Review

β-Thalassemia in Bangladesh: Current Status and Future Perspectives

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Abstract: β-thalassemia, a life-threatening inheritable hemoglobin disorder caused by mutations in the HBB gene, poses a significant public health challenge in the world. Although no comprehensive work has been carried out in Bangladesh, the world prevalence and small-scale works indicated the possibility of a high prevalence of this disease in the country. Therefore, this review aims to explore the present situation of β-thalassemia in Bangladesh and propose approaches to mitigate its impact in the future. Limited awareness, a high incidence of consanguineous marriage, and inadequate access to healthcare are possible factors responsible for the high prevalence of thalassemia in Bangladesh, while the absence of public health policy and a national health insurance system further exacerbate the situation. The understanding of the genetic landscape and modern treatment strategies for β-thalassemia is hindered by the lack of comprehensive data on the mutation spectrum. In addition to conventional therapy such as blood transfusion, advanced practices such as splenectomy, hematopoietic stem cell transplantation, and emerging therapies such as gene therapy show promise for future cures but have yet to be widely implemented in this country. To effectively address the challenges of β-thalassemia, it is crucial to adopt comprehensive strategies, including a public awareness campaign, public health intervention, mandatory premarital screening, genetic counselling, and a national thalassemia prevention program. Additionally, understanding the spectrum of mutations and new therapeutic interventions is crucial for advanced healthcare strategies.

Keywords: β-thalassemia; Bangladesh; premarital screening; consanguineous marriage

1. Introduction

β-thalassemia is the most common autosomal recessive monogenic disorder categorized by abnormal or reduced production of β-globin subunits of hemoglobin due to mutations in the HBB gene, resulting in anemia [1,2]. Based on the descending order of severity, β-thalassemia is classified as β-thalassemia-major, intermedia, and minor or carrier status [3]. β-thalassemia major is mainly due to (β0) or compound heterozygous (β+) mutations of the HBB gene, where the patients have greatly reduced β-globin synthesis. Individuals with β-thalassemia major usually come to medical attention within the first 2 years of birth and require regular blood transfusions to survive [3]. Affected infants fail to thrive, gain weight normally, and become progressively pale. Feeding problems, diarrhea, irritability, fever, and progressive enlargement of the abdomen due to splenomegaly and prominence of the cheekbones tend to obscure the base of the nose and expose the upper teeth; puffiness of the eyelid and a tendency to a mongoloid slant of the eyes are common presenting symptoms [4]. Homozygous for β+ or compound heterozygous for β0 or β+ genes are responsible for β-thalassemia intermedia. In β-thalassemia intermedia, patients with an Hb of much below 7 or 8 gm/dL excess energy consumption due to profound hemolysis can produce small stature, poor weight gain, poor energy levels, susceptibility
to infection, and yellow discoloration of the skin, eyes, and mucous membranes caused by an increased amount of bilirubin in the blood [4]. β-thalassemia minor is due to underproduction or zero production of one of the HBB genes (β+/β and β0/β). Also called the carrier state, which is clinically asymptomatic. While β-thalassemia minor may present in diverse manners, typical symptoms encompass fatigue, weakness, pallor, diminished appetite, delayed growth, abdominal distension, frequent infections, and anemia. E-beta thalassemia, also known as beta-thalassemia with abnormal hemoglobin E, occurs when there is a combination of mutations in the HBB gene, resulting in reduced or absent production of beta-globin chains along with the presence of an abnormal hemoglobin variant called hemoglobin E. This combination leads to a spectrum of clinical presentations, ranging from mild anemia to more severe forms, depending on the specific mutations involved and their interaction with hemoglobin E. E-beta thalassemia is more commonly found in India, Bangladesh, and Southeast Asia [5].

Worldwide, approximately 1.5% of people are β-thalassemia carriers [6]. Although the overall combined number of patients with the disease and carriers is known in most countries, significant variations occur even within small geographic regions [7]. Existing findings suggest that the prevalence of β-thalassemia has increased in all geographic regions throughout the years in South Asia, including Bangladesh [7,8]. Unfortunately, a comprehensive study on β-thalassemia is yet to be designed in Bangladesh. In this study, we will discuss the current situation of β-thalassemia and propose future perspectives, which will help to gain insights into possible actions needed to mitigate this inherited disease in Bangladesh.

2. Status of β-Thalassemia in Bangladesh

2.1. Prevalence of β-Thalassemia Carrier and Patients in Bangladesh

β-thalassemia is suspected to be one of the most common life-threatening hemoglobin disorders in Bangladesh. Assessing the frequency and impact of hemoglobinopathies in Bangladesh is difficult due to a lack of comprehensive data, and the existing statistics may not accurately reflect the entire population. Although a complete study has not been conducted yet, preliminary research has indicated that this disease is becoming a significant public health issue in Bangladesh. It is estimated that 6–12% of the population, or roughly 10–19 million people, are carriers of β-thalassemia in Bangladesh [9]. Approximately 6000 to 8000 newborns with thalassemia are born in Bangladesh each year [10]. The current situation necessitates a comprehensive investigation to accurately assess the extent of β-thalassemia in Bangladesh and effectively tackle this health concern [11]. In 2005, a study conducted on school children in six districts of Bangladesh using hemoglobin electrophoresis revealed that the overall prevalence of the β-thalassemia trait was 4.1%, while carriers among tribal children were 4.2%. The highest prevalence was observed in Barisal Division at 8.1%, followed by Rajshahi Division at 5.5%, Sylhet Division at 5.2%, Dhaka Division at 3.2%, Chittagong at 2.9%, and Khulna Division at 2.4% [10]. Many nations throughout the world exhibit regional disparities in the incidence of hemoglobinopathies. Micromapping plays a crucial role in determining the carrier status of a certain region [10]. Uddin et al. conducted a study on around 600 patients with anemia for a three-month period. Among the patients, the study found that β-thalassemia minor (21.3%) had the highest prevalence compared to other forms. The proportion of males and females was nearly identical, resulting in equal occurrences in both genders [12]. A study examining the occurrence of thalassemia and its association with liver function, categorized by gender and age groups, found that the median age of the population was 16 years among 53 patients. The study also revealed that a majority of individuals at risk of liver dysfunction were male (60.4%), while females accounted for approximately 39.04% [13]. Furthermore, findings from this study underscored the increasing age-related complications associated with β-thalassemia [12]. In 2020, a nationwide survey on β-thalassemia variants aimed to assess the prevalence of thalassemia carriers across the country. A total of 1877 individuals participated, revealing that 11.89% of the population carried the thalassemia mutation. Among
these carriers, 2.28% exhibited the β-thalassemia trait. Notably, participants from Rangpur exhibited the highest carrier frequency at 27.1%, while those from Khulna displayed the lowest frequency at 4.2% among the eight surveyed divisions [13].

2.2. Factors Responsible for β-Thalassemia in Bangladesh

One of the major factors for this significant increase in the prevalence conditions in Bangladesh is consanguineous marriage, with a nationwide prevalence rate of 6.64%, peaking at an extreme 17.6% in the southeast region [14]. Due to the autosomal recessive pattern of β-thalassemia disease, there is a 25% chance of offspring having this disease if both parents are carriers. Despite being in the thalassemia belt, Bangladesh lacks comprehensive data on thalassemia epidemiology, clinical aspects, mortality, and treatment outcomes, leading to insufficient public awareness [15]. Additionally, the absence of a national health insurance system and organized awareness programs exacerbates the situation [16]. Recent findings revealed that only ~48% of the overall population had heard about thalassemia, and Bangladesh is also influenced by various socio-economic and healthcare factors. Economic indicators, including income levels and education, play a crucial role in thalassemia. Lower socio-economic status is often linked to reduced awareness and delayed medical intervention [11].

These findings indicate the need for educational programs, health counselling, pre-marital screening, prenatal screening, and campaigning to prevent thalassemia. Premarital screening aims to identify β-thalassemia carriers among couples planning to marry [17], whereas prenatal screening can be carried out by analyzing the fetal gene around the fourth to fifth month of development or by sampling chorionic villi at 11 weeks of gestation. Genetic counselling is also crucial, as it serves as a valuable resource for individuals and families seeking guidance, support, and information about genetic conditions, empowering them to make informed decisions and navigate the complexities of genetic health effectively [1]. Personalized healthcare is crucial for improving the health of individuals with thalassemia in Bangladesh, as it requires tailored interventions based on everyone’s genetic profile, clinical severity, and specific complications. Despite the increasing prevalence of thalassemia, public awareness in Bangladesh is alarmingly low. One recent study demonstrated that only 47.4% of the respondents had heard of thalassemia. Moreover, 49.8% of participants were knowledgeable that consanguineous marriages are an important risk factor of thalassemia [16], and 98% of parents heard the term thalassemia after their children were diagnosed with thalassemia [18].

2.3. Mutation Spectrum

Globally, more than 500 disease-causing mutations have been characterized in the HBB gene, nearly all of them affect the β-globin locus and are extremely heterogeneous [11]. Though the prevalence of β-thalassemia in Bangladesh is relatively high, the complete mutation spectrum is yet to be elucidated. Recent findings from different studies revealed that different mutations were most prevalent in their cohort, as shown in Table 1. In 2017, Aziz et al. described a novel mutation (HBB: c.235_236insC) in exon 2 of the β-globin gene, found in a family from Nowgaon, Bangladesh [19]. Recent findings of different studies revealed different mutations as most prevalent in their cohort: Codon 41/42 (-TTCT) was 22.22% [20], IVS-I-5 (G > C) was 39.1% [21], and IVS-I-5 (G > C) was 56.25% [22]. Most of the study has predominantly employed traditional electrophoresis, amplification refractory mutation system-polymerase chain reaction (ARMS-PCR), and Sanger sequencing methodologies, while the utilization of high-throughput techniques such as next-generation sequencing (NGS) has been notably lacking. Particularly, validated molecular diagnosis approaches and postnatal screening are still unavailable.
<table>
<thead>
<tr>
<th>Studies</th>
<th>Screening Process</th>
<th>Total Population</th>
<th>Mutation Pattern</th>
<th>Frequency of Mutation (%)</th>
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<tr>
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<td>4813</td>
<td>Hb E β-thalassemia</td>
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<td>c.92 + 130G &gt; C</td>
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<td>c.151A &gt; G *</td>
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<td></td>
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<td></td>
<td>c.126_129delCTTT</td>
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<td></td>
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<td>c.27_28insG</td>
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<td>c.47G &gt; A</td>
<td>1.35</td>
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<td></td>
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<td></td>
<td>c.79G &gt; A + c.92 + 5G &gt; C</td>
<td>0.9</td>
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<tr>
<td>[22] PCR and direct DNA sequencing</td>
<td></td>
<td>16</td>
<td>IVS-I-5 (G &gt; C.)</td>
<td>56.25</td>
</tr>
</tbody>
</table>

*: Novel mutation; not reported in Bangladeshi population and also globally.
2.4. Socio-Economic Impacts of β-Thalassemia

Families affected by beta-thalassemia encounter significant financial burdens due to the high cost of treatment, including regular blood transfusions and iron chelation therapy [16]. Though in Bangladesh no study has been conducted to reveal the effects of the disease on the education and employment status of the patients, several studies have demonstrated that the financial strain associated with beta-thalassemia often leads to decreased access to education and limited employment opportunities for both patients and their caregivers, perpetuating cycles of poverty. Managing beta-thalassemia requires frequent medical visits and monitoring, resulting in productivity losses for patients and their caregivers as they must take time off work or school [25]. The stigma surrounding beta-thalassemia can lead to social isolation, discrimination, and limited social support networks for affected individuals and their families, exacerbating the psychosocial impact of the condition [26]. Moreover, the management of beta-thalassemia places strain on the healthcare system in Bangladesh, diverting resources from other essential health services and contributing to inefficiencies within the system.

2.5. Challenges in Diagnostics and Screening Programs

The success of any diagnostics and screening program relies on public awareness and acceptance, as well as cost-effectiveness. Notably, the cost of diagnosis in Bangladesh is a critical barrier, with β-thalassemia screening incurring approximately USD 10–USD 15, where households bear about 64.3% of the total healthcare costs, as the government of Bangladesh spends only USD 26.60 per capita for healthcare services [27,28]. Moreover, the nation’s Muslim-majority population, with strong religious beliefs and consanguineous marriage traditions, tends to harbor negative views on premarital screening, further impeding screening initiatives [29].

Furthermore, in Bangladesh, multidisciplinary expertise and support facilities for standard β-thalassemia management are not usually available in most public hospitals and private clinics [11]. As a consequence of inadequate access to healthcare, a significant proportion of β-thalassemic patients in Bangladesh might die even without knowing their disease conditions. The most conservative direct medical cost for thalassemia patients ranges from BDT 127,000–309,000 (USD 1154–2810) per year, which is almost unaffordable compared to the low monthly income, suggesting a huge economic burden that could render seeking treatment for most β-thalassemia patients unviable in Bangladesh [11].

2.6. Public Health Policies and Interventions

The absence of a comprehensive national policy dedicated to β-thalassemia prevention remains a major gap in Bangladesh’s public health landscape [11]. Overcrowd and resource shortages in public hospitals limit their capacity to effectively address β-thalassemia cases, whereas resourceful private hospitals remain inaccessible to the general population due to the associated high costs, contributing to a high treatment drop-out rate [11,30]. The government of Bangladesh has forced the Infectious Diseases Act to raise awareness of, prevent, control, and eradicate infectious or communicable diseases, but no such initiatives were taken in cases of genetic diseases such as β-thalassemia [31]. Though in 2019, the government of Bangladesh launched national guidelines on thalassemia management for physicians [32], there is still no national-level thalassemia prevention program [33]. While there are existing thalassemia societies such as the Bangladesh Thalassemia Foundation, Thalassemia Welfare Society, Thalassemia Society of Doctors, and some healthcare centers, they struggle to address the vast population’s needs [33]. Observances of World Thalassemia Day on 8 May, serve as a platform for awareness, but a centralized national program is yet to be established [33]. As it has already been proven in several countries worldwide that implementation of mandatory national prematitis screening programs could drastically reduce the incidence of infants born with thalassemia major, the Ministry of Health, Bangladesh, has announced a recent intention to start a national screening program for thalassemia [16].
A number of intervention strategies, including mandatory premarital screening, genetic counselling, and prenatal diagnosis (PND) with an option for termination of the affected pregnancy, are implemented in different countries for the prevention of thalassemia [9]. While some countries have achieved a high level of success (80–100%) in preventing the births of children with thalassemia [17], PND and therapeutic abortion remain unacceptable in Bangladesh because of cultural and religious restrictions [9].

2.7. Treatment and Patient Management of β-Thalassemia in Bangladesh

In the standard treatment of β-thalassemia, a multidisciplinary approach is utilized, which includes a wide range of medical specialities such as pediatric hematology, pediatrics, transfusion medicine, endocrinology, cardiology, dentistry, dieticians, psychology, psychiatry, and social work, in addition to a robust blood bank system and infrastructure [11]. In Bangladesh, the majority of public hospitals and private clinics do not typically provide access to these multidisciplinary expertise and support facilities. Consequently, most of the β-thalassemia major patients are dependent on blood transfusions for a lifetime [34]. All thalassemia children require at least one to four bags of blood each month; around 80% of families face difficulties in collecting blood because of donors and support from NGOs. Only 31% of the estimated blood demand is met by voluntary blood donors [18]. The unavailability of iron chelator medicines has been a major problem raised by families; only 43% of patients use iron chelators [11]. In addition, patients with regular blood transfusions are in danger of developing post-transfusion hepatitis. Bangladesh also detected higher positive cases of hepatitis C (HCV) among multi-transfused thalassemia patients [35]. But in low- to middle-income countries, including Bangladesh, the economic burden serves as a barrier to accessing HCV antiviral therapy [36]. The increased risk of HCV infection in β-thalassemia patients is mainly connected with median age, duration, and mean amount of blood transfused. So, it is required to be vaccinated before starting regular vaccination [37].

3. Strategies for Prevention and Control

3.1. Genetic Counselling and Screening

Genetic counselling is mandatory to encourage premarital and prenatal genetic testing to identify carriers and provide informed choices for family planning. Prior studies have noted the positive attitudes of Bangladeshis toward premarital testing [16,18]. These findings suggest that there is a likelihood of widespread acceptance of genetic counselling among the general population in the future.

3.2. Public Awareness Campaigns

To raise public awareness, comprehensive awareness programs need to be implemented in places including schools, communities, and healthcare facilities to spread information about β-thalassemia, its consequences, and preventive measures. Furthermore, detailed information regarding β-thalassemia should be spread through radio, television, newspaper, and social networking sites, including Facebook and Twitter. Informational leaflets and booklets should be distributed in schools, colleges, and universities. Every hospital, family planning clinic, and even marriage registry office should have posters, leaflets, and festoons containing information on β-thalassemia [33].

3.3. Education in Schools

While taking prior studies into account, strategies should extend to targeting high/secondary school students for β-thalassemia education and screening to embed awareness and prevention into the societal fabric [16,38]. β-Thalassemia education needs to be integrated into the school curriculum to ensure that the younger generation understands the importance of genetic screening and thalassemia prevention.
3.4. Government Policies and Regulations

The government should implement and enforce policies that encourage genetic testing and counselling, ensuring accessibility and affordability of screening services. The Ministry of Health should also provide adequate training to health workers to discourage consanguineous marriages among the public and arrange thalassemia prevention programs all over Bangladesh [16]. Moreover, support networks and counselling services should be provided for families with thalassemia patients, addressing the emotional and practical challenges they may face. The government should also pay attention to strengthening healthcare infrastructure to facilitate early diagnosis, treatment, and management of β-thalassemia cases.

3.5. Research and Innovation

Large-scale research is necessary to calculate the actual burden of β-thalassemia in Bangladesh and address this health issue [11]. So, investment needs to be made in research to explore new treatment options, including gene therapy, and collaborate with international organizations to share knowledge and resources. Even the high prevalence of inherited hemoglobin disorders in Bangladesh necessitates a shift in anemia prevention strategies, as universal iron chelation may have unintended negative consequences. Therefore, accurate community-based estimates are vital to planning effectively for both inherited blood disorders and anemia prevention [39].

3.6. Incentives for Healthcare Professionals

In Bangladesh, incentivizing healthcare professionals for β-thalassemia prevention is crucial. This can be achieved by offering financial rewards, professional recognition, and training opportunities. Government initiatives should include special allowances or bonuses for professionals (doctors, nurses, health workers, and family planning workers) actively contributing to β-thalassemia awareness, genetic counselling, and screening programs. Additionally, creating a conducive working environment and career advancement prospects in β-thalassemia-related fields can further motivate healthcare professionals to actively participate in prevention efforts. Continuous education and skill development programs should be promoted, ensuring that healthcare professionals stay updated on the latest advancements in β-thalassemia prevention and care.

Besides these, following possible recommendations of the World Health Organization (WHO), including recognition of hemoglobinopathies as a major health problem, the development of a national registry, the establishment of national blood services and specialized patient care centers, and the extension of international collaboration, is also necessary to recognize and respond to the challenges posed by the prevalence of hemoglobinopathies [32].


4.1. Splenectomy

Thalassemia major and thalassemia intermedia are both characterized by severe hemolysis, which leads to an overactive spleen in patients with these conditions. Splenectomy is the recommended method of treatment for thalassemia major patients in order to lessen the increased blood intake and associated severe iron overload. However, due to the increased risk of infection and thrombotic complications, splenectomy is not often used [40]. The procedure of splenectomy has traditionally been utilized in patients diagnosed with β-thalassemia as an alternative to the practice of blood transfusion [41,42]. This procedure is therefore recommended for patients who exhibit symptoms such as hypersplenism, cytopenia, early satiety, increased blood requirement, or symptomatic splenomegaly accompanied by pain in the left upper quadrant [43,44].

4.2. Hematopoietic Stem Cell Transplantation

Hematopoietic stem cell transplantation (HSCT) offers a beacon of hope for β-thalassemia patients, promising a potential cure for this debilitating blood disorder for the last two
decades. However, its feasibility and limitations underscore a complex landscape. Recognized as a time-consuming and expensive procedure, the success of HSCT hinges on a robust institutional infrastructure network. While traditionally relying on perfectly matched donors, the landscape is rapidly evolving [45,46]. Novel approaches such as unrelated organ transplants, cord blood transplants, and haplo-identical transplants serve as innovative strategies to expand the donor pool [47].

However, the limited availability of bone marrow transplant (BMT) centers, particularly in regions such as Bangladesh, poses challenges, with a mere fraction of total BMTs done to thalassemic patients. Unfortunately, in Bangladesh, there are only four bone marrow transplant (BMT) centers available [34]. Only two thalassemic patients have received bone marrow transplants out of 210 total patients as of April 2023 [34]. To address this issue, there is a need for the improvement of BMT facilities that are reserved solely for thalassemia patients.

4.3. Gene Addition

The patient after myeloablation goes through a process in which autologous human stem cells are injected with a lenti-viral/retroviral vector carrying the complete regulatory and beta-globin-producing genes in vitro. Subsequently, the transformed stem cells are infused back into the patient [48]. The standard procedure for gene therapy involves the removal of hematopoietic stem cells (HSCs), the modification of their genetic code outside of the body, and the subsequent reintroduction of these cells into the hematopoietic compartments through a myeloablative conditioning regimen [49].

4.4. Gene-Editing Therapy

Modulating regulators for globin genes to enhance chain synthesis is a distinct strategy that has emerged with a better understanding of the molecular mechanisms regulating globin gene expression [50]. BCL11a is a promising candidate for gene-editing techniques because it is a transcription factor that controls the transition from HbF to HbA. Inhibiting BCL11a may reactivate HbF development in thalassemia patients, offering a potential treatment option [51]. Zinc finger nucleases (ZFN), transcription activator-like effector nucleases (TALEN), and CRISPR-Cas9 nucleases have been used for editing [52]. After development and scaling, these strategies are expected to advance to clinical trials soon. If proven effective, safe, and long-lasting, these approaches could greatly improve conditions for individuals with β-thalassemia. So far, in Bangladesh, only gene therapy has been used to treat a 22-month-old boy named Raihan with spinal muscular atrophy (SMA), a rare neurodegenerative disease. This was carried out at the National Institute of Neurosciences and Hospital (NINS) with the collaboration of Novartis Bangladesh Ltd. (Dhaka, Bangladesh). The total cost of this gene therapy was 2.1 million dollars (22 crores BDT) [53]. Clinical trial centers for Food and Drug Administration-approved gene therapy products for patients with transfusion-dependent β-thalassemia are now available in high-income countries such as the United States (41.1%), China (26%), and Italy (6.8%) [54]. Though the timeline for the widespread availability of gene therapy remains uncertain, there is hope that in the future, the cost of gene therapy will be affordable and available for thalassemia treatment.

5. Conclusions

β-thalassemia stands as a significant concern within the public health context. The burden of this disease is fueled by the interaction of several factors, including high carrier rates, consanguineous marriages, poor awareness, and inadequate access to healthcare, as described in this article. Understanding the mutation spectrum, which is crucial for personalized care and targeted interventions, remains a pressing need. While the complexities of managing β-thalassemia can be daunting, this study also paints a picture of hope and opportunity. Public awareness campaigns, mandatory premarital screening, and accessible genetic counselling hold immense potential for preventing thalassemia births. When it comes to the management of β-thalassemia, Bangladesh has made significant
progress despite the limitations of its healthcare system. By centralizing blood collection and improving donor recruitment, blood transfusion, which is the foundation of treatment, needs to be strengthened even further. Emphasizing the availability of iron chelators and comprehensive healthcare support are vital for managing β-thalassemia in Bangladesh. Additionally, increasing access to BMT facilities through alternative donor options such as unrelated organ transplants, cord blood transplants, and haplo-identical transplants is crucial for effective treatment. Emerging therapies such as gene therapy offer hope for a definitive cure, but progress in these methods, including gene addition and gene editing techniques, requires robust research pipelines and international collaborations. In sum, addressing thalassemia in Bangladesh requires a multi-pronged approach. We need to increase public awareness, prevention strategies, access to quality healthcare services, and advanced treatment options. Bangladesh can ensure a brighter future for its β-thalassemia-affected population by promoting collaboration and research initiatives.

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