties due to ear problems	66.7%	18.5%	11.1%	3.7%	0.0%
Concern about ear problems	57.4%	20.4%	9.3%	11.1%	1.9%

Table 6. Correlation between The Otology Questionnaire Amsterdam (OQUA) scores and severity of sickle cell disease.

Score	Spearman's rho	*P* value
Earache	0.434	**0.004***
Ear Pressure Sensation	0.412	**0.002***
Itching	0.230	**0.113**
Tinnitus	0.441	**0.002***
Hearing loss	0.361	**0.020***
Loss of Taste	0.210	**0.289**
Dizziness	0.501	**0.002***
Impact Domain	0.612	**<0.001***

Moreover, our studied sample was mainly from the eastern province with the Arab-Indian haplotype explaining the higher baseline hemoglobin.

SNHL can present suddenly or progressively; it could be bilateral or unilateral, mild or severe, and may be permanent or transient (18). Our study participants showed both unilateral and bilateral SNHL with a mild presentation in almost all patients (18.4%). In addition, of our sample, 9.2% showed a high-frequency hearing loss, which might support the hypothesis of high-frequency hearing loss preceding the onset of generalized hearing loss suggested by Friedmann et al. (25) and Todd et al. (20). Nonetheless, inferences regarding the onset and course of the disease are limited by the nature of our study design.

Regarding gender differences, our data showed that hearing loss in the right ear was significantly higher in male patients compared to females. Comparatively, a local study in Qatif showed a higher prevalence of SNHL among males, yet the difference was not statistically significant (28). In contrast, Aderibigbe et al. reported that females consistently had worse hearing thresholds, in both ears, at all frequencies (24). Those findings were contrary to Onakoya et al. and Todd et al. reports of SNHL being equally distributed between males and females (20, 29)

The logistic regression analysis on the risk factors of SNHL in SCD did not yield statistically significant

results in our studied sample. Similarly, Towerman et al. failed to identify a correlation between sex, SCD type, and history of stroke (22). Al Okbi et al. also failed to find a correlation between SCD genotype, baseline hemoglobin levels, and hearing loss (19).

Multiple explanations have been offered for the varying prevalence rates of SNHL among SCD patients, including severe sickle cell crises with frequent hospitalizations, inadequate clinic follow-up, noncompliance with sickle cell medications and high platelet counts (>450x109/I), Iron chelation therapy such as Deferasirox and ototoxic antibiotics (10,19,27).

Al Jabar et al. reported an association between the chronic course of the disease, manifested by multiple hospital admissions due to VOC, and the occurrence of SNHL (18). Furthermore, a study in our region highlighted a significant correlation between the first VOC before age six and SNHL (28). On the other hand, a study published in Nigeria failed to establish a link between the frequency of VOC and the degree of hearing loss (29).

Although hearing loss could be subclinical in some SCD patients, as suggested by existing literature (18-20, 24, 25) our implementation of the Otology Questionnaire Amsterdam (OQUA) confirmed the presence of other otologic manifestations in SCD patients. The reported otologic manifestation in our study sample was earache, pressure sensation, itching, tinnitus, hearing loss, ear discharge, loss of taste, and dizziness. Furthermore, the occurrence of otologic symptoms, including earache, ear pressure sensation, tinnitus, hearing loss, and dizziness, varied significantly with different severities of SCD. This finding suggests that ear-related complications in SCD are not limited to hearing loss, and clinicians should be aware of other potential complications. In addition, a higher impact score in the OQUA correlated with more severe SCD, indicating that such otologic symptoms could influence a patient's quality of life.

One of the frequently reported complaints in our patients is dizziness, which has been associated with an increased risk of falling and a negative impact on the quality of life (23, 30). Therefore, it is hypothesized that the vestibular system is involved in the pathophysiological mechanisms that explains the numerous otological symptoms in SCD patients (23). The cochlea and vestibular apparatus appear to be affected by arterial occlusion induced by sickling RBCs in the terminal arteries of the vestibular and auditory labyrinth (23, 31). Hypoxia is thought to trigger damage to the organ of Corti, specifically the stria vascularis, which is essential for the endolymph's ionic and electrical balance (23, 31). Therefore, it is plausible to hypothesize that damage to the vestibular system's cristae ampullaris and dark cells can influence balance function (23, 31). Crystallization of RBCs, vestibular labyrinthine ossification, hemorrhage, and reperfusion injury are additional potential causes of vestibular damage (23, 31). Severe SCD is roughly characterized by frequent VOC and end-organ damage, including skeletal, retinal, cardiac, pulmonary, renal, or brain involvement (32). Hence, it is safe to suggest that severe SCD would damage the vestibular and auditory systems further, giving rise to more otological and vestibular symptoms and negatively impacting the quality of life.

Furthermore, our findings of associated otologic symptoms were in agreement with Piltcher et al. as he observed history of hearing loss, tinnitus, and dizziness in 50% of SCD patients (21).

The study is subject to certain limitations, including the cross-sectional design, which precludes establishing causality. The relatively small sample size, the absence of a validated scoring system to classify SCD severity, and the potential recall bias concerning the frequency of hospital, ICU admissions and emergency department visits are other limitations.

Conclusion

Sensorineural hearing loss is not an uncommon complication in patients with sickle cell disease. The severity of various otological symptoms including earache, tinnitus, ear pressure symptoms, dizziness, and subjective hearing loss correlated significantly with SCD disease severity. Screening for ear-related complaints is therefore encouraged during patient encounters. Although our study did not demonstrate any significant risk factors for hearing loss in SCD, future research with larger sample sizes and longitudinal study designs may help clarify the risk factors.

Conflicts of Interest: All authors declare that they have no commercial associations (e.g., consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Authors' Contribution: All authors contributed equally to the conception, conduction, drafting, and revision of the study. All authors have reviewed and approved the final version of the manuscript. The corresponding author attests that all the listed authors have met the authorship criteria.

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