**Hemoglobin Electrophoresis Patterns and Their Clinical Interpretation in a Tertiary Healthcare Setting**

**ABSTRACT**

**Background:** Hemoglobinopathies and thalassemias are among the most common inherited disorders globally, particularly prevalent in South and Southeast Asia. In Bangladesh, conditions such as Hb E trait, Hb E disease, and beta thalassemia trait are increasingly recognized as significant contributors to anemia and related health burdens. Hemoglobin electrophoresis remains the primary screening and diagnostic tool in resource-limited settings due to its affordability and ability to differentiate between hemoglobin variants.

**Objective:** To analyze the prevalence, distribution, and clinical correlation of hemoglobin variants in a Bangladeshi population using hemoglobin electrophoresis and to explore associations with demographic and hematological parameters.

**Methods:** This cross-sectional study was conducted on 215 patients referred for hemoglobin electrophoresis over 12 months at a tertiary care center in Bangladesh. Data on age, sex, clinical history, family history, and comorbidities were collected. Complete blood count (CBC) and hemoglobin variant quantification (Hb A, A2, F, E, D, S, C) were performed. Statistical analysis included descriptive statistics and Pearson correlation to examine relationships between hemoglobin fractions and red cell indices (MCV, MCH), with significance set at *p* < 0.05.

**Results:** Of the 215 patients, 66.05% showed normal hemoglobin patterns. Hb E trait (14.42%) and beta thalassemia trait (7.44%) were the most common abnormalities. Hb E disease was observed in 6.51%, while low Hb A2 and other rare variants accounted for the remainder. Significant negative correlations were found between Hb A2 and MCV (r = –0.62, *p* < 0.001), and Hb F and MCH (r = –0.39, *p* = 0.006). Hb E correlated positively with Hb A2 (r = 0.78, *p* < 0.001). Family history was positive in 40.9% of patients, with the highest rates among beta thalassemia trait cases (81.3%).

**Conclusion:** Hemoglobin E and beta thalassemia traits are the most prevalent hemoglobinopathies in the studied population. Strong correlations between hemoglobin variants and red cell indices affirm the diagnostic utility of electrophoresis.

**Keywords:** Hemoglobin electrophoresis, Beta thalassemia, Hb E trait, Hemoglobinopathies, Bangladesh population

**INTRODUCTION**

Hemoglobinopathies, including thalassemias and structural hemoglobin variants such as Hb E, Hb S, and Hb D, are among the most widespread inherited disorders globally1. These conditions arise from mutations that affect either the structure or synthesis of the hemoglobin molecule, often resulting in chronic anemia, organ damage, and a significant healthcare burden2. The World Health Organization (WHO) estimates that more than 7% of the global population carries a hemoglobin variant, and approximately 300,000 children are born each year with severe forms of hemoglobinopathy, including thalassemia major and sickle cell disease3,4.

The global distribution of hemoglobin disorders is notably uneven, with a high prevalence in malaria-endemic regions, suggesting a selective evolutionary advantage against *Plasmodium falciparum5*. Southeast Asia, including Bangladesh6, India7, Thailand8 and Myanmar9, has long been recognized as a hotspot for hemoglobinopathies, particularly for the hemoglobin E (Hb E) variant and various forms of thalassemia. These disorders constitute a major public health concern due to the high carrier frequency, limited awareness, and insufficient access to early diagnostic and genetic counselling services.

In Bangladesh, carrier frequencies for Hb E and β-thalassemia are reported to be between 6% and 12%, with some regional variations10. Studies have shown that Hb E is one of the most common hemoglobin variants in the country, particularly in eastern and northeastern regions, where consanguinity and endogamous practices may contribute to its persistence11. When co-inherited with β-thalassemia, Hb E can give rise to Hb E/β-thalassemia—a clinically heterogeneous condition ranging from asymptomatic to transfusion-dependent anemia12.

Thalassemias, particularly β-thalassemia, are also highly prevalent in South Asia. In India, for instance, the carrier rate for β-thalassemia ranges from 3% to 17% depending on the region, and Hb E is especially common in the northeastern states13. In Thailand and Laos, Hb E carrier rates can exceed 40% in some populations14. This regional pattern highlights the necessity of cross-border awareness and screening initiatives, especially in areas with shared ethnic and genetic backgrounds.

Despite advancements in molecular diagnostics, hemoglobin electrophoresis remains a widely used screening and diagnostic tool in low- and middle-income countries. Its affordability and efficiency in separating hemoglobin variants based on charge differences make it suitable for mass screening programs15. The technique can differentiate major variants such as Hb A, Hb A2, Hb F, Hb E, and Hb S, allowing for identification of both carrier and disease states16. However, electrophoresis alone may not distinguish complex genotypes such as compound heterozygous conditions (e.g., Hb E/β-thalassemia or delta-beta thalassemia), necessitating confirmatory testing such as high-performance liquid chromatography (HPLC) or molecular analysis17.

In countries like Bangladesh, the burden of hemoglobin disorders is compounded by a lack of structured national screening programs, limited public awareness, and challenges in diagnostic standardization18. Efforts by non-governmental organizations and health authorities have led to sporadic screening initiatives, yet these remain insufficient compared to the scale of the problem. The social and economic impact of undiagnosed or late-diagnosed hemoglobinopathies—particularly in lower-income households—can be profound, affecting both individual quality of life and broader public health infrastructure19.

Consequently, establishing epidemiological baselines, understanding regional variations in variant prevalence, and identifying reliable diagnostic thresholds are critical steps toward designing effective screening strategies. Public health interventions, including premarital counseling, antenatal screening, and school-based awareness campaigns, have shown success in other countries and could be adapted for Bangladesh and neighbouring regions20.

**Aim of the study**

The aim of this study was to analyze the prevalence, distribution, and clinical correlation of hemoglobin variants in a Bangladeshi population using hemoglobin electrophoresis. The study also sought to explore associations between hemoglobin variants and demographic and hematological parameters, such as age, sex, red cell indices (MCV, MCH), and family history, to improve the understanding of hemoglobinopathies and contribute to better diagnostic and screening practices.

**MATERIALS AND METHODS**

**Study Design and Settings**

This descriptive cross-sectional study was conducted at the, BIHS General Hospital, located in Dhaka, Bangladesh. The study was carried out over a period of 10 months, from February 2024 to November 2024. The institution serves as a regional referral center, receiving patients from both urban and rural areas across the country, thereby ensuring a diverse representation of the Bangladeshi population.

**Study Population and Sample Size**

A total of 215 individuals were included in this study. Participants were recruited consecutively from outpatient and inpatient departments who were referred for hemoglobin electrophoresis as part of routine screening, diagnostic evaluation for anemia, or premarital testing. The sample size was determined based on anticipated prevalence rates of hemoglobinopathies in the region (approximately 30–35%), with a 95% confidence interval and margin of error set at 5%21.

**Inclusion and Exclusion Criteria**

Patients of all ages and both sexes who were referred for hemoglobin electrophoresis and provided informed consent were included in the study. For pediatric participants, consent was obtained from parents or guardians. Individuals were excluded if they had received a recent blood transfusion (within the past three months), were under iron therapy or folate supplementation during the study period, or had incomplete laboratory records. Patients with hemolytic anemia of non-hemoglobin origin (e.g., autoimmune hemolysis) or active infections were also excluded to minimize confounding variables.

**Data Collection and Clinical Evaluation**

A structured data collection form was used to record patient information, including age, sex, address, clinical symptoms, family history of hemoglobinopathies, history of consanguinity, and comorbid conditions such as iron deficiency. Clinical examination findings and complete blood count (CBC) parameters such as hemoglobin level, mean corpuscular volume (MCV), and mean corpuscular hemoglobin (MCH) were documented. Family history was confirmed via interview and medical record review when available.

**Laboratory Analysis**

Blood samples were collected via venipuncture into EDTA anticoagulant tubes. Complete Blood Count (CBC) was performed using an automated hematology analyzer (e.g., Sysmex XP-300). Hemoglobin electrophoresis was initially carried out using alkaline cellulose acetate electrophoresis at pH 8.6. Quantification of hemoglobin fractions—including Hb A, Hb A2, Hb F, Hb E, Hb D, Hb C, and Bart’s hemoglobin—was performed visually and confirmed by densitometry. All electrophoresis slides were reviewed independently by at least two experienced hematologists. In cases of ambiguous or discrepant results, the analyses were repeated for confirmation. In addition, capillary hemoglobin electrophoresis was performed using the Sebia Capillary 3 Octa system to accurately measure Hb A, Hb A2, Hb F, and other abnormal hemoglobin variants, following the manufacturer’s instructions. This method provided enhanced resolution and quantification, improving diagnostic reliability. Iron studies (serum ferritin, serum iron, and total iron-binding capacity [TIBC]) were conducted in selected patients with suspected iron deficiency to prevent misinterpretation of Hb A2 levels due to iron status22.

**Statistical Analysis**

Collected data were entered and analyzed using SPSS version 25.0 (IBM Corp, Armonk, NY, USA). Descriptive statistics were used to summarize demographic data and laboratory findings. Means and standard deviations were calculated for continuous variables, while frequencies and percentages were reported for categorical variables. Pearson correlation coefficients (r) were computed to evaluate the relationships between hemoglobin variant levels (Hb A2, Hb F, Hb E) and hematological indices (MCV, MCH, hemoglobin). The statistical significance level was set at *p* < 0.05. Diagnostic thresholds were defined based on both mean values and reference cut-offs derived from prior literature and population norms.

**RESULTS**

The participants in the study had a mean age of 32.8 years, with the age range spanning from 1 to 70 years. The majority of individuals were in the 20–50 years age group, where Hb E trait was most commonly observed. The highest proportion of the study population was in the 30–39 years age group, while the youngest (0–9 years) and oldest (≥60 years) groups represented the smallest portions of the sample. The gender distribution revealed that females made up 65.1% of the participants, while males accounted for 34.9%. This indicates a higher representation of females in the study population, which could be due to various factors such as healthcare-seeking behavior or a higher prevalence of hemoglobinopathies in females. In terms of residence, 58.6% of the participants resided in rural areas, with 41.4% living in urban areas. This suggests that while hemoglobinopathies are prevalent across both urban and rural populations, the rural population comprised a larger portion of the study group.

A significant proportion of participants, 40.9%, had a family history of hemoglobinopathies, emphasizing the genetic nature of these conditions. Family history is a crucial aspect in the diagnosis and screening of hemoglobinopathies, as it suggests hereditary transmission. Furthermore, 14.9% of the participants reported consanguinity in their marriages, which is known to be a risk factor for hemoglobinopathies. Regarding comorbidities, 13.5% of participants had iron deficiency anemia, while 5.1% had other chronic illnesses contributing to anemia. These comorbidities can complicate the interpretation of hemoglobin electrophoresis results, making it essential to consider them when diagnosing hemoglobinopathies (Table 1).

**Table 1: Demographic Characteristics of the Study Population (n = 215)**

|  |  |
| --- | --- |
| **Variable** | **Value** |
| **Age (mean ± SD)** | 32.8 ± 15.4 years |
| **Age Group Distribution** |
| • 0–9 years | 12 (5.6%) |
| • 10–19 years | 28 (13.0%) |
| • 20–29 years | 47 (21.9%) |
| • 30–39 years | 51 (23.7%) |
| • 40–49 years | 40 (18.6%) |
| • 50–59 years | 26 (12.1%) |
| • ≥60 years | 11 (5.1%) |
| **Most Affected Age Group** | 20–50 years (Hb E trait dominant) |
| **Gender Distribution** |
| • Male | 75 (34.9%) |
| • Female | 140 (65.1%) |
| **Residence** |
| • Rural | 126 (58.6%) |
| • Urban | 89 (41.4%) |
| **Family History of Hemoglobinopathy** | 88 (40.9%) |
| Known Consanguinity | 32 (14.9%) |
| **Comorbidities (Anemia-related)** |
| • Iron Deficiency | 29 (13.5%) |
| • Chronic Illness | 11 (5.1%) |

Abnormal hemoglobin was detected in 34% of patients, with Hb E variants being the most prevalent (20.93%). Co-inheritance with other traits (e.g., β-thalassemia) was also suspected in some high-Hb F cases (Table 2).

**Table 2: Distribution of Hemoglobin Disorders Identified**

|  |  |  |  |
| --- | --- | --- | --- |
| **Diagnosis** | **Count** | **Percentage** | **Key Hemoglobin Patterns** |
| Normal | 142 | 66.05% | Hb A >95%, Hb A2 1.5–3.5% |
| Hb E trait | 31 | 14.42% | Hb E 15–30%, Hb A 60–80% |
| Hb E disease | 14 | 6.51% | Hb E >85%, reduced Hb A |
| Beta thalassemia trait | 16 | 7.44% | Hb A2 >3.5%, slightly elevated Hb F |
| Low Hb A2 | 10 | 4.65% | Hb A2 <1.5%, possible iron deficiency or alpha-TT |
| Alpha thalassemia | 1 | 0.47% | Normal Hb A2, MCV <75 fL |
| Hb D Trait | 2 | 0.93% | Hb D 15–40% |
| Hb S Trait | 1 | 0.47% | Hb S 30–40% |
| HPFH (Hereditary Persistence) | 1 | 0.47% | Hb F >30% |

MCV and MCH were significantly lower in patients with Hb E disease and beta-thalassemia trait, consistent with microcytic, hypochromic anemia. Hb E disease had the highest anemia rate (92.9%) (Table 3).

**Table 3: Hematological Parameters by Diagnosis**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Diagnosis** | **Mean MCV (fL)** | **Mean MCH (pg)** | **Mean Hb (g/dL)** | **Microcytosis (%)** | **Anemia (%)** |
| Normal | 82.4 ± 6.3 | 27.1 ± 2.1 | 13.6 ± 1.2 | 12.7% | 18.3% |
| Hb E trait | 74.8 ± 4.9 | 24.5 ± 1.8 | 12.2 ± 1.4 | 61.3% | 54.8% |
| Hb E disease | 69.6 ± 5.2 | 21.8 ± 2.0 | 10.3 ± 1.6 | 71.4% | 92.9% |
| Beta thalassemia trait | 66.3 ± 4.7 | 20.2 ± 1.5 | 11.8 ± 1.5 | 87.5% | 75.0% |
| Low Hb A2 | 80.2 ± 6.5 | 26.2 ± 2.4 | 12.8 ± 1.2 | 31.0% | 20.0% |
| Alpha thalassemia | 67.4 ± 5.8 | 22.1 ± 1.9 | 11.0 | 100% | 100% |

Family history and consanguinity were strongly associated with beta-thalassemia trait and Hb E disease. Iron deficiency was common among Hb E patients, possibly confounding the Hb A2 values (Table 4).

**Table 4: Family History and Comorbidity by Diagnosis**

|  |  |  |  |
| --- | --- | --- | --- |
| **Diagnosis** | **Family History Positive (%)** | **Known Consanguinity (%)** | **Iron Deficiency (%)** |
| Hb E trait | 48.4% | 19.3% | 16.1% |
| Hb E disease | 64.3% | 28.6% | 21.4% |
| Beta thalassemia trait | 81.3% | 31.3% | 18.8% |
| Other disorders | 22.1% | 11.5% | 9.6% |

The analysis revealed that Hb A2 levels were negatively correlated with MCV and MCH, supporting its diagnostic role in identifying β-thalassemia trait. Hb E levels showed a strong inverse relationship with Hb A and hematologic indices, indicating its impact on red cell parameters. A statistically significant association was observed between family history and abnormal hemoglobin variants (notably Hb A2 and Hb E), highlighting a potential hereditary pattern. Additionally, iron deficiency was found to mildly suppress Hb A2 levels, which can act as a diagnostic confounder in thalassemia screening (Table 5).

**Table 5: Correlation of Hemoglobin Variants with Hematological Parameters**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Parameter** | **Hb A2 (r)** | **p-value** | **Hb F (r)** | **p-value** | **Hb E (r)** | **p-value** |
| MCV | –0.62 | <0.001 | –0.43 | 0.004 | –0.56 | <0.001 |
| MCH | –0.59 | <0.001 | –0.39 | 0.006 | –0.50 | <0.001 |
| Hb A | –0.89 | <0.001 | –0.45 | 0.002 | –0.92 | <0.001 |
| Hemoglobin (g/dL) | –0.41 | 0.008 | –0.35 | 0.011 | –0.47 | 0.003 |
| Family history (Yes) | +0.54 | <0.001 | +0.22 | 0.041 | +0.38 | 0.006 |
| Iron deficiency | –0.25 | 0.033 | +0.07 | 0.47 | –0.19 | 0.067 |

Table 6 outlines the diagnostic thresholds used for interpreting hemoglobin variants. An Hb A2 level >3.5% is indicative of beta thalassemia trait, while a level <1.5% suggests alpha thalassemia or iron deficiency anemia (IDA). Hb E levels between 15–30% point to Hb E trait, whereas levels >85% are consistent with Hb E disease. Elevated Hb F (>10%) may suggest delta-beta thalassemia or Hereditary Persistence of Fetal Hemoglobin (HPFH). These cut-offs are critical for differentiating hemoglobinopathies during screening.

**Table 6: Diagnostic Cut-Offs Used in Interpretation**

|  |  |  |
| --- | --- | --- |
| **Hemoglobin Variant** | **Diagnostic Threshold** | **Diagnostic Use** |
| Hb A2 | >3.5% | Beta thalassemia trait |
| Hb A2 | <1.5% | Suggestive of alpha thalassemia or IDA |
| Hb E | 15–30% | Hb E trait (heterozygous) |
| Hb E | >85% | Hb E disease (homozygous) |
| Hb F | >10% | Delta-beta thalassemia / HPFH suspicion |

**DISCUSSION**

This study aimed to evaluate the spectrum and distribution of hemoglobinopathies using hemoglobin electrophoresis in a population sample of 215 individuals in Bangladesh. The findings underscore a significant prevalence of abnormal hemoglobin variants, especially hemoglobin E (Hb E), and reveal important hematological and demographic patterns that align with both regional and international trends23. Normal hemoglobin profiles were found in 66.05% of participants, while the remaining 33.95% exhibited abnormal findings, consistent with earlier studies conducted in Southeast Asia and Bangladesh, where abnormal hemoglobin variants are endemic due to high gene frequencies and historical consanguinity patterns24,25. Among abnormal cases, Hb E trait was the most frequent (14.42%), followed by beta-thalassemia trait (7.44%) and Hb E disease (6.51%). This trend corroborates earlier research reporting Hb E as the most common variant in Bangladesh, particularly in regions bordering India and Myanmar26.

The observed frequency of beta-thalassemia trait (7.44%) is comparable to national prevalence estimates ranging from 6–10%, suggesting that despite public health efforts, carrier frequency remains high [3]. The co-occurrence of high Hb A2 (>3.5%) and reduced MCV and MCH in these cases strongly supports their classification as beta-thalassemia carriers. Two cases with elevated Hb F (>10%) may represent delta-beta thalassemia or hereditary persistence of fetal hemoglobin (HPFH), which are rare but clinically significant conditions requiring molecular confirmation.

The most affected age group was 20–50 years, particularly for Hb E trait and beta-thalassemia carriers. This distribution is likely a reflection of the diagnostic focus on reproductive-age adults during premarital or antenatal screening. A female predominance was seen in most groups, especially Hb E trait (female:male ratio 2.1:1), possibly due to higher healthcare-seeking behavior among women or more frequent referral during pregnancy screening programs.

Children with abnormal hemoglobin patterns, including a case of HPFH with Hb F >30%, highlight the importance of early screening. Elevated Hb F in neonates and infants was expected physiologically; however, persistent elevation beyond infancy may indicate underlying genetic persistence or compound heterozygosity.

Hematological indices provided strong discriminatory value between normal and abnormal hemoglobin profiles. For instance, MCV and MCH were significantly reduced in beta-thalassemia trait (66.3 fL, 20.2 pg) and Hb E disease (69.6 fL, 21.8 pg). These findings are consistent with the microcytic, hypochromic anemia typical of thalassemic syndromes and reinforce the use of complete blood counts (CBC) in preliminary screening.

Notably, anemia (Hb <11 g/dL) was present in 92.9% of Hb E disease cases and 75% of beta-thalassemia carriers. These rates are higher than some international reports, possibly due to coexisting nutritional deficiencies or undiagnosed iron deficiency anemia, which was present in over 13% of the total study population. Iron deficiency can mask or mimic thalassemia, particularly by lowering Hb A2, thereby complicating the diagnostic process27.

Positive family history was seen in 40.9% of all participants and was particularly high in beta-thalassemia trait (81.3%) and Hb E disease (64.3%), reinforcing the autosomal recessive inheritance pattern of these disorders. Consanguinity was reported in 14.9% of all cases, and notably in 31.3% of beta-thalassemia traits, supporting previous data suggesting a direct relationship between consanguineous marriage and carrier frequency28,29.

Comorbid iron deficiency was observed in 13.5% of cases, further underscoring the need for iron studies in thalassemia screening. Overlapping iron deficiency can obscure or misclassify Hb A2 values, leading to underdiagnosis or misdiagnosis, particularly in women of childbearing age.

Statistical analysis revealed several significant correlations. Hb A2 negatively correlated with MCV (r = –0.62) and MCH (r = –0.59), typical of beta-thalassemia carriers. Hb E levels showed a strong inverse correlation with Hb A (r = –0.92), reflecting the replacement of Hb A by Hb E in homozygous individuals. Additionally, family history correlated positively with Hb E (r = 0.38) and Hb A2 (r = 0.54), indicating strong genetic clustering in affected families. Interestingly, iron deficiency negatively correlated with Hb A2 (r = –0.25), though not with Hb F, suggesting that iron status may confound thalassemia detection but has less impact on fetal hemoglobin expression30.

The findings of this study align with multiple regional reports indicating a high prevalence of Hb E and beta-thalassemia in South Asia31,32. However, compared to some Indian and Thai studies, the rate of Hb E disease was slightly lower, possibly due to selection bias or differences in population structure. The use of electrophoresis as the sole diagnostic modality is a limitation when compared to HPLC-based studies, which provide better resolution of overlapping peaks and quantification of borderline variants.

**CONCLUSION**

This study provides valuable insights into the prevalence and distribution of hemoglobinopathies and thalassemias in a Bangladeshi population. Hb E trait and beta-thalassemia trait were the most common disorders identified, reflecting the high burden of these inherited hemoglobinopathies in the region. Hemoglobin electrophoresis remains a critical diagnostic tool for screening these disorders, especially in resource-limited settings. The study revealed significant correlations between hemoglobin variants and red blood cell indices, further emphasizing the utility of electrophoresis in diagnosing thalassemia and other hemoglobinopathies. Early detection through screening, particularly in at-risk populations, could lead to better management and reduced morbidity from these genetic disorders.

**Limitations**

While this study provides a comprehensive analysis of hemoglobinopathies in the Bangladeshi population, there are several limitations that must be considered. First, the sample was restricted to patients referred for hemoglobin electrophoresis at a tertiary care center, which may introduce selection bias and limit the generalizability of the findings to the wider population. Second, while the study included a broad range of hemoglobin variants, molecular genetic testing was not conducted to confirm some diagnoses, such as compound heterozygous states or rare variants. Additionally, the absence of longitudinal data limits the ability to assess the clinical outcomes of patients over time. Lastly, potential laboratory errors or inconsistencies in result interpretation, such as the case of inconsistent Hb E-trait patterns, could impact the accuracy of the findings.

**Recommendations**

To improve the management and diagnosis of hemoglobinopathies in Bangladesh, the following recommendations are made:

1. **Expand Screening Programs:** Given the high prevalence of hemoglobinopathies, it is crucial to implement large-scale newborn screening programs to detect carriers and affected individuals early. This can help in reducing the impact of these disorders on public health.
2. **Molecular Genetic Testing:** Incorporating molecular genetic testing in conjunction with hemoglobin electrophoresis can provide more definitive diagnoses, especially for compound heterozygous states and rare hemoglobinopathies.
3. **Public Awareness and Genetic Counseling:** There should be an emphasis on public awareness campaigns and genetic counseling services for individuals diagnosed with hemoglobinopathies. These services can help families understand the inheritance patterns and the potential risks of passing on hemoglobin variants to offspring.
4. **Improved Diagnostic Infrastructure:** Enhancing laboratory infrastructure with automated systems, better quality control, and more advanced diagnostic tools (such as high-performance liquid chromatography, HPLC) could improve the accuracy and reliability of hemoglobinopathy diagnosis.
5. **Further Epidemiological Studies:** Additional population-based studies should be conducted to estimate the regional prevalence of various hemoglobin variants and identify demographic factors that influence the distribution of these disorders. Long-term cohort studies could also help in understanding the clinical outcomes of patients with different hemoglobinopathies, facilitating better management and treatment strategies.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that they have no known competing financial interests OR non-financial interests OR personal relationships that could have appeared to influence the work reported in this paper.

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