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Research Paper

A Systematic Review of Health-Related Quality Of Life in Beta Thalassemia From A Global Perspective

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ABSTRACT:
BACKGROUND: *Thalassemia is an inherited blood disorder leading to chronic organ damage. Recent advances in treatment have increased life expectancy and now it is a chronic disease with various social and emotional impairments. Thus HRQOL assessment has fundamental role disease management and treatment. There are several general as well as disease specific questionnaires which are reliable and validated measures to access disease burden. Surprisingly the number of HRQOL assessment studies via these validated questionnaires are limited in numbers especially in Category B countries as per GGN (Global Globin Network). It included countries like Australia, Bangladesh, Belgum, China, India, Indonesia, Iran, Netherlands, Nigeria, Pakistan, Portugal, South Africa, Spain, Thailand, Turkey, Vietnam. The difference mainly lies in the presence of all 9 Major qualitative variables and few minor quantitative variables*
OBJECTIVES: *To systematically review publications concerning HRQOL of Beta Thalassemia children and to get a global perspective of differences, similarities, questionnaires used and outcomes evaluated.*
METHODS *:A systematic review of literature was conducted according to PRISMA guidelines, PUBMED database, Web of Science, Google Scholar and MEDLINE was systematically searched for studies published between January 1st 2019 to May 12 2023 .The QOL studies was assessed based on Systematic Review Data Extraction conducted using Standardised procedure collection form (Author, Year Of Publication, Country of Publication, Study design, ,Age and number of patients ,HRQOL questionnaire, Language and clinical outcomes. We identified a total of 50 potential studies. Among these 15 were finally considered in the Systematic Review. The inclusion criteria were as follows:1. Only studies on HRQOL assessment in Thalassemia patients by using PROMIS, SF- 36, PEDSQL 4.0 .2. Only pediatric studies included. Exclusion criteria: Thalassemia studies not related to HRQOL not included.*
RESULTS: ***1.*** *The evaluation of HRQOL was done variably in all continents but differences in frequency of assessment observations.*
2.HRQOL of Thalassemia patients were assessed less in Southeast Asia and Africa.
3.Generic HRQOL questionnaire frequently used (PROMIS, SF 36 and PedsQL) while TRANQOL which is Transfusion related quality of life assessment which is disease specific is very rarely used.
CONCLUSION*: HRQOL is a broad multidimensional concept and outcome, bridging boundaries between social, mental and medical services. It is also incorporated into clinical research as well as practice worldwide. Further the disease specific outcomes like Transfusion burden, Chelation in Thalassemia and healthcare system especially in low and Middle income countries have significant impact on health related quality of life.*
KEY POINTS :1. *Beta Thalassemia, a genetic hemoglobinopathy has evolved into a chronic disease affecting the patients' lives in various domains like social, psychosocial, emotional, physical school functioning and later work functioning.*
2.The management should also go beyond Blood transfusion, Chelation and delve into these problems too in every Thalassemia case.
3. The management of all Thalassemia cases should come under one umbrella and be regarded as a National and International burden and to be shared, managed, prevented within those guidelines to minimise the burden.

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I. INTRODUCTION:

Beta -Thalassemia is a group of inherited haemoglobin disorders characterised by **impaired** production of Haemoglobin and affected individuals need RBC transfusion every 2-5 weeks (Thalassemia Major) for survival (**2**). Chronic transfusion **results** in Iron accumulation which is lethal if not treated and hence the need for Chelation

of Iron. Patients develop complications both due to disease process and subsequent iron overload. All of these issues can adversely impact the patient quality of life. The only curative therapy known is Allogenic (HSCT) Hematopoietic Stem Cell Transplantation which not only inflicts a significant one time cost but also recurrent costs at 1, 2 and following years after HSCT in this review we would like to focus on the fact that despite this knowledge why HRQOL of these patients does not seem to be improving for Thalassemia patients. Not only that the rate of increase of new Thalassemia patients in the majority of Thalassemia Belt countries excepting for few countries like CYPRUS (3) which outshone itself by showing how Prevention Programmes done diligently pave the way for reducing the National burden. Statistics show that between 1991 and 2001 only FIVE (5) Thalassemia babies were born, 1 every 2-3 years. NO Thalassemia babies have been born for last 5 years. The existing Thalassemia patients are living longer and working as normal populations.

About Transfusion and Chelation which is a conservative medical care that requires multidisciplinary care with dedicated and experienced units (4). However long-term transfusion and chelation therapy is highly challenging for many countries where the disease is prevalent representing a major and sustainable health burden even from a global perspective.

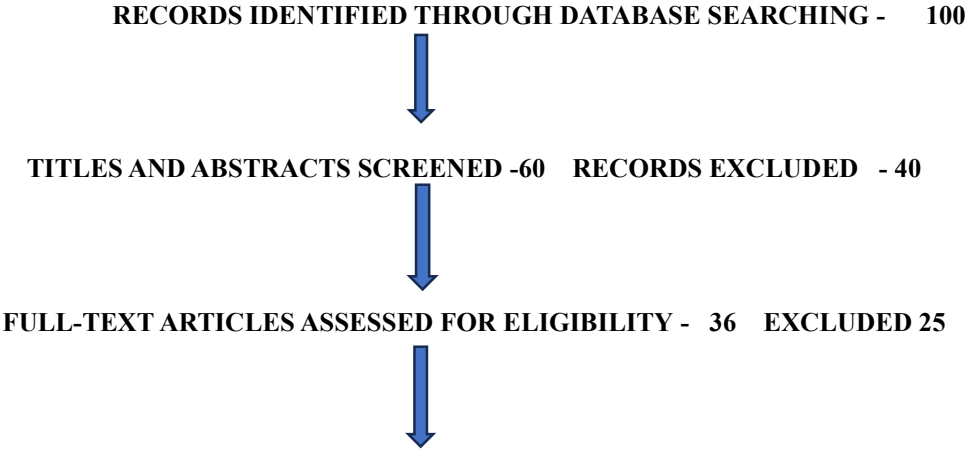
Hematopoietic Stem Cells Transplantation or MUD unrelated with an HLA identical Matched Related Donor (MRD) or Matched Unrelated Donor (MUD) is the only curative option available for Beta Thalassemia Major patients (6). Further 30-year overall survival and Thalassemia Free Survival across the age and risk groups was found to be 82.6 +_ 2.6 % and 77.8 +_ 2.9% respectively in studies published by an Italian group. (7). Cost constraints remain a major hurdle to undergo HSCT. And many families opt to remain in Transfusion -Chelation therapy.

Health related quality of life includes 3 broad domains. Physical. Psychological and social functioning including school functioning which is an essential component. All these may be effected by illness and or treatment. Quality of life assessment is usually either General or Disease specific. TRANQOL is the first disease-specific questionnaire which measures the HRQOL in patients with Transfusion Dependent Thalassemia. It has 4 versions, Child Self report, Parent Self report, Adult Self report and Parent Proxy Report. PEDSQL 4.0 measures the essential core domains for pediatric HRQOL. It involves Physical. Emotional, Social and School Functioning. It consists of Application form for 2-4, 5-7, 8-12 and 13-18 years Thalassemia Life Index (ThAL L) includes different items such as general physical health, coping, body image, appearance and confidence, social relationships and autonomy. The PROMIS scale provides self-reported health measures in the domains of Physical, Mental and Social health. Under each domain there are sub-domains associated with symptom function, affect, behaviour, cognition, relationships or function

II. MATERIALS AND METHODS:

We conducted a systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (8). A literature search was conducted on 10 th September 23 in the databases of PUBMED, COCHRANE LIBRARY, GOOGLE SCHOLAR. We identified 80 papers published between 2019 to 2023.. The studies selected for our systematic review met the following criteria; they investigated HRQOL assessment in Thalassemia by using the PROMIS, SF36, PEDSQL and TRANQOL EVERY article type accepted including Observational studies, Systematic Review, Randomised clinical trials, Qualitative reviews and case reports.

Figure – 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses(PRISMA)



Author	Year	Type of study	Authors' geographical location	Keywords	Main Findings
Md. Jubayar Hossain et al[1]	2023	Cross-Sectional	Bangladesh	Health Policy Health Services Public Health HRQOL	The significant findings are the HRQOL of Male Patients is more vulnerable compared to female patients and Overall HRQOL of Thalassemia patients is associated with high blood transfusion status, disease severity, comorbidities (26%)and medical expenses (52%)
Giovanni Caocci et al [2]	2023	Cross-sectional	Cagliari. Italy	Beta Thalassemia Splenectomy HRQOL	No difference in Physical and Mental health related domains in Comparison to non- splenectomised patients of Beta Thalassemia. Further comorbidities percentage >79% with more than 3 comorbidities
Bijit Biswas et al[3]	2023	Cross-sectional observational	Kolkata India	Social Discrimination knowledge Caregivers' Qol Beta Thalassemia	The QOl of study participants was significantly correlated with carers' QOL, Mothers' Education, Parents Working status, Place of Residence Blood transfusion frequency, Pretransfusion haemoglobin and Comorbidities
GGN Consensus Paper[4]	2022	Project wide initiative of Human Variome Project (HVP)	Malaysia, south Africa Cyprus Indonesia Thailand Philippines	GGN Thalassemia low middle income countries Epidemiology HVP	Proposal of a universally applicable system for evaluating and grouping of countries based on qualitative indicators according to Quality of care, treatment and prevention of Thalassemia
Pamela Kohlbry et al [5]	2022	Cross-sectional	San Marcos CA USA	Thalassemia QOL Westbank Gaza	Scores were low across all domains Indicating poor quality of life. Compared with countries Thalassemia patients in Palestine had lower quality of life scores in most domains.
Sherif M Badawy et 2021 al [6]	2021	Systematic review	Chicago	Stem Cell Transplantation QOL	Stem cell Transplantation has positive impact on several QOL domains in Beta thalassemia patients. QOL outcomes should be reported in all ongoing SCT, Gene Editing Trials in Thalassemia
MS Hossain et al [7]	2021	Cross-Sectional	Dhaka	Thalassemia Prenatal Diagnosis Premarital Parental Perspectives	Poor parental knowledge regarding Thalassemia including Premarital diagnosis and challenges faced while caring for children

Author	Year	Geographical location	Type of Study	Key words	Main Findings
Mona Hamdy et al[8]	2021	Egypt	Cross-sectional	Thalassemia Major QOL Blood Transfusion	QOL is compromised in Thalassemia patients. Its' Assessment should be performed for all Thalassemia patients to determine and implement necessary interventions
Phakalip Sinlapamongkolkul Et al[9]	2020	Thailand .	Analytical Study Single Centre	PEDSQL Predicter QOL Thalassemia	HRQOL studies have improved from previous Decade. Some socio-demographical and clinical characters may present negative impact on HRQOL

Ali Hasanpur Dekhodi et al [10]	2020	Iran	Clinical Trial Study	Aquatic Exercise Beta Thalassemia	Research revealed that exercise in water affected quality of life haemoglobin , Haematocrit, Iron and Ferritin levels such that QOL and Blood indicators showed significant difference in experimental group
Sachet Melt Ananda et al[11]	2020	Srilanka	Case control study	Psychological symptoms Thalassemia	Higher proportion of patients with Transfusion Dependant Beta Thalassemia had psychological symptoms. Scores in many domains including Emotional , Conduct, Hyperactive symptoms, Mothers with children with Thalassemia had significantly higher depressive symptoms which were significantly associated with psychological symptoms among the children
Asrul Akmal Shafie et [12]	2020	Cross-sectional	Malaysia	Children HRQOL PEDSQL 4.0Transfusion dependant Thalassemia	HRQOL has improved over last decade. However further efforts to improve school functioning dimensions are a must
Rajat kumar Agarwal et al[13]	2019	Institutional study using Thecae	Bangalore, Hyderabad, Belgaum India	Thalcare ICT	Creating a sort of patient specific forum for asynchronous teamwork
A.Thiyagrajan et al[14]	2019	Cross-sectional Analytical	Chennai India	HRQOL Thalassemia Psychological well being family income	Major factors focussed was parents psychological wellbeing which was proved to be significantly associated with child's HRQOL.

III. RESULTS:

This review **analysed** 14 studies related to HRQOL in children and adolescents effected by Beta-Thalassemia worldwide. Supplementary materials 1(Tables 1 and 2) characteristics of Thalassemia studies that have been selected. Most studies conducted in Bangladesh (2), India (3), Chicago (1), Italy (2) Thailand (1) Iran (3) Malaysia (2), Srilanka (1). HRQOL seems to be poorly investigated in the countries where it is most prevalent. Education and economic issues seems to be the Root cause of these. Our data shows a dirt of multiple studies in Southeast Asian countries. Further opportunities for HRQOL after HSCT and Gene therapy are limited as the numbers are too low due to socioeconomic issues. The majority of studies are done after conventional Transfusion and Chelation therapy.

HRQOL studies are mostly related to Italy and Greece with the Success story of North Cyprus published in 2009 by Gulsen Bozkurt (35).

In a cross-sectional analytical study by A. Thiyagrajan et al 125 Thalassemia patients and 125 parents (either Father or Mother) were enrolled and KIDSCREEN-10 and RYFF Psychological well- being scale were used for measuring HRQOL respectively. They found that Three factors such as Family Income, Children and Parents Education significantly contributed to the children's HRQOL among Thalassemia affected children. Additionally, the parents' psychological well- being is positively correlated with children's quality of life.

Another cross-sectional observational study from India by Bijit Biswas et al for 1 year was conducted in Calcutta National Medical college and Hospital, Kolkata, India who studied 328 Beta- Thalassemia Children. They found that the participants QOl correlated with the Cares' QOL, Mothers' educational level, blood transfusion frequency Pre- trans fusional Hb level and comorbidity status. Among these the majority are modifiable attributes. Thus these must be prioritised in interventions targeting the HRQOL. At every opportunity awareness and prevention programs to avert the birth of a new Thalassemia should be utilised.

A novel Observational study on Information Technology-Assisted Treatment Planning and Performance Assessment for Severe Thalassemia Care in Low and Middle income countries done by Engineers is worth mentioning. Here 1110 patients with severe Thalassemia from Five centres in India were followed for one-year period. The impact of consistent use of a web based platform designed to assist comprehensive management of severe Thalassemia (Thal Care) on key indicators of quality of care.

Recently from Bangladesh a cross-sectional study by Mad Jubayer Hossein et al of 356 Thalassemia patients receiving treatment from Bangladesh Thalassemia Foundation were selected from August to November 2021.This study assessed HRQOL using SF-36 Questionnaire Socio-demographic data were also collected. The

findings were similar to the previous study excepting that they found increased vulnerability in male patients compared to females.

Another cross-sectional study conducted for one year at Dhaka in Bangladesh was done on 365 patients. This study superimposes the fact that poor parental knowledge regarding Thalassemia including Prenatal diagnosis and the challenges faced while caring for their children. This emphasizes the fact that not just money but community participation is a must to follow the steps of the success in Cyprus.

A case -control study done by Sacheth Mettananda et al was conducted in the three largest Thalassemia centres in Sri Lanka. Psychological morbidity of children was assessed using the strengths and Difficulties Questionnaire and depressive symptoms of mothers was assessed by the Centre for Epidemiological Studies Depression Scale. Here 288 thalassemia patients and equal number of controls are recruited. Abnormal emotional, conduct, hyperactivity and peer relationship symptom scores were reported by 18%,17%,9%, and 14% of patients with Thalassemia respectively. Prevalence of abnormal psychological symptom scores in all domains were significantly higher among patients compared to controls.

Iran has published many papers on HRQOL.A clinical trial study done by Hasanpour Dehkordi et al divided about 40 Thalassemia patients into 2 groups. One experimental and the other control group. The experimental group performed exercise in water three times per week for eight weeks in the pool after obtaining consent. In this research three times recording of results done. Once Qol questionnaire 24 hours before the intervention, 24 hrs after the last session of the exercise program and 2 months after the end of the exercise program. They concluded that use of regular exercise program combined with drug therapy and blood transfusion can be useful in the treatment.

On the Malaysian front a cross-sectional HRQOL survey of 368 Thalassemic children with Transfusion dependency was done by Asrul Akmal Shafie et al using the PedsQL™ 4.0 Generic core scales. Their inference was that the HRQOL of Thalassemic Children has improved over the last decade however further effort is needed to improve the school functioning dimension.

A single institution study of HRQOL in Thai children was done by Phakatip Sinlapamongkolkul et al using the EQ-5D-Y on Thai pediatric Thalassemic patients and comparing with PedsQL Scores from Parent Proxies and children. Within their limited data it appeared that EQ-5D-Y was more useful and long term research was needed to improve the the QOL of these patients. Further their overall HRQOL score was higher compared to their previous one.

In a cross-sectional study from Egypt Mona Hamdy et al using the consecutive sampling technique did the HRQOL assessment of 112 patients using SF-36 questionnaire. They concluded with similar findings that it is definitely compromised and interventions need to be implemented focussing on the affected domains.

Quality of life in Thalassemia patients from countries with Low resources like those living in West Bank and Gaza can be severely affected.

In a cross-sectional study by Giovani Cocci et al., Cagliari Italy 114 patients were enrolled. 29 patients underwent splenectomy, no statistically significant differences were observed in any of the scales SF-36 between splenectomies and not splenectomies patients. These patients however required fewer RBC units per month, with only 27.6 per cent of them transfusing more than 1unit per month compared with 72.9 per cent of the non-splenectomies group. Therefore, in conclusion the researcher's results suggest that the long term HRQoL of splenectomies patients was similar to that reported by the non splenectomized patients. However, despite a lower burden of annual transfusion requirement, they found that splenectomy was associated with the higher prevalence of cardiovascular diseases and diabetes. Future research should evaluate the role of the new erythropoietic stimulators in potentially improving the HRQol and reducing RBC transfusions.

In a published study, about quality of life in Thalassemia patients in the West Bank and Ghaza by Pamela Kohlbry et al. from California state University, USA concluded the lack of access to healthcare and blood transfusions and geopolitical challenges may explain the low quality of life scores of patients with Thalassemia in Palestine. Here, 104 patients and their families were enrolled and surveyed using the 36-item Short Form Health Survey, version 2 (SF36v2) PedsQL and PedsQL family impact module. Scores were low across all domains indicating poor quality of life.

Further in a Consensus Paper published by Global Globin Network by Bin Hashid Halim Fikhri et al, which is a project-wide initiative of Human Variome /Global Variome Project (HVP) a proposal of a universally applicable system for evaluating and grouping of countries based on qualitative indicators according to quality of care, treatment and prevention of hemoglobinopathies like Thalassemia.

IV. DISCUSSIONS AND CONCLUSIONS

Beta-thalassemia is a rare genetic disease with Hematopoietic Stem Cell Transplantation (HSCT) as the only curative option. Due to increase socioeconomic constraints along with lack of awareness prevents the Thalassemia families from choosing these options and preferring frequent lifelong blood transfusions with

chelation and other complimentary therapies. These further greatly affect patients' life's economically, psychologically and socially. A crucial contribution is provided by prevention programs such as population screening, parental education, prenatal diagnosis and genetic counselling which support raising awareness of the severity and complications of the disease.

It is well known for long time that Beta-thalassemia affects the HRQoL. Despite this, nothing much has been done to address these issues. It is essential to think of these outcomes and try to fill the gaps in the psychological support and social interaction of these patients. These goal can only be achieved with robust network of prevention programs.

Psycho-social support and family therapy should be an essential aspect in the care of any Thalassemic patient to promote HRQoL. Promoting community knowledge and planning of the presence of these patients in the community should be included in the healthcare policies of these patients.

HSCT should be an option offered to every Thalassemic patient in the Thalassemia belt irrespective of the socioeconomic and regional differences.

References:

[1]. Md. Jubayer Hossain., Md. Wahidul Islam., Ummi Rukaiya Munni., Rubaiya Gulshan .,Sumaiya Akter Mukta., Md. Sharif Miah., Sabia Sultana. Sci Rep. 2023 May 12;13(1):7734 doi:10.1038/s41598-023-34205-9. Quality of life among Thalassemia patients in Bangladesh using SF-36 questionnaire. DOI-PUBMED

[2]. Giovanni Caocci., Olga Mulas., Brunella Mola., Alessandro Costa., Susanna Barella., Fabio Efficace. Long term health related quality of life and clinical outcomes in patients with beta-Thalassemia after splenectomy. J Clin Med 2023 Mar 28; 12(7):2547. Doi:10.3390/jcm12072547-DOI-PUBMED

[3]. Bijit Biswas., Narendra N Naskar., Keya Basu., Aparajita Disrupt., Rivu Basu., Bobby Paul. An Epidemiological study of quality of life of children with beta thalassemia and its correlates in Kolkata, West Bengal, India. Cureus.2023 Mar 29; 15(3): e36888.eCollection 2023 Mar-Doi-PUB

[4]. Bin Hashim Halim-Fikri., Carsten W. Lederer., Atif Amin Baig., Site nor Assyuhada Mat-Ghani et al. Global Globin Network Consensus Paper: Classification and stratified Roadmaps for improved Thalassemia Care and Prevention in 32 countries' Peers Med. 2022apr;12(4): 552.doi:10.3390 / jpm 12040552-DOI-PUBMED

[5]. Dr. (Prof) Archamma Varghese.The contributing factors responsible to impact the disease burden and quality of life among thalassemia children and their parents. International journal of nursing and medical sciences 2022:11(3)01-19IJNMS ISSN 2454-667

[6]. Ai Mardhiyah., Henny Suzana Mediani.,Santhana Letcmi Panduragan., Iyus Yosep., Linlin Lindayani. Hope and quality of life among adolescent with Thalassemia: A cross-sectional study in Indonesia. OAMJMS doi.org/10.3889/oamjms.2022.9597

[7]. Pamela Kohlbry ., Bashar al-Karmi and Robert Yamashita. Quality of life of patients with Thalassemia living in the West Bank and Gaza. East Mediterr Health J.2023;29(6):.doi.org/10.26719/emhj.23.045

[8]. Sherif M Badawy., Usman Beg., Robert liem.,Sonali Chaudhury., Alexis A Thomson.A systematic review of Qol in Thalassemia after stem cell Transplant.Blood adv.2021 Jan 26;5(2):570-583.doi 10.1182/blood advances.2020002948.

[9]. Mohammad Sorowar Hossain., Md Mahbub Hasan., Mary Petrov Paul Telfer., Abdullah al Mosabbir.Orphanet J Rare Dis 2021 Jul 16;16(1): 315.doi:10.1186/s13023-021-01947-6-DOI-PUBMED

[10]. Mona Hamdy .,Iman Hassan Draz.,Inas Talat Ei Sayed.,A zza Ali Fahmy Ayyad., Marwa Rashad Salemd.Assessment of quality of life among Beta-Thalassemia patients attending Hematology Outpatient clinics at Cairo University hospital.doi.org/10.3889/oamjms.2021.5692

[11]. Phaktip Sinlapamongkolkul., Pacharapan Surapolchai . HRQol in Thai children as evaluated by PedsQL and EQ-5D-Y: A single center experience. Mediterr J Hematol Infec Dis 2020 Jul 1:12(1): e2020036-doi:10.4084/MJHID.2020.036 -DOL-PUBMED

[12]. AliHasanpour Dehkordi., Toba Hasani., Kiavash Fekri., Fatemeh Deris., Shahram Etemadifar.Effects of Aquatic exercise on dimensions of qol and blood indicators in thalassemia. Int J Prev Med 2020 Aug 19: 11: 128.doi: 10.4103/ijpvm_290_19.DOI-PUBMED

[13]. Sachith Metttananda., Ravindu Peiris., Hashan Pathiraja., Miyuru Chandradasa., Dayananda Bandara., Udaya De Silva., Chamila Mettananda., Anuja Premawardhena.PLoS One 2020 Feb 11;15(2) doi: 10.1371/journal.pone.0228733.Psychological morbidity among Beta Thalassemia children with transfusion dependency and their parents.DOI-PUBMED

[14]. Asrul Akmal Shafie ., Irwinderv KaurbChhabra., Jacqueline Hui Yi Wong., Noor Syahireen Mohammed.Health related quality of life in beta thalassemia; A cross-sectional study in Malaysia.Health qual Life Outcomes 2020 May 14;18(1):141-DOI-PUBMED

[15]. Rajat kumar Agarwal., Amit Sedai., Kumari Ankita., Lalith Parmar., Rakesh Dhanya., Sunil Dhimal.Information technology assisted treatment planning and performance assessment of Thalassemia in low and middle income countries. JMIR med Inform.2019Jan 23;7(!)doi :10.2196/medinform.9291.

[16]. Fabio Tedone., Piero Lamendola ., Stephania Lopatriello ., Davide Cafiero., Daniele Piovani and Gian Luca Forni. Quality of life and burden of disease in Italian patients with transfusion dependent Beta- thalassemia. J Clin Med.2022 Jan;11(1):15 doi:10.3390/jcm11010015 PMC8745153PMID:35011757

[17]. Shaikha Alshams ., Samer Hamidi and Hacer Ozgen Narci. HRQol and associated factors of children with Transfusion Dependent Thalassemia in Dubai, UAE.doi:10.5539 /gjhs. v13n7p18. Global Journal of Health Science; Vol.13, No .7;2021ISSN 1916-9736

[18]. Francesca Rodigari., Giorgia Brugnera., Raffaella Colombatti. Health related quality of life hemoglobinopathies from a global perspective. Front.Pediatr.,25 August 2022. Sec. Pediatric Hematology and Malignancies. Vol 10-2022 .//doi.org/10.3389/ped2022.886674 DOI

[19]. Francesca Greco., Franca Merino. Social impact and quality of life in patients with Thalassemia: a systematic Review. EMJ Hematol.2022; DOI/10.33590/emjhematol/22-000-41.

[20]. Dr. Prof. Achamma Vergese. Thalassemia disease specific Qol health model. (IOSR-JNHS) p-ISSN:2320-1940 vol 9 ser. (Jul-Aug 2020)

[21]. Gulsen Bozkurt. Results from the north Cyprus Thalassemia Prevention Program.IJHR vol 31,2007-issue 2.doi.org/ 10.1080/03630260701297204

[22]. TIF Abstract Book.14th International Conference on Thalassemia and other Hemoglobinopathies and 16 th TIF Conference for Patients and Parents
[23]. Henny Suzana Mediani., Ikeu Nurhidateh., Lilis Lusiani., Ramdan Panigoro.Predicting Factors Impact to QOl of School Age Thalassemic children in Indonesia.2021 JOA Pharmacy Edu and Research.
[24]. Ali T Taher., Rayan Bou FakhredinAntonis KattamisVip Viprakasit.Improving outcomes and QoL.Recommendations.doi.org 10.1080/17474086
[25]. Lailil Fatkuriyah., Ainul Hidayati.doi.org/10.36720/nhjk. v1i1.340 Jan-Jun 2022 Factors related to quality of life in Thalassemia major
[26]. Rabeya Yousef., Shaima Akhtar., Salam M Wasek., Sushmita Sinha., Rahnuma Ahmed., Mainul Haque.Thalassemia: A review of challenges to the families and caregivers.DOI :10.7759/cureus.32491
[27]. Atefeh Dehnoalian., Shirin Madadkar Dehkhordi., Mehri Alaviani. The impact of Educational counselling program on QOL in Thalassemia.doi.org/10.5812/jjcdc.55980