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Epidemiology of B. Thalassemia in Karbala City, Iraq

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ABSTRACT

Inherited B-thalassemia is the most frequent single-gene disorder globally (1). The high prevalence in the middle east can be attributed to the high prevalence (25-60%) of consanguineous marriages (7). About 60000 new patients are born annually with thalassemia worldwide (3). **Objectives:** Is to determine the incidence and complications of thalassemia in Karbala holy city. **Methods:** The retrospective hospital record-based study was carried out in Karbala teaching hospital of children, dead patients were excluded, the total number was 529, and the information was collected from April 2021 till April 2022. **Results:** The total number of patients was 529, n432(81.66%) of them were B-thalassemia major the rest were B-thalassemia intermedia, males were 253(47.83%), females were 276(52.71%), most of them were consanguinity positive n430(81.29%), n328(62%) diagnosed at <12mounth age, the most common complication was splenomegaly 89(16.82%), n394(74.48%) were treated with exjade while 59(11.15%) on deferral. **Conclusion:** Prevention of thalassemia is the most viable strategy to reduce the burden of thalassemia patients on families and manage a sustainable healthcare system, public education about thalassemia should be provided through regular meetings addressed to health professionals including health workers and family members.

INTRODUCTION

Inherited hemoglobin disorders are emerging as a public health concern globally. An estimated 320 000 babies are born each year with a clinically significant hemoglobin disorder [1]. Nearly 80% of these births occur in developing countries. Most conservative estimates suggest that at least 5.2% of the world's population (over 360 million) carry a significant hemoglobin variant and there are more than 100 million β-thalassemia carriers, with a global prevalence of 1.5%[1],[2],[3].

β-Thalassemia is most prevalent in certain malaria-prone parts of the world including Africa, all Mediterranean countries, the Middle East, the Indian subcontinent, and Southeast Asia [1],[4],[5],[6]. The high prevalence in the Middle East can be attributed to the high prevalence (25–60%) of consanguineous marriages [7]. About 60 000 new patients are born annually with thalassemia worldwide [3]. According to the Thalassemia International Federation, only about 200 000 patients with thalassemia major are alive and registered as receiving regular treatment around the world [8].

Most thalassaemias are inherited as recessive traits.

From a clinical point of view, the most relevant types are α and β thalassaemias, resulting from the decrease of one of the two types of polypeptide chains (α or β) that form the normal adult human hemoglobin molecule (Hb A, α2β2).[9].

β thalassemia includes three main forms: thalassemia major (TM)variably referred to as 'Cooley's anemia' and 'Mediterranean anemia', thalassemia intermedia and thalassemia minor also called 'β thalassemia carrier', 'β thalassemia trait' or 'heterozygous β thalassemia'. Apart from the rare dominant forms, Affected infants fail to thrive and become progressively pale. Feeding problems, irritability, recurrent bouts of fever due to a hypermetabolic state or intercurrent infection, and progressive enlargement of the abdomen caused by the spleen and liver enlargement may occur [10,11].

Treatments available for thalassemia patients are regular blood transfusion programs and chelation treatment, diets selection with lower and less absorbable forms of iron, the use of regulators of hepcidin, ferroportin, and other proteins of iron metabolism involved in the transport of iron, activators of Fetal hemoglobin production (HbF) production, and combinations of such treatments [12],[13],[14],[15]. have considerably improved the survival of patients with thalassemia. Using Luspaterceptor ACE-536 is a recombinant fusion

protein that binds to specific ligands of the TGF-β superfamily and enhances erythroid maturation. It is the most recently approved therapy (FDA and EMA) for the management of transfusion-dependent thalassemia (TDT). [16].

Prevention is a cost-effective strategy; premarital screening (PMS) has been successful in many parts of the world as a primary preventive program[17].[18]. PMS has yet to be established in countries where the consanguineous marriage rate is high (40%); more than 85% of which are between first cousins and traditional marriages, which may make its acceptance difficult. Thus, PMS for inherited diseases is an important method to minimize their occurrences among high-risk populations and to reduce the social, emotional, and financial burden on the family and society [18].

Cardiovascular (CV) complications represent the leading cause of mortality in patients with thalassemia, (both major and intermedia)[19]. The patient age at which cardiac death occurs depends primarily on access to transfusions and chelation. In transfused, but unchelated patients, the typical age at death is 10 years, primarily of cardiac causes [20,30]. CV mortality has significantly declined, reflecting the overall mortality reduction due to thalassemia [21]. This improvement is due to the implementation of modern diagnostic and therapeutic modalities like MRI-guided chelation therapy [22]. This progress is not occurring in thalassemia populations with limited access to modern therapy and therefore the global burden of CV disease in thalassemia remains high, affecting 42% of patients [23, 24].

Iron overload and viral hepatitis are the two main causes of liver disease in patients with thalassemia leading to ultimate cirrhosis. The incidence of hepatocellular carcinoma (HCC) in thalassaemic patients has increased lately due to prolonged survival [25].

Growth failure in β (TM) has been recognized for many years and has persisted despite advanced therapy [26, 27].

Endocrine abnormalities are the most common complications of (TDT). The prevalence varies, depending on the severity of the defective genetic background, the hemoglobin concentration, the degree of iron load, and the increased survival to adulthood [28].

Infections and their complications were previously the second commonest cause of death in (TDT)[29].

Objectives:

The objectives of this study were to determine the incidence, trend, and complications of thalassemic patients in Karbala holy city.

METHODS:

A retrospective hospital record-based study was carried out in Karbala teaching hospital of children, dead patients were excluded from our study Data were acquired from patients' files and the centers' registries. The total number of registered patients is (529). All the information regarding their socio-demographic profile and their thalassemic status were collected from April 2021 to April 2022.the registration since 1997.

Designed and pre-tested standard proforma from the hospital records.

Limitations death can't be estimated exactly due to either the patient transferring to other centers or stopping visiting the center, which are both not included in the study. The registered deaths were 46 and they were also not included.

RESULTS

The total numbers of patients involved in the study were 529 patients,432(81.66%) of them were beta thalassemia major while 97 of them were thalassemia intermedia the are registered in karballa department of hematology between the years 1997-1998, the study was done between April 2021 and April 2022.

The deceased patients were not included in this study.

Table (1): Types of thalassemia in the sample

	No .of each type of thalassemia in the sample	**The percentage of each type of thalassemia in the sample**
thalassemia major	**432**	**81.66%**
thalassemia intermedia	**97**	**18.34%**

Males were 253(47.83%) and females were276(52.71%), most of them were consanguinity positive 430(81.29%), and unrelated parents were99(18.7%).

The smallest patient's age is 4 months and the oldest one is 24 years old.

Table (2): Gender distribution of the patents.

gender	Preparing meals and women	Presence percentage in the sample
Male	**253**	**47.83%**
Female	**276**	**52.17%**

Table (3): Relative of parents of thalassemic patients.

	Parents are relatives	Parents are not related
The number for each group	430	99
Presence percentage in the sample	81.29%	18.71%

Age of most patients <12 months at the time of diagnosis were 328 of the500(62.00%) which was the highest percentage among all of them followed by ages from 13-24months=73(13.80%), and the lowest was the ages between 25-60 months which were=58 out of 529 (10.96%).

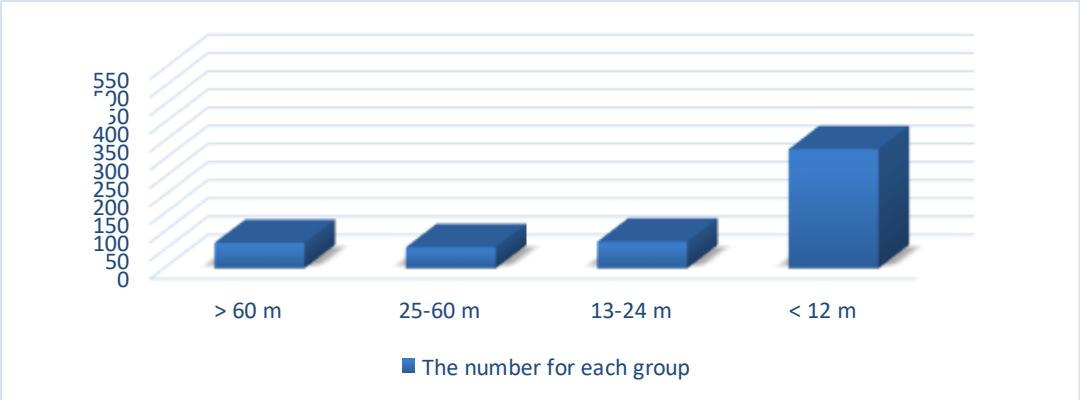

Figure 1. Age of patient at the time of diagnosis

Karbala has five districts and the largest population number is the central district which justifies that the most cases came from the center of holly city of karbala =199(37.62%) followed by is followed by Al-Hur district 108 of 529patients (20.42%), AL-Hindya and AL-Hussainiya districts are equal in numbers of registered patients=80 (15.12%) and Ain Al-Tamer were 18(3.40%) patients.

Table (4): Distribution of patients according to areas of Karbala city.

	Almarkaz	Alhur	Alhindya	Al-Hussainiya	Ain Al-Tamar
Population of each area	199	108	80	80	18
Percentage of patients for each area	37.62%	20.42%	15.12%	15.12%	3.40%

Most of them has average socioeconomic status303(57.28%) poor were177(33.46%), acceptable and good were 11(2.08%),38(7.18%) respectively.

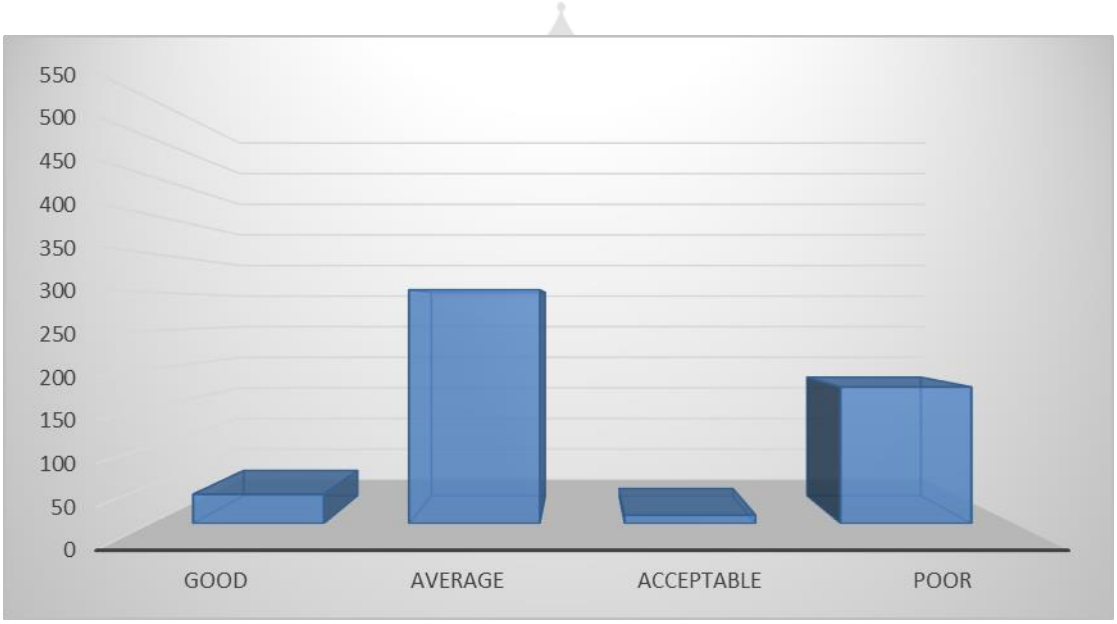

Figure 2. The socioeconomic stability of thalassemic patients.

114 of 529(21.5%) were under school age, or they leave school while 265 (50.09%) were students the rest were earners 133(25.14%) and employees 17(3.22%).

Table (5): Educational levels for thalassemia patients.

	Out of school age	Student	Officer	earner
The number of patients for each of the functional and educational levels	114	265	17	133
Percentage of educational levels for thalassemia patients in the sample taken	21.55%	50.09%	3.22%	25.14%

We found that 280(52.93%) patients were the only member of their families, while 249 of 529 they divided according to the numbers of members involved from 2-3 were227 (42.91),4-5 were 20(3.78%), more than 5 were 2(0.38%).

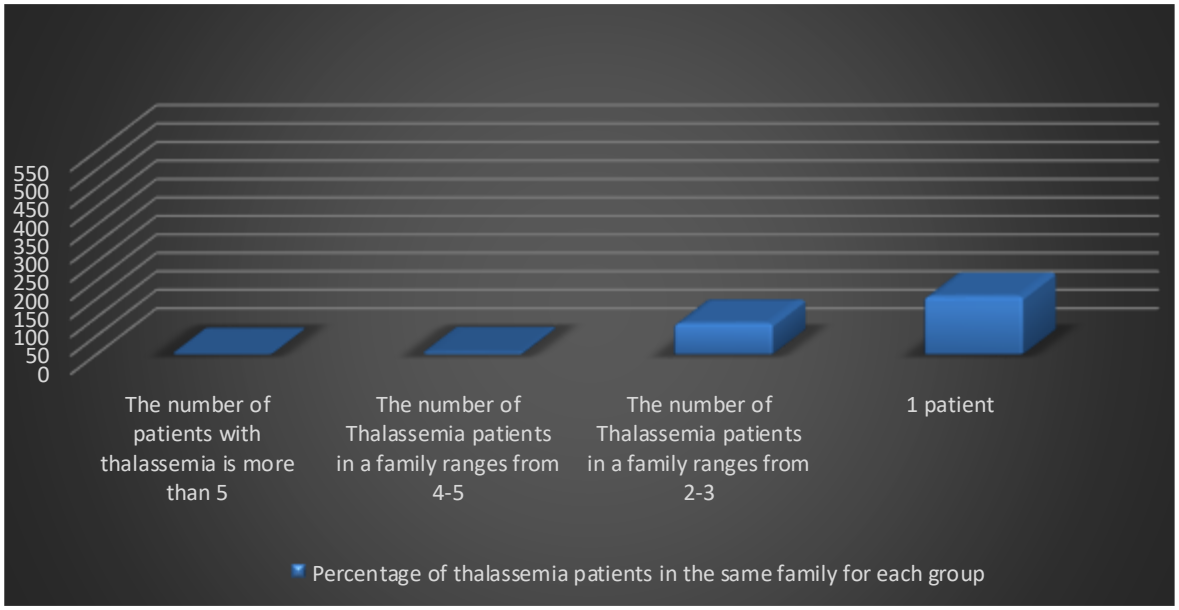

Figure 3. No. of thalassemic patients in the same family.

The number of death due to thalassemia major and its complications can't be collected prissily because some registered patients were stooped visiting the center and others transferred to other centers.

A patient that has another family member who died from thalassemia or its complications were56 of 529, the 473 left out of 529 have no death in their families.

Table (6): No. of death due to thalassemia in the same family

	zero	1-2 death	3-4 death	The number of dead people is more than 4
The number of people who died in Thalassemia patients in the same family	473	52	3	1
Percentage of persons who died among Thalassemia patients in the same family for each group	89.41%	9.83%	0.57%	0.19%

Of the registered patient, the patients diagnosed with hepatitis C=28(5.29%), and hepatitis B = was 4(0.76%).

Table (7): No. of thalassemic patients infected with hepatitis C virus and hepatitis B virus

	hepatitis C virus	hepatitis B virus	total
Number of people infected with hepatitis C virus and hepatitis B virus	28	4	32
Percentage of individuals infected with hepatitis C virus and hepatitis B virus	5.29%	0.76%	6.05%

Of the the529,85(16.06%) done splenectomy 16 (3%) of them have done cholecystectomy, and 7(1.32%) of them have done both.

Table (8): Types of operations in thalassemic patients.

	&splenectomy	cholecystectomy	Splenectomy
The number of people with thalassemia for each type of operation	7	9	78
Percentage of patients with thalassemia for each type of operation	1.32%	1.7%	14.74%

Regarding complications 89 of 529 has splenomegaly, the next most common complication was hypoparathyroidism 77(14.37%),40 of 529 with delayed puberty (7.56%), 33 (6.24%) of 529 has allergies, 15 (2.84%) with diabetes, 10(1.89%) were with cardiac problems and 7 (1.32%) out of 529 were having hypothyroidism.

Table (9): Complications of thalassemic patients.

	diabetic	Splenomegaly	hypothyroidism	hypoparathyroidism	cardiac problem	hepatitis	Delay puberty	allergy
no	15	89	7	77	10	32	40	33
Percentage of each type of thalassemia complication	2.84%	16.82%	1.32%	14.37%	1.89%	6.049%	7.56%	6.24%

Of them 520 (98.30%) are taken folic acid,394(74.48%) were on exjade while 59(11.15%) were on deferral .10 on anti-failure and 13 (2.5%) were treated with insulin, and 7 were treated with hydroxyurea, (1.32%).

Table (10): Drugs used by thalassemic patients.

Drugs	Folic acid	Exjade	Desferal	insulin	hydroxyurea	anti failure
No	520	394	59	13	7	10
%	98.30%	74.48%	11.15%	2.5%	1.32%	1.9%

DISCUSSION

The total numbers of patients involved in the study were 529patients,432 of them were beta thalassemia major while 97 of them were thalassemia intermedia they are registered in the Karbala department of hematology between the years 1997-1998, the study was done between April 2021 and April 2022.

The deceased patients were not included in this study.

Males were 253(47.83%) and females were276(52.71%), While other studies showed male predominance (Bhaswati et al [31]Harsha et [32]and Sur et al [33]reported 65.5%, 56%of male patients respectively.in 2016, a higher male predominance was reported among Saudi children with thalassemia as 70% were males, with a male to female ratio of 2.3:1[34]Yemen, our results are much similar to a study done in Dubai in 2013 which showed no significant difference in the incidence of thalassemia in both sex as 50.5% of their patients were male[35]. Our result may be due to both sexes being equally important to their parents.

most of them were consanguinity positive 430(81.29%), and unrelated parents were99(18.7%). this may be due to the tradition of Arabic tripes to preferring cousins' marriage, other studies showed similar results Zamani et al. among parents of pediatric thalassemia patients of the Baloch population in Iran [36], similarly, in Tunisia,2013 as the reported study showed that thalassemia is highly concentrated in small towns where the marriage occurs between close relatives [37]. on the contrary, lower consanguinity was detected in a study done in western India in 2010 as Shah et al,[38]. reported that Muslim patients with thalassemia result in consanguinity marriage.

Age of most patients <12 months at the time of diagnosis were 328 of the500(62.00%) which was the highest percentage among all of them followed by ages from 13-

24months=73(13.80%), and the lowest was the ages between 25-60 months which were=58 out of 529 (10.96%). Our results are similar to those of Modell and Berdoukas who reported that 60% of their patients had presented clinically in the first year of life with the main age being 6 months [39], this may be due to improvement of diagnostic facilities with time.

Karbala has five districts and the largest population number is the central district which justifies that the most cases came from the center of holly city of karbala =199(37.62%) followed by is followed by Al-Hur district 108 of 529patients (20.42%), AL-Hindya and AL-Hussainiya districts are equal in numbers of registered patients=80 (15.12%) and Ain Al-Tamer were 18(3.40%) patients. This is similar to a study done in Yemen where a large number of registered patients were from large cities like the capital Sana'a which make the patient easily seek medical care because of the availability of hospitals in comparison to the peripheries so the registration will be more. [40]

Most of them have average socioeconomic status303(57.28%) poor were177(33.46%), acceptable and good were 11(2.08%),38(7.18%) respectively. It was found that factors such as family income and parents and children's education have a direct association with the quality of life of children with thalassemia. And the burden of the disease on the family and functional and physical limitations due to pain or anemia or complication of iron overload of a patient with thalassemia may lead to poor economic status [41,42,43].

114 of 529 were out of school, while 265 (50.09%) were students the rest were earners 133(25.14%) and employees 17(3.22%). A similar finding in a study done by Soheir Adam in Saudi Arabia in 2019…were showed only12(11.4%) were college graduates, and most (81.77.2%) are either finished school or still, students,87(82.9%) were unemployed among the 18(17.1%) were employed 7 were working in manual and clerical jobs. Education is a key indicator of income, family growth, sustenance, and well-being. [44]. Education plays a more role in psychological, emotional, and social well-being than the other aspects of well-being [45]. Health outcomes are also influenced by education [46]. Education makes a person a job; income.

The number of patients who have other family members with thalassemia was were249 of 529 divided according to the numbers of members involved from 2-3 were227(42.91),4-5 were 20(3.78%), more than 5 were 2(0.38%).and patients who were the only member involved in their families were 280(52.93%).this is due to parent's unawareness about the disease and the effect consanguinity marriage on it. a similar study done by Shami and Tariq

in Pakistan indicated that almost 70% of families have more than one β- thalassemic child (i.e., two or three) they also reported previously that β - thalassemia patients come mainly from parents with low levels of education and income in Pakistan [47].

A patient that has another family member who died from thalassemia or its complications were56 of 529, 52 of them has 1-2 death, and the 473 left out of 529 have no death in their families due to thalassemia or its complications.

Of the registered patient, the patients diagnosed with hepatitis C=28(5.29%), and hepatitis B = was 4(0.76%). A similar study done at Quetta showed that 30% of thalassemic patients were positive for anti-HCV antibodies, and 14% for hepatitis (19). Another study done at Peshawar shows 8.4% and 56.8% seropositive for HCV antibodies and HBsAg respectively. [48].

Of the the529,85(16%) were done splenectomy while 16of them have donecholecystectomy.7 of them have done both.

A study in turkey shows that 79(38%) of 207 patients with thalassemia intermedia and 590(37%) of 1594 patients with thalassemia major underwent splenectomy [49].

Regarding complications, the most common complication of blood transfusion and iron overload among our studied cases was splenomegaly 89 of 529 has splenomegaly, the next most common complication was hypoparathyroidism 77(14.37%),40 of 529 with delayed puberty (7.56%), 33 (6.24%) of 529 has allergies, 15 (2.84%) with diabetes, 10(1.89%) was with cardiac problems and 7 (1.32%) out of 529 were having hypothyroidism. The reasons are probably multiple transfusions, lower pretransfusion hemoglobin level, inadequate chelation therapy, and severe anemia, if not treated well, similar studies likeBorgna-Pignatti *et al*.[50] reported that the prevalence of complications in Italian thalassemic patients includes heart failure in only 7%. In 2013, Belhoul *et al*. [35] reported a much lower incidence rate of cardiomyopathy (1.8%) among their thalassemic patients studied in Dubai.

In contrast, Yemen registered cardiac dysfunction in the form of cardiomyopathy, representing 19.3% of the total studied cases and around half of the complicated cases (46.7%), followed by liver disease (11%), nephropathy (6.4%), and infection (hepatitis) (3.7%).[60]. In addition, around 15.1% prevalence of cardiac involvement was reported among Sicilian thalassemic patients [51].

Of them520 (98.30%) are taken on folic acid,394(74.48%) were on exjade and 59(11.15%) on deferral .10 of 529 are treated with anti-failure. And 13 were treated with insulin(2.5%) and 7 were treated with hydroxyurea, a percentage of(1.32%).In contrast to our study, a similar study carried out by Bejaoui and Guirat[52] in Tunisia reported that deferoxamine (deferral) was the most commonly used iron chelator (57.3%), whereas oral chelators had been administered only to 29.1% of their patients [52]. Our result is in agreement with a similar study from western India carried out by Shah *et al*. [53], who reported that out of 67% of their thalassemic patients who received chelation therapy, 98% were receiving oral chelation therapy and only 2% were taking desferrioxamine therapy because of the difficulties associated with transfusion as it is injected subcutaneously and requires a long duration of infusion of 8 h. In addition, the noticeably increased percentage of patients receiving oral chelation therapy in India was because of the reduced cost of oral chelating drugs through the manufacture of similar cheaper formulations locally in India [54,55,56]. In 2017, a study carried out in Bangladesh showed that the majority of thalassemic patients used oral chelator therapy, whereas only 9.4% of the patients used intravenous Desferal [17].

CONCLUSION

Thalassemia is one of the major public health problems world wild. Prioritizing thalassemia awareness and access programs for the targeted population should be designed through innovative approaches. The high complication and mortality rates in our country are because of multiple reasons: lack of knowledge of thalassemia and its genetic aspects, late detection of the disease, unavailability of some of the chelator agents because of the unstable current situation, low incomes of the concerned population, all of which lead to difficulties in the follow-up of the patients. Public education about thalassemia should be provided through periodic meetings addressed to health professionals including doctors, nurses, working in the community, and family members. Providing free iron chelating therapy sufficiently and regularly for all patients is important. Money donation is important to decrease the financial and psychological load on the patient and their families.

Prevention of thalassemia is the most viable strategy to reduce the burden of thalassemia patients on families and to manage a sustainable healthcare system. because the management of thalassemia is multifaceted and expensive. However, its prevention is cost-effective. Preventive measures such as health education, carrier screening, PMS, genetic counseling,

and prenatal diagnosis remain the best ways to decrease the incidence of the disease, which might be reflected in financial savings, and social and health benefits.

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