Research Article

Complications of Thalassemia and Life Expectancy Among Children and Adults in South Asia a Systematic Review

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ARTICLE:

Background: Thalassemia is a hereditary blood disorder marked by the production of abnormal hemoglobin, leading to varying degrees of anemia. The prevalence of thalassemia is relatively high in South Asia, making it a significant public health concern in the region.

Objective: To evaluate the complications in thalassemia (TDT, NTDT) patients and their life Expectancy in South Asia.

Methods: A systematic approach was used using PRISMA guidelines. Google Scholar and PubMed databases were searched to select 8 articles using Specific Keywords. Studies reporting on the complications of thalassemia and life expectancy in South Asian populations were included. Data were extracted and synthesized using a systematic approach to evaluate the impact of thalassemia on patients' health and life expectancy.

Results: In 8 selected articles complications in thalassemia patients (TDT and NTDT) including age groups children and adults in South Asia we found that in thalassemia major patients major complications due to iron overload after multiple transfusions are, hepatomegaly 41%, splenomegaly 14-56%, Endocrine complications, Hypothyroidism 4 -25%, Cardiac complications (10-12%) that reduce life expectancy rapidly, bone abnormalities i.e osteoporosis 59%, infections Hep-C (3-67%) and Hep-B and Extramedullary Hematopoiesis. While NTDT/ thalassemia intermedia also presents with many clinical complications even though transfusions are less frequent. NTDT/TI complications include iron overload, inadequate erythropoiesis, and hypercoagulability. Bone abnormality osteoporosis (81%), extramedullary Hematopoiesis 20%, thrombosis, and pulmonary hypertension.

Conclusion: Thalassemia Major/Intermedia has been associated with serious complications that reduce the life expectancy of those infected in South Asia. The study revealed that early diagnosis and timely access to specialized care and treatment play a significant role in increasing the life expectancy of thalassemia patients.

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Keywords: Thalassemia, Beta thalassemia, Hemoglobinopathies, Thalassemia trait, Beta thalassemia major, Non-transfusion dependent thalassemia or Transfusion dependent thalassemia, life expectancy, South Asia.

INTRODUCTION:

Thalassaemia refers to any inherited genetic defects that influence the production of α-or β-globin chains and, as a result, proper erythropoiesis and hemoglobin's oxygen-carrying capacity. This illness is inherited as an autosomal recessive disorder and is divided into two types: α- and β-thalassemia. Due to an unbalanced globin synthesis, patients with thalassemia illness frequently experience persistent hemolytic anemia and inefficient erythropoiesis. [1] β -thalassemia is classified into three types based on genetic and clinical characteristics: thalassemia major, thalassemia intermedia, and thalassemia minor. Patients with β -thalassemia major (TM) have two defective copies of the β-globin chain and Patients with β -thalassemia major (TM) have two faulty copies of the β-globin chain and experience severe transfusion-dependent microcytic anemia for the first two years of life. Individuals with thalassemia minor or the carrier status have one faulty copy of the β -globin chain and are usually clinically quiet. [1-3] Compared to β-TM, beta thalassemia intermedia (β-TI) is a condition of intermediate severity with a delayed onset of microcytic anemia and milder clinical signs. It is a type of non-transfusion-dependent thalassemia (NTDT), which includes α-thalassemia intermedia.[2] Almost 80% of these births take place in underdeveloped countries. According to the most conservative estimations, at least 5.2% of the world's population (about 360 million people) has a significant hemoglobin variation [3]. There are around 100 million beta-thalassemia carriers worldwide, with a global prevalence of 1.5% [4]. Africa, all Mediterranean countries, the Middle East, the Indian subcontinent, and Southeast Asia are the most prevalent parts of the world [3, 5]. Over 50,000 new patients are born each year with a severe form of thalassemia (beta-thalassemia major and HbE beta-thalassemia) around the world. South Asia, a hemoglobinopathies site, is home to 23% of the world's population (about 1.7 billion people) [4,5], With a carrier prevalence of about 5%, thalassemia is considered a severe public health problem in Pakistan. Every year, almost 5000 new cases of beta-thalassemia major (TM) are diagnosed [6] Red blood cell trans-fusion requirements are currently used to classify thalassemia patients into two groups: transfusion-dependent thalassemia (TDT) and non-transfusion-dependent thalassemia (NTDT). People suffering from transfusion-dependent thalassemia (TDT), which includes people with severe forms of thalassemia such as homozygous β^0-thalassemia or hemoglobin E /β-thalassemia, require regular blood transfusions for survival. Patients with non-transfusion -dependent thalassemia require an infrequent red blood cell transfusion in certain conditions, such as pregnancy, surgery, or infections. Patients with NTDT include those with mild thalassemias, such as hemoglobin H illness, as well as some cases of hemoglobins E/β-thalassemia. [7, 8] Repeated blood transfusions raise iron levels in the body and precipitate iron in key organs like the liver, glands, and heart, potentially leading to major problems such as cirrhosis, cardiovascular illnesses, diabetes, hypothyroidism, hyperparathyroidism, and hypogonadism.[9] Thalassemia major and thalassemia intermedia are the two main forms of thalassemia, both of which offer

considerable health issues for affected persons, particularly in South Asia, where thalassemia is highly common.

Despite the high prevalence of thalassemia in South Asia, there is a significant knowledge gap regarding the comprehensive understanding of complications associated with thalassemia major and thalassemia intermedia, as well as their impact on life expectancy among affected children and adults in this region. There is a notable lack of comprehensive systematic evaluations that particularly address the complications of thalassemia and life expectancy among children and adults in this region. Existing research frequently focuses on thalassemia in a global setting or specific countries. Therefore, this study aimed to evaluate the complications in thalassemia (TDT, NTDT) patients and their life Expectancy in South Asia.

MATERIAL AND METHODS:

This systematic review was conducted by searching two databases (google scholar, PubMed). Articles published between January 2014 to July 2023 were searched. MeSH and Non- mesh keywords were used, like. Thalassemia, complications, iron overload bone abnormalities or endocrine disorders, cardiac complications, life expectancy, and South Asia Boolean operators AND OR were used.

Articles that were not published in the English language were excluded. Also, the study selection procedure did not include. All clinical trials (RCTS), meta-analyses, perspectives, case reports, case series, and grey literature.

The articles were searched by using the following inclusion criteria from the relevant databases. The paper was published in the last ten years. The Geographic area was defined. Articles addressing South Asia were included. All age groups were included. Cross-sectional, case-control studies, Systematic Reviews, and scooping reviews were included.

After removing duplicates, the author (M.A, N.B, M.S) checked the titles and abstracts by following the eligibility criteria. The articles selected were subjected to the next phase, and after reading the Full text. The authors selected the articles. In case of confusion, the other authors (S.A, A.A, KJ) read the papers to finalize their eligibility.

PRISMA guidelines were used, and a Prisma flow sheet was developed to extract the material. All the relevant data were extracted according to the selection criteria. The summary table contains information on Authors, titles, and publication dates. More specifically, the data about the complications of TDT and NTDT were included. The table format assisted the authors in completing a detailed over-review of the data selected in the first phase.

RESULTS:

The PRISMA flow diagram in Figure 1 shows the authors' article selection procedure while selecting the articles. The authors searched two databases (Google Scholar, PubMed) and identified 940 articles. From these first records, 90 duplicates were removed by the authors. The remaining 850 articles were left for review. We reduced the total number of articles to 45 after screening titles and abstracts by following exclusion criteria. Articles that are not available in full text. RTCs, clinical trials, and book chapters were excluded, Articles published in languages other than

English language were also excluded. The remaining articles were given full reading and the final 8 articles were selected that met the inclusion criteria, studies mentioning complications of thalassemia, and The Geographic area was defined. Articles addressing South Asia were included.

Figure 1: Prisma flow diagram

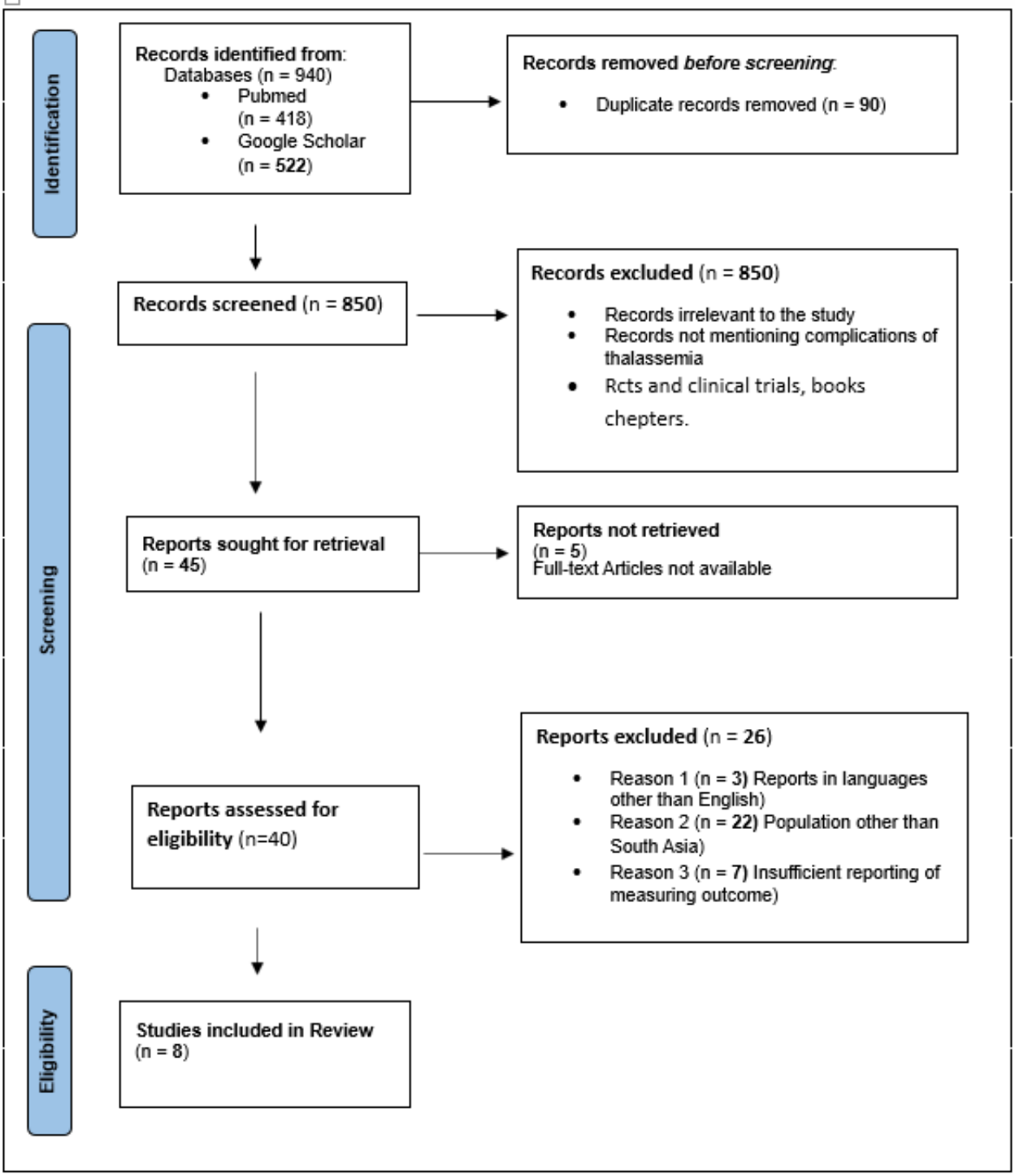

Fig. 1 PRISMA flowchart showing the selection of studies (PRISMA, Preferred Reporting Items For Systematic Reviews and Meta-Analysis

Table: 1 Summary of selected 8 studies:

SR. NO.	TITLE	AUTHOR/YEAR	LOCATION /AREA	DISEASE OF	AGE	STUDY TYPE	SAMPLE SIZE	COMPLICATIONS IN THALASSEMIA MAJOR/ TDT	COMPLICATIONS IN THALASSEMIA INTERMEDIA/ NTDT	LIFE EXPECTANCY
1	Endocrine and Bone Complications in β-Thalassemia Intermedia: Current Understanding and Treatment	Inati A, et al. (2015) [2]	Lebanon and others	β-Thalassemia Intermedia	Children and adults	Review Article		**Endocrine complications:** **Growth Retardation** short stature is almost 25%. **Delayed puberty** Hypogonadism 24% of patients **Diabetes** 9.4% and 7.1% **Hypothyroidism** 4% to 24.4% **Parathyroid** 6.7% **Adrenal functions** 61% Dyslipidemias **Bone Abnormalities:** **Osteoporosis** 59.8% **Osteopenia** 22.6%. **Extramedullary Hematopoiesis**: less than 1%	**Endocrine complications:** **Growth Retardation** short stature is almost 25% **Delayed puberty** Hypogonadism 24% **Diabetes** 2% to 24% **Hypothyroidism** 2 to 3% **Bone Abnormalities:** **Osteoporosis** 81.6% **Osteopenia** 8% **Extramedullary Hematopoiesis**: 20%	
2	PREVALENCE OF CARDIAC COMPLICATIONS IN PATIENTS WITH MAJOR THALASSEMIA IN IRANIAN PATIENTS: A SYSTEMATIC REVIEW AND META-ANALYSIS	Mahmoodi Z, et al. (2019) [9]	Iran	β-Thalassemia Major	Children and adults	Review Article	2516 patients	**Cardiac complications**: left ventricular (LV) systolic dysfunction, and Diastolic dysfunction, Pulmonary hypertension, Valvular disease, Arrhythmias Pericarditis 11% (10%-12%)	NR	After the appearance of symptoms of heart failure life expectancy decreases rapidly

3	Epidemiology of Thalassemia in Gulf Cooperation Council Countries: A Systematic Review	Abu-Shaheen A, et al (2020) [10]	Saudi Arabia	α-thalassemia	Children and adults	Review Article		**Splenomegaly:** 14 to 56% of α-thalassemia with the size of the spleen ranged from 1 to 13 cm **Hepatomegaly:** 41% **Jaundice:** 14 to 35·9% **Infections** 30% of α-thalassemia patients suffer osteomyelitis. **Anemia:** Severe in β-Thalassemia major pt.	NR	severe anemia in β-Thalassemia major pt. if untreated, decreases the life expectancy of children to 3 years or less
4	Non-Transfusion-Dependent Thalassemia: An Update on Complications and Management	Sleiman J, et al (2018) [11]	Lebanon and others	*β*-Thalassemia Intermedia	Children and adults	Review Article		**Cardiac Disease** **Pulmonary Hypertension** 1.1% **Extramedullary Hematopoiesis** <1%	**Thrombosis:** Portal Vein Thrombosis, DVT/ Deep Vein Thrombosis, Pulmonary Thromboembolism, Cerebral Thrombosis, And Recurrent Arterial Thrombosis. **Silent cerebral infarcts** rate is Approximately 27–60% **Cardiac Disease:** cardiac failure Left ventricular dysfunction And cardiogenic death **Pulmonary Hypertension** 4.8% **Leg Ulcers** **Hepatobiliary Complications:** Cirrhosis liver fibrosis Hepatocellular carcinoma**, Extramedullary Hematopoiesis** 20%	

								Bone Disease **Endocrinopathies/Delayed Growth** Hypogonadism hypothyroidism Hypoparathyroidism diabetes mellitus Adrenal insufficiency **Renal Disease**	
5	Investigating the Role of Ferritin in Determining Sexual Underdevelopment in Beta-Thalassemia Major Patients: A Cross-Sectional Analysis From Pakistan	Shahid Z, et al. (2021) [12]	Pakistan	Beta-thalassemia maior	13 and 30 years.	multicentric cross-sectional study	120 participants	**Sexual Underdevelopment** **Pre-pubescent stage** 40% **pubescent and post-pubescent stage** 60%	NR	
6	Thalassemias in South Asia: clinical lessons learned from Bangladesh	Hossain MS, et al. (2017) [5]	Bangladesh	Beta-thalassemia	Children and	Review Article		**Infections:** Post transfusion Hepatitis Hepatitis B **Hepatitis C** ranges from 3 to 67.3%		Most children with thalassemia major die before the age of five. A thalassemia Major patient's life expectancy is around 30 years.
7	Epidemiology and risk factors of transfusion transmitted infections in thalassemia major: a multicenter study in Pakistan	Yasmeen H, et al. (2019) [13]	Pakistan	β-thalassemia major	Children and adults	Original Article. non-probable sampling.	350 TDT Pt.	**Transfusion transmitted infections:** **seropositive**: 42.8% **HBV infected** (7.4%), **HCV infected** (29.4%) **Co-infected** (6%).	NR	

8	Review of disease-related complications and management in adult patients with thalassemia: A multi-center study in Thailand	Chuncharunee S, et al. 2019 [8]	Thailand	Thalassemia	Adults above18 years	A multicenter cross-sectional study	433 patients	**Heart failure** 4% **Pulmonary hypertension** 9.5% **Extramedullary hematopoiesis** 12.5% **Gallstone** 34.6% **Fracture** 3.1% **Infection** 6.3% **Diabetes mellitus** 7.9% **Hypothyroid** 7.1% **Hypogonadism** 11% **Thrombosis** 4% **Leg ulcer** 0%	**Heart failure** 2.3% **Pulmonary hypertension** 7.9% **Extramedullary hematopoiesis 4.9%** **Gallstone** 24.8% **Fracture** 1% **Infection** 10.1% **Diabetes mellitus** 1.6% **Hypothyroid** 1.6% **Hypogonadism** 2.3% **Thrombosis** 1% **Leg ulcer** 1.3%

In 8 selected articles complications in thalassemia patients (TDT and NTDT) including all age groups children and adults in South Asia we found that in thalassemia major patients major complications due to iron overload after multiple transfusions are, hepatomegaly 41%, splenomegaly 14-56%, Endocrine complications i.e short stature 25%, Hypothyroidism 4 -25%, Cardiac complications (10-12%) that reduce life expectancy rapidly, bone abnormalities i.e osteoporosis 59%, /infections Hep-C (3-67%) and Hep-B and Extramedullary Hematopoiesis. While NTDT/ thalassemia intermedia also presents with Despite less frequent transfusions, there were numerous clinical complications. The combined effect of various pathophysiological variables, such as iron overload, ineffective erythropoiesis, and hypercoagulability, causes complications in NTDT/thalassemia intermedia. Bone abnormality osteoporosis (81%), extramedullary Hematopoiesis 20%, thrombosis i.e silent cerebral infarcts 27-60% and pulmonary hypertension 4.8%

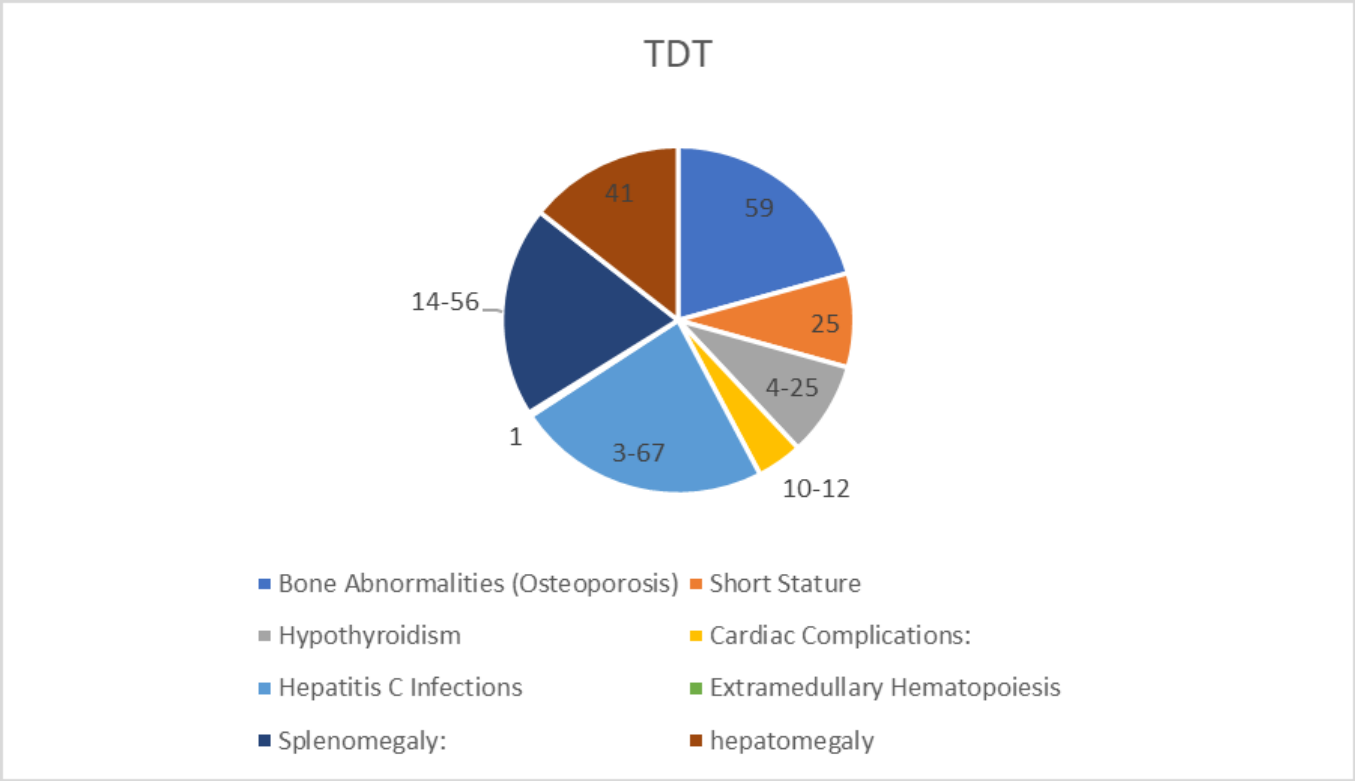

Figure 1: Complications of transfusion-dependent thalassemia (TDT)/ thalassemia major

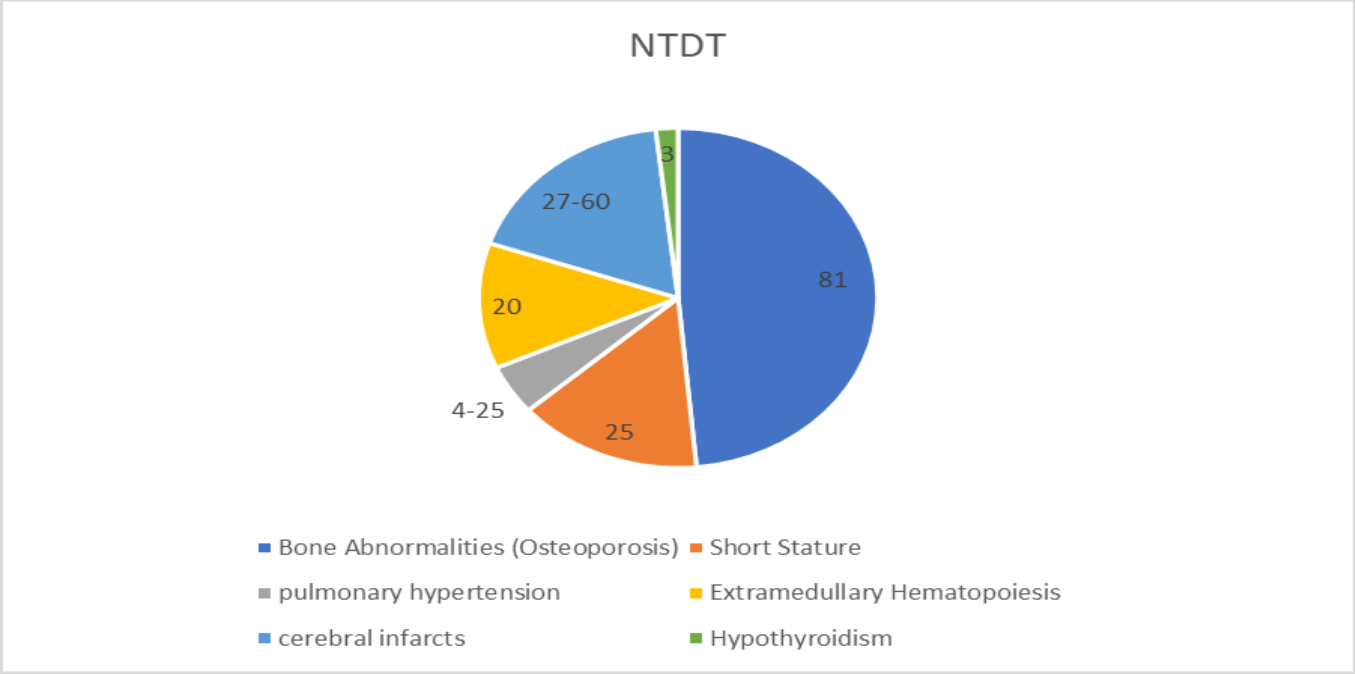

Figure 2: Complications of Non-transfusion-dependent thalassemia (NTDT)/ thalassemia Intermedia.

DISCUSSION:

The findings of this study indicate that complications occur in thalassemia patients (TDT and NTDT) of all ages in South Asia in thalassemia major patients due to repetitive blood transfusions, as well as hemolysis and increased intestinal absorption results in iron overload. Iron overload and increased cardiac output primarily impair cardiac structure and function in thalassemia patients, resulting in a variety of complications such as hepatomegaly, splenomegaly, endocrine issues, hypothyroidism, and Cardiac problems that shorten life expectancy very rapidly, bone abnormalities such as osteoporosis, blood transfusion infections such as Hep-C and Hep-B, and Extramedullary Hematopoiesis. NTDT/ thalassemia intermedia, on the other hand, has significant clinical problems despite receiving less frequent transfusions. The combination of various pathophysiological variables, such as inefficient erythropoiesis, iron overload, and hypercoagulability, causes complications in NTDT/ TI. Major complications of thalassemia intermedia include Osteoporosis, extramedullary hemopoiesis, thrombosis, pulmonary hypertension, and bone abnormallities.

According to an Iranian study, beta-thalassemia patients with increased blood ferritin levels are two to four times more likely to develop cardiac or hepatic iron overload, which can lead to significant mortality [14]. Similarly, a Turkish investigation found that regular monitoring for various endocrinopathies in beta-thalassemia patients with elevated serum ferritin levels was required [15]. Even though beta-thalassemia has a poor disease progression, safer transfusion procedures and adjuvant chelation therapy have significantly improved the life expectancy of beta-thalassemic patients[16,17]. Living with complications for an extended period may be unbearable for the patient and can result in costs for both the patient and the healthcare system[18]. Most large thalassemic patients will live a long life, but when indications of heart failure develop, life expectancy drops rapidly [19]. Heart failure is still regarded as one of the leading causes of death in thalassemia patients. As a result, early detection of cardiac dysfunction is critical. [20] A heterozygous couple's offspring have a 25% chance of having -thalassemia major children, a 25% risk of having heterozygous children, and a 50% chance of having normal children.[21] a study in Pakistan showed that after splenectomy in thalassemia patients Respiratory and wound infection was the problem in 9 out of 14 patients.[22] Splenectomy in children with extensive splenomegaly is both safe and successful with proper perioperative treatment.[23] Thalassemic children have severe psychosocial problems. Teenagers have a high rate of psychotic and sexual issues.[24] Anemia in pregnant females is a major problem have a relation to adverse pregnancy outcomes. [25] A major issue that has been discovered is the lack of inter/ intra-institutional coordination /referral linkage, as well as the lack of defined protocols for case management and laboratory diagnosis of thalassemia patients in Punjab Pakistan. [26] A recent study has demonstrated that β-TI is not a minor condition, but rather one linked with higher morbidity and a broader spectrum of organ dysfunction and consequences than previously assumed. This

condition has a high prevalence of endocrine and bone problems, which demand constant monitoring, therapy, and follow-up. The keys to successful care are early recognition of these complications, the implementation of appropriate treatment, including transfusion regimens and chelation therapy, as well as specific treatment of each complication. [2]

This study reviewed the complications in thalassemia major and thalassemia intermedia patients and their life Expectancy in South Asia. The systematic review employed a comprehensive search strategy to identify relevant studies from multiple databases i.e. Google Scholar and Pubmed. This study specified clear inclusion and exclusion criteria for selecting relevant studies. The study presented the results in a clear and structured manner, using a table and pie charts for the descriptive summary. This ensures that readers can easily understand the findings and their implications.

Limitations of this review were the included studies in the systematic review exhibit substantial heterogeneity in terms of study design, patient characteristics, interventions, and outcomes assessed. This heterogeneity could affect the ability to perform a meta-analysis and may limit the comparability and generalizability of the findings. There is a possibility of publication bias, where studies with positive or statistically significant results are more likely to be published, while those with negative or non-significant findings may be underrepresented. Bias is not assessed in our study. The review may be limited to studies published in specific languages, such as English. Relevant research published in other languages could be missed, potentially leading to a partial representation of the available literature. Some studies that are included in our review article have not reported all relevant data, or key information required for analysis. This can limit the ability to extract data for specific outcomes or impact the comprehensiveness of the review. The review may primarily focus on studies from certain countries within South Asia due to data availability, and language restrictions. This could result in an uneven representation of thalassemia cases across the region. Some studies have not reported all relevant outcomes or only focused on certain aspects of thalassemia, leaving other critical complications or factors unexplored.

The recommendation for further research is to conduct comparative studies between different countries and regions in South Asia to explore variations in thalassemia complications and life expectancy. Interventional studies should be designed and implemented to evaluate the effectiveness of different treatment approaches in managing complications and improving life expectancy in thalassemia patients. These studies could help to identify optimal treatment regimens and inform evidence-based clinical guidelines. Further research should be conducted on the benefits and cost-effectiveness of early thalassemia diagnosis and screening programs in South Asia. To emphasize the importance of genetic counseling and carrier screening to enable informed family planning decisions and reduce the incidence of thalassemia. So that barriers could be to accessing specialized thalassemia care and treatment in different regions of South Asia. the impact of multidisciplinary care teams, including hematologists, pediatricians, psychologists, and social workers,

on improving outcomes for thalassemia patients should be evaluated, the effectiveness of health education and awareness campaigns targeted at the general public, healthcare professionals, and policymakers to increase knowledge about thalassemia, its complications, and preventive measures should be Assessed. The factors that influence life expectancy in thalassemia patients, including access to healthcare, socioeconomic status, disease management, and treatment adherence should be investigated in further research. Understanding these factors can inform strategies to improve outcomes and increase life expectancy.

CONCLUSION:

The review highlighted the significant burden of Thalassemia Major and Thalassemia Intermedia complications in South Asia. Iron overload, organ damage, blood transfusion infections, and cardiac, endocrine, and bone problems were recognized as key concerns, emphasizing the importance of comprehensive therapy. Thalassemia has been found to have a significant impact on the life expectancy of affected people in South Asia. The analysis found that early diagnosis and timely access to specialized care and treatment play an important role in enhancing thalassemia patients' life expectancy. The findings of the study have significant public health implications. Early diagnosis, genetic counseling, and greater access to specialized care have emerged as essential elements of effective thalassemia control and preventive measures.

ACKNOWLEDGMENTS:

We would like to express our sincere gratitude and appreciation to Dr. Muhammad Tufail, Dr. Saira Tariq for their unwavering support and assistance in this research work. Their valuable guidance and input have been instrumental in ensuring the success of our publication. We are truly grateful for their contributions.

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