Predictability of Thalassemia Using AI

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Thalassemia represents one of the most common genetic disorders worldwide, characterized by defects in hemoglobin synthesis. The affected individuals suffer from malfunctioning of one or more of the four globin genes, leading to chronic hemolytic anemia, an imbalance in the hemoglobin chain ratio, iron overload, and ineffective erythropoiesis. Despite the challenges posed by this condition, recent years have witnessed significant advancements in diagnosis, therapy, and transfusion support, significantly improving the prognosis for thalassemia patients.

thalassemia blood disease deep learning prediction machine learning

1. Introduction

A series of hereditary blood diseases known as thalassemia are characterized by the abnormal or reduced production of one or more hemoglobin genes [1]. It ranks among the most common five birth complications [2]. There is a high prevalence of thalassemia worldwide, particularly in Southeast Asian nations. αT and βT are the two main classifications of defective globin [3]. Alpha-thalassemia may also result in hemoglobin H (HbH) disease, anemia, and hydrops fetalis syndrome. The amount of alpha-chain produced determines the disease's severity. The major form of alpha-thalassemia has placed a heavy burden on society and harms the general population's standard of living. Children with βT major experience impaired growth, hemolytic anemia [4], and aberrant development of the skeleton. For the remainder of their lives, the afflicted youngsters will require regular blood transfusions. Intermediary βT is less severe than βT major and may call for sporadic blood transfusions. Patients who depend on transfusions will experience an iron burden [5] and need chelation therapy to get rid of extra iron. Some young patients with βT major may benefit from bone marrow transplants [6]. Normal life expectancy is experienced by those who have the thalassemia trait. By the age of 30, βT major patients frequently pass away from cardiac problems brought on by iron overload.

2. Thalassemia

The generation of healthy alpha- or beta-globin chains, which make up hemoglobin, is impacted by a series of autosomal recessive hemoglobinopathies known as thalassemia. α- or β-globin chain [1][6] amalgamation problems may result in anemia, early oxidation of the blood, and inefficient erythropoiesis. Thalassemia patients may have extramedullary hematopoiesis and bone marrow enlargement as a result of chronic, severe anemia. Patients with microcytic anemia and normal or increased ferritin levels should be suspected of having thalassemia. Although

genetic testing is necessary to confirm the diagnosis, hemoglobin electrophoresis can highlight shared traits across various thalassemia subtypes. Generally, thalassemia in carriers and trait states is asymptomatic.

Hydrops fetalis is a common birth defect brought on by alpha-thalassemia major. Beginning in early childhood (often before the age of two), βT major requires lifelong transfusions. Based on gene deletion or mutation, αT and βT intermedia present differently, and severe variants cause symptomatic anemia and need transfusions, whereas milder ones merely need monitoring. Transfusions, iron chelation therapy, hydroxyurea [7], hematopoietic stem cell transplantation [8], and Luspatercept [9] are all used in the treatment of thalassemia to reduce iron overload brought on by gastrointestinal absorption of iron, hemolytic anemia [10], and recurrent transfusions. Thalassemia consequences include perivascular iron deposition, bone marrow enlargement, and extramedullary hematopoiesis. A few of the morbidities that may arise from these issues include damage to the skeletal system, endocrine system [11], heart [12][13][14], and liver [5]. Life expectancy for people with thalassemia has greatly risen over the past 50 years thanks to better monitoring [5] of iron overload, increasing availability of transfusions of blood, and iron chelation treatment. Genetic counselling and screening in high-risk populations can reduce the prevalence of thalassemia [1]. Africa, India, the Mediterranean, Southeast Asia, and the Middle East [15][16][17] have the greatest rates of thalassemia prevalence. Preventative initiatives incorporating premarital and preconception counselling and testing may be contributing to a decline in incidence in these areas. Carriers of αT and βT make up around 5% and 1.5%, respectively, of the global population.

The globin chains in a physiological situation are a balanced mixture of α globin chains and non-α globin chains, primarily β-chains, which, when combined with α-chains, form adult hemoglobin (HbA), with δ-chains, form a minor portion of adult hemoglobin, called HbA2, or with γ-chains, form fetal hemoglobin (HbF). If one of the globin chains is not produced as much as it should while the other chains are still being produced normally, the developing red blood cell (RBC) will accumulate the other (unpaired) globin chains. In this manner, if α-gene is not produced in adequate quantities, an accumulation of β-gene will increase causing αT; likewise, if the production of β-gene chains declines, ultimately, accumulations in α-gene chains cause βT [18].

2.1. Alpha (α) Thalassemia

The term “alpha-thalassemia” (or “αT”) denotes a class of genetic blood illnesses categorized in a normal blend of β-globin chains [19] but diminished the creation of α-globin chains, which are both components of the hemoglobin molecule. Growing RBCs symbolize the buildup of unpaired globin chains. The formation of α-globin chains is regulated by four genes, two on each chromosome, implicating the possibility of several types of carriers.

2.1.1. Silent Carrier

One (out of four) non-functional genes is present in a thalassemia alpha plus (α+) carrier [3], also referred to as αT minimal. Due to this, it may be very challenging to diagnose these carriers using a straightforward microscopic examination of their blood in a lab. These types of carriers can only be accurately identified through very specialized DNA analysis tests conducted in laboratories.

2.1.2. Alpha Zero (α0) Thalassemia Carrier

Two (out of four) α-genes are either missing (deleted) or inactive. The two defective or deleted genes [20] might be situated either on the same chromosome (cis position) or on two distinct chromosomes (trans-position), depending on their specific location.

2.1.3. Alpha (α) Intermedia Thalassemia

The condition identified as HbH ailment [21] is present when three α-globin genes are defective or absent, resulting in clinically significant anemia. This stops the additional α-chains from uniting with the α-globin chains to make common HbA, even if the α-globin genes are still completely functioning. Instead, a new hemoglobin (β4) called HbH is formed in the patient's blood by joining the free-globin chains together. HbH can efficiently deliver oxygen to the tissues, just like common HbA, despite not being the hemoglobin typically found in human adult RBCs. Nevertheless, because of its relative instability, the molecule constantly breaks down, which results in premature red cell death or breakdown (hemolysis), which can cause mild to severe anemia in the affected person as well as other related health concerns such as splenic enlargement that ranges from mild to severe, tiredness, gallstone development, and deformed bones.

2.1.4. Hb Constant Spring

Undetectable HbH, mutant allele causes a reduction in pf alpha globin activity Bart's—Hydrops Fetalis [1]. This leads to no production of any α-chains, resulting in hemoglobin; a different type of hemoglobin termed Hb Barts (γ4) is created when free α-globin chains, which typically combine with α-globin chains to form the fetus's hemoglobin (HbF), come together. Since this form of hemoglobin is unable to transport oxygen, life cannot be sustained by it [22]. Severe anemia brought on by this condition affects the unborn child and damages its heart.

2.2. Beta (β) Thalassemia

Minor, intermedia, and major are the three main types of βT [19][23].

2.2.1. Beta (β) Thalassemia Minor

Caused by a mutation in one gene, they are formerly identified as "βT carrier" [24], or heterozygous βT", and a majority of individuals have two different alleles.

2.2.2. Beta (β) Thalassemia Intermedia

The mutation of two beta genes escalated thalassemia minor to thalassemia intermedia [25][26].

2.2.3. Beta (β) Thalassemia Major

Two genes of the individuals defected with severe impairment in beta gene production are also known as "Cooley anemia" [27] and "Mediterranean anemia". Like minor thalassemia, it has two different or multiple alleles of β0 or β+

genes. Balance in the globin chain is controlled by a specific form of beta gene modification. β0 means no generation of β-globin at all controlled by the defective allele. β++ denotes an allele with some residue beta globin generation (typically about 10%). The drop in the production of β-gene in β+ is minuscule. There are over 300 distinct βT alleles [28].

2.3. Other Variants of Thalassemia Carrier

One of the chromosomes that a person inherits from their mother or father is the only one that has a mutant gene [29]. They do not exhibit any clinical symptoms; thus, they do not need any kind of medical care or ongoing monitoring. They have some modifications in their RBCs, which are typically smaller and sometimes contain less hemoglobin, and are only detected by special blood tests but are not adequate to entail improvement.

Thalassemia can result in numerous types of disorders due to affected alleles, which might differ in their medical significance and requirement of blood transfusions. It comprises of two basic groups: one, TDTs that involve transfusion and two, NTDT [1][30] without the requirement of blood transfusion rendering to phenotyping. Without routine RBC transfusions, TDT patients would have numerous problems and have limited life expectancy. Patients with severe HbE/βT [31], βT major, HbH hydrops, or transfusion-dependent HbH illness, as well as those who have survived HbBart's hydrops, fall into this group. For lifetime, the cornerstone of TDT care is transfusion therapy, while ineffective transfusion therapy might cause issues such as deprived development, deformities of face and bone or even making them fragile, spleen and liver enlargement, and everyday physical activity impairment.

Iron toxicity to vital organs is one of the foremost medical complications for thalassemia carriers. Higher intestinal absorption of nutritional iron and repetitive blood transfusions are the sources of iron accumulation. The iron content per unit of transfused blood is 200 mg, so patients who are regularly transfused develop iron overload [3][32]. Iron toxicity affects prime organs such as the liver and heart [7][33] and causes several endocrine disorders through the hypothalamus/pituitary axis, hypothyroidism, including growth obstruction, diabetes mellitus [34][35][36][37], and hypogonadism.

References

1. Baird, D.C.; Batten, S.H.; Sparks, S.K. Alpha- and Beta-thalassemia: Rapid Evidence Review. Am. Fam. Physician 2022, 105, 272–280. Available online: https://pubmed.ncbi.nlm.nih.gov/35289581/ (accessed on 10 May 2023).
2. Weatherall, D.J.; Clegg, J.B. Inherited haemoglobin disorders: An increasing global health problem. Bull. World Health Organ. 2001, 79, 704–712. Available online: https://pubmed.ncbi.nlm.nih.gov/11545326/ (accessed on 10 May 2023).
3. Taher, A.T.; Weatherall, D.J.; Cappellini, M.D. Thalassaemia. Lancet 2018, 391, 155–167.
4. Fibach, E.; Dana, M. Oxidative Stress in β-Thalassemia. Mol. Diagn. Ther. 2019, 23, 245–261.

5. Kattamis, A.; Kwiatkowski, J.L.; Aydinok, Y. Thalassaemia. Lancet 2022, 399, 2310–2324.
6. Muncie, H.L.; Campbell, J. Alpha and beta thalassemia. Am. Fam. Physician 2009, 80, 339–344. Available online: https://pubmed.ncbi.nlm.nih.gov/19678601/ (accessed on 10 May 2023).
7. Musiałek, M.W.; Rybaczek, D. Hydroxyurea—The Good, the Bad and the Ugly. Genes 2021, 12, 1096.
8. Bazinet, A.; Popradi, G. A General Practitioner's Guide to Hematopoietic Stem-cell Transplantation. Curr. Oncol. 2019, 26, 187–191.
9. Hatzimichael, E.; Timotheatou, D.; Koumpis, E.; Benetatos, L.; Makis, A. Luspatercept: A New Tool for the Treatment of Anemia Related to β-Thalassemia, Myelodysplastic Syndromes and Primary Myelofibrosis. Diseases 2022, 10, 85.
10. Jamwal, M.; Sharma, P.; Das, R. Laboratory Approach to Hemolytic Anemia. Indian J. Pediatr. 2020, 87, 66–74.
11. Mahmoud, R.A.; Khodeary, A.; Farhan, M.S. Detection of endocrine disorders in young children with multi-transfused thalassemia major. Ital. J. Pediatr. 2021, 47, 165.
12. Akiki, N.; Hodroj, M.H.; Bou-Fakhredin, R.; Matli, K.; Taher, A.T. Cardiovascular Complications in β-Thalassemia: Getting to the Heart of It. Thalass. Rep. 2023, 13, 38–50.
13. Meloni, A.; Pistoia, L.; Positano, V.; De Luca, A.; Martini, N.; Spasiano, A.; Fotzi, I.; Bitti, P.P.; Visceglie, D.; Alberini, G.; et al. Increased myocardial extracellular volume is associated with myocardial iron overload and heart failure in thalassemia major. Eur. Radiol. 2022, 33, 1266–1276.
14. Dimitroglou, Y.; Anagnostopulous, F.; Aggeli, C.; Delicou, S.; Xydaki, A.; Patsourakos, D.; Tousoulis, D. Severity of heart failure and health-related quality of life in beta-thalassemia patients: A cross-sectional study. Ann. Hematol. 2020, 99, 2037–2046.
15. Hoffmann, J.J.M.L.; Urrechaga, E.; Aguirre, U. Discriminant indices for distinguishing thalassemia and iron deficiency in patients with microcytic anemia: A meta-analysis. Clin. Chem. Lab. Med. (CCLM) 2015, 53, 1883–1894.
16. Zheng, L.; Huang, H.; Wu, X.; Su, L.; Shen, Q.; Wang, M.; Lin, N.; Xu, L. Screening of Some Indicators for Alpha-Thalassemia in Fujian Province of Southern China. Int. J. Gen. Med. 2021, 14, 7329–7335.
17. Husna, N.; Handayani, N.S.N. Molecular and Haematological Characteristics of alpha-Thalassemia Deletions in Yogyakarta Special Region, Indonesia. Rep. Biochem. Mol. Biol. 2021, 10, 346–353.
18. Bain, A. Management of Transfusion Dependent Thalassaemia (TDT): A Short Guide; Thalassaemia Internation Federation: Nicosia, Cyprus, 2022.

19. Gao, J.; Liu, W. Advances in screening of thalassaemia. Clin. Chim. Acta 2022, 534, 176–184.
20. Stephens, A. The Diagnosis and Significance of Alpha Thalassaemia. In Practical Management of Haemoglobinopathies; Blackwell Publishing Ltd.: Oxford, UK, 2004; pp. 40–44.
21. Galanello, R.; Cao, A. Alpha-thalassemia. Genet. Med. 2011, 13, 83–88.
22. Porter, D.; Taher, J. Guidelines for the Management of Transfusion Dependent Thalassaemia (TDT), 4th ed.; Thalassaemia International Federation: Nicosia, Cyprus, 2021.
23. Cao, A.; Galanello, R. Beta-thalassemia. Genet. Med. 2010, 12, 61–76.
24. Choudhry, V.P. Thalassemia Minor and Major: Current Management. Indian J. Pediatr. 2017, 84, 607–611.
25. Musallam, K.M.; Taher, A.T.; Rachmilewitz, E.A. β-thalassemia intermedia: A clinical perspective. Cold Spring Harb. Perspect. Med. 2012, 2, a013482.
26. Taher, A.; Isma'eel, H.; Cappellini, M.D. Thalassemia intermedia: Revisited. Blood Cells Mol. Dis. 2006, 37, 12–20.
27. Cunningham, M.J. Update on Thalassemia: Clinical Care and Complications. Hematol. Oncol. Clin. N. Am. 2010, 24, 215–227.
28. Welcome to the Globin Gene Server. Available online: https://globin.bx.psu.edu/ (accessed on 5 August 2023).
29. Nigam, N.; Kushwaha, R.; Yadav, G.; Singh, P.K.; Gupta, N.; Singh, B.; Agrawal, M.; Chand, P.; Saxena, S.K.; Bhatt, M.L.B. A demographic prevalence of β Thalassemia carrier and other hemoglobinopathies in adolescent of Tharu population. J. Fam. Med. Prim. Care 2020, 9, 4305–4310.
30. Shash, H. Non-Transfusion-Dependent Thalassemia: A Panoramic Review. Medicina 2022, 58, 1496.
31. Lama, R.; Yusof, W.; Shrestha, T.R.; Hanafi, S.; Bhattarai, M.; Hassan, R.; Zilfalil, B.A. Prevalence and distribution of major β-thalassemia mutations and HbE/β-thalassemia variant in Nepalese ethnic groups. Hematol. Oncol. Stem Cell. Ther. 2021, 15, 3.
32. Erten, M.; Tuncer, T. Automated differential diagnosis method for iron deficiency anemia and beta thalassemia trait based on iterative Chi2 feature selector. Int. J. Lab. Hematol. 2022, 44, 430–436.
33. Rustam, F.; Ashraf, I.; Jabbar, S.; Tutusaus, K.; Mazas, C.; Barrera, A.E.P.; de la Torre, D. Prediction of β -Thalassemia carriers using complete blood count features. Sci. Rep. 2022, 12, 19999.
34. Porter, J.B.; Garbowski, M. The Pathophysiology of Transfusional Iron Overload. Hematol. Oncol. Clin. N. Am. 2014, 28, 683–701.

35. Marsella, M.; Ricchi, P. Thalassemia and hepatocellular carcinoma: Links and risks. J. Blood Med. 2019, 10, 323–334.
36. Soliman, A.T.; Yassin, M.A.; De Sanctis, V. Final adult height and endocrine complications in young adults with β-thalassemia major (TM) who received oral iron chelation (OIC) in comparison with those who did not use OIC. Acta Biomed. 2018, 89, 27–32.
37. De Sanctis, V.; Soliman, A.T.; Canatan, D.; Tzoulis, P.; Daar, S.; Di Maio, S.; Elsedfy, H.; Yassin, M.A.; Filosa, A.; Soliman, N.; et al. An ICET-A survey on occult and emerging endocrine complications in patients with β-thalassemia major: Conclusions and recommendations. Acta Biomed. 2019, 89, 481–489.