FACTORS RELATED TO QUALITY OF LIFE AMONG CHILDREN WITH THALASSEMIA MAJOR: A LITERATURE REVIEW

By Lailil Fatkuriyah
Review Article: Systematic Review, Meta-Analysis, Integrative Review, Scoping Review

FACTORS RELATED TO QUALITY OF LIFE AMONG CHILDREN WITH THALASSEMAIA MAJOR: A LITERATURE REVIEW

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Abstract
Background: Thalassemia major is a chronic disease in children that harms quality of life by interrupting physical function, emotional function, social function, and school function.

Objectives: This study aims to identify factors contributed to quality of life among children with thalassemia major.

Design: The research design used systematic review based on the PRISMA guideline.

Data Sources: The source of the articles used three databases including Pubmed, Science Direct, and NCBI with keywords: “quality of life” AND “children” AND “thalassemia major”. The articles were searched from July to September 2021.

Review Methods: The data in this study were obtained by reviewing articles from previous studies using PRISMA checklist and PICOS. To assess the quality of article, JBI Critical Appraisal Tools was also used as a guideline.

Results: There were 6 articles reviewed according to the inclusion criteria. All the studies showed that the score of quality of life among children with thalassemia major was lower than that of healthy children. The school function among children with thalassemia major was known to have the lowest score from this review. Factors contributed to quality of life among children with thalassemia major according to this review were chelation therapy, pretransfusion hemoglobin, age during the first transfusion, frequency of transfusion, child’s age, family income, parents’ education, hepatomegaly, body mass index, and serum ferritin levels.

Conclusion: This review notifies the necessity of developing strategies in improving the quality of life of children with thalassemia major that involves parents, health services, schools, and the government.

Keywords: Quality of Life, Children, Thalassemia Major, Literature Review.

INTRODUCTION
Thalassemia is a genetically inherited blood disorder that causes a high mortality rate in children, especially in developing countries. According to the Thalassemia International Federation (2014), thalassemia is characterized by the absence and the lack of one of the globin chains, either α or β, which are the main components of the normal hemoglobin molecule, which causes short-lived red blood
cells and ineffective erythropoiesis. As a result, the patient will experience chronic anemia along with its clinical symptoms and complications. Thalassemia major is the most severe type among several types of thalassemia because it requires blood transfusions every 2-4 weeks and continuous iron chelation therapy (Mikael & Al-Allawi, 2018). The process of the disease and its long-term treatment leads to the emergence of physical and psychological changes, which cause the low quality of life of the patients.

Indonesia is one of the countries with a high risk of thalassemia. According to the Ministry of Health of the Republic of Indonesia (2019), the prevalence of thalassemia major in Indonesia, based on the data of the Indonesian Pediatrician Association’s Hematology Skill Competency Test in 2016, reached 9,121 people. Based on the data of the Indonesian Thalassemia Foundation/Parent Association of Thalassemia Patients, people with thalassemia in Indonesia had increased from 4,896 people in 2012 to 9,028 people in 2018.

According to Sipto (2019) physical changes of patients with thalassemia major, especially in developing countries, include growth retardation, pallor, muscle hypotrophy, hepatosplenomegaly, genu valgum, foot ulcers, and bone deformities caused by the expanding bone marrow (e.g., deformities of the craniofacial area or mongoloid face). Patients with thalassemia are also at risk of complications due to iron overload, which causes heart failure, cardiac arrhythmia, liver abnormalities, and endocrine disorder (Taher & Saliba, 2017). These physical changes and weaknesses have a psychosocial impact on children with thalassemia, such as low self-esteem, shame, helplessness, and withdrawal from the social environment (Hockenberry, Wilson, & Rodgers, 2016; Yıldız, Sültihan, Fidancı, & Kızılderili, 2016).

Regular blood transfusions can compensate for chronic anemia, prevent bone deformities, support normal growth, improve activity tolerance, and improve children’s quality of life. On the other hand, long-term blood transfusion has several risks, such as triggering iron overload, transfusion-transmitted infections, and alloimmunization (Shah, Saya, Trompeter, Drasar, & Piga, 2019). Thus, patients with thalassemia major should receive iron chelation therapy as well to remove excess iron. However, like blood transfusions, iron chelation therapy also has the potential to cause side effects. According to a study of 100 children with thalassemia major conducted by Ejaz, Baloch, and Arif (2015), several side effects of chelation therapy included anemia (70%), abdominal pain (41%), nausea (31%), and vomiting (15%).

In addition to facing the possible side effects of therapy, children with thalassemia major have low academic achievement since they are frequently absent from school for regular transfusions and treatment in the hospital. In addition, the symptom of chronic anemia causes the lack of concentration on children so that their academic performance in class is also not optimal (Shafie et al., 2020). These severe conditions can affect the quality of life of children with thalassemia major, which is generally shown by having low physical, emotional, social, and academic functions (Assyieen, Azrin, Zulkifli, & Zulfahil, 2017).

Nurses need to know the factors related to the quality of life of children with thalassemia major and their implications for each quality of life dimension. Therefore, they may be able to plan appropriate interventions to improve the quality of life of the children. Based on the background above, this review aims to identify factors related to the quality of life of children with thalassemia major.

**METHODS**

**Design**

This study design used a systematic review method. The data in this study were obtained by reviewing articles from previous studies using PRISMA checklist and PICOS. Data collection was conducted using three databases, including Pubmed, Science Direct, and NCBI.
Search Methods

The search of research articles was started from January to September 2021. The keywords used in the article identification were “Quality of Life” AND “Children” AND “Thalassemia Major”. The inclusion and exclusion criteria were determined using PICOS framework: 1) Population, children with thalassemia major aged 2-18 years; 2) Interest, quality of life was should be measured using Pediatrics Quality of Life (PedQL™) 4.0; 3) Context, the research was done in countries located on the “thalassemia belt”; 4) Outcome, articles that contains quality of life covering four specific dimensions of quality of life such as physical function, emotional function, school function, and social function; 5) Study design, cross-sectional, case study, and experimental study with full text; 6) Publication years, 2017-2021; 7) Language, English.

Search Outcome

Based on an initial literature search, researchers obtained 333 articles that match the keywords (PubMed: 197, Science Direct: 54, NCBI: 82). A total of 24 are duplicate articles. The articles then were screened by the title, and as many as 256 were excluded. Through the abstract screening, 42 articles were excluded because they involved either respondents with thalassemia minor or those with thalassemia intermedia. The remaining 11 articles were eligible to be assessed. After conducting a critical appraisal, only 6 of 11 articles reach >50%. Three articles obtained were cross-sectional studies. The remaining articles were case control studies. Studies both using cross-sectional and case control design were rated 6 out of 8 points on the checklist. The process of article selection is also shown in the following flow diagram.

Quality Appraisal

Researchers analyzed the quality of each study included in review using The JBI Critical Assessment Tools that provides several criteria to assess research quality. The criteria assessment was rated “yes”, “no”, “unclear” or “invalid”. Each criterion with a score of “yes” was rated one point, and the other scores was zero. All the criteria of each study were then summed up. Only study that reaches at least 50% were included in the review. Low-level studies were excluded to avoid bias in the validity result.

Data Abstraction

The article selection in this study was done through high qualified databases using determined keywords and PICOS framework. The selection process was guided by PRISMA flow chart. To obtain high-level studies, researchers rated each study using JBI Critical Appraisal Tools.

Data Analysis/ Synthesis

This study used a descriptive analysis which describe the research results through a
narrative method. The data obtained from each study include: author, year, research design, number of samples, instruments, statistical analysis, and the study results of each article. articles that could be used in the preparation of this literature review. The articles that can be used in the preparation of this literature review have been described in Table 1.

RESULTS

Based on the results of the Quality Appraisal, it was found that there were 6

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<td>1.</td>
<td>Quality of life in children with thalassemia major following up at a tertiary care center in India (GOTQoL) (Asyikeen et al., 2017)</td>
<td>D: Case control S: 36 children with thalassemia major and 50 healthy children V: Quality of life I: PCQoL™4.0 A: Mann Whitney U test, Kruskal-Wallis H test</td>
<td>1. The lowest mean score: school function 2. Factors related QoL: Chelation therapy, parents, parents consider themselves informed about the condition, parents know about bone marrow transplantation</td>
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<td>2.</td>
<td>Quality of life among adolescents aged 14 to 18 years with beta-thalassemia major (TM) in Qatar (Nashwan et al., 2018)</td>
<td>D: Cross sectionnal S: 40 children with thalassemia major and 40 healthy children V: Quality of life I: PedQL™4.0 A: Pearson correlation</td>
<td>1. The lowest mean score: school function 2. There was no statistical difference between thalassemia and healthy group on physical, emotional, and social function.</td>
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|   | **5.** Health-related quality of life and associated factors among thalassemia major patients, Southeast of Iran (Bazi et al., 2017) | **D:** Cross sectional  
**S:** 80 children with thalassemia major and 80 healthy children  
**V:** Quality of life  
**I:** PedsQL™ 4.0  
**A:** Mann-Whitney U test, Kruskal-Wallis H test | 1. The lowest mean score: social function  
2. Factors related QoL: compliance with chelation therapy, pretransfusion hemoglobin, Body Mass Index, liver function |
|---|---|---|---|
|   | **6.** Health-related quality of life in pediatric and adolescent patients with transfusion-dependent thalassemia in upper Egypt (single center study) (Hakeem et al., 2018) | **D:** Case control  
**S:** 64 children with thalassemia major and 64 healthy children  
**V:** Quality of life  
**I:** PedsQL™ 4.0  
**A:** Pearson’s correlation, Chi square, ANOVA, t-test | 1. The lowest mean score: physical function and school function  
2. Factors related QoL: age of starting transfusion, hepatomegaly, household income, ferritin serum |

### DISCUSSION

**Quality of Life**

The total score of quality of life among children with thalassemia major in all studies was significantly lower than that of healthy children. All studies also showed scores on all dimensions of the PedsQL among children with thalassemia were lower than the control group. This is in line with previous research which proved that all essential aspects of children’ quality of life such as physical function, social function, emotional function, and school (preschool) function among children with thalassemia are lower than healthy children (Sultana, Humayun, Noor, & Zafar, 2016). Thalassemia has affected not only physical aspect but also psychosocial aspect among sufferers. Chronic anemia and thalassemia related complication due to ineffective erythropoesis and iron overload will increase morbidity and mortality. Physical deformities, developmental delay, delayed puberty, and dependence on blood transfusions lead children to feel different from their peers, thus negatively impact the child’s psychosocial health.

The results of six studies showed that the academic function of the children in the thalassemia group had the lowest score among the four dimensions. It corresponds with the study conducted by Shafie et al. (2020) and Sultana et al. (2016) which proved that the academic function of children with thalassemia had the lowest score. It can be caused by the chronic anemia symptom that causes children to get tired quickly, lose energy while studying at school, and have difficulty understanding lessons. Moreover, regular blood transfusions and regular check-ups caused children to miss the class. Hockenberry et al. (2016) stated that children with thalassemia major had cognitive deficits, including difficulties in reasoning, remembering, and paying attention. Thus, regular school attendance and academic achievement become the challenges for children with thalassemia.

**Chelation Therapy**

Studies in this review showed that children who received chelation therapy had better physical function than those who did not (Ankush, Dias, Silveira, Talwadker, & Souza, 2018). Moreover, children who received chelation therapy regularly had a higher quality of life score than those who did not receive chelation therapy regularly (Bazi, Sargazi-aval, Safa, & Miri-moghadam, 2017). It is supported by the study conducted by Caocci et al (2012), which showed that delaying the start of iron chelation therapy caused the low quality of life.
of the children. Excess iron stored in the heart, liver, or pancreas causes various complications, such as congestive heart failure, arrhythmias, and hepatic cirrhosis, which can be life-threatening. In contrast, Dhira et al. (2016) found that children with thalassemia who received iron chelation therapy had a lower quality of life than those who did not receive chelation therapy, either orally or by injection. The reason is that the iron chelation therapy, on the other hand, also causes side effects, such as pain in the injection area, abdominal pain, nausea, and vomiting (Sazlina, Asauji, & Juni, 2015).

**Pretransfusion Hemoglobin**

In this review Bazi et al. found that pretransfusion hemoglobin (Hb) was significantly associated with physical function. In accordance with the study of Ismail et al. (2013) which proved that thalassemic children with pretransfusion Hb >9 g/dl had a higher total quality of life score than those with pretransfusion Hb 7-9 g/dl or <7. Low pretransfusion Hb caused several symptoms such as fatigue, physical weakness, and reduced mental alertness which then affect quality of life, particularly in physical function. It can be concluded that pretransfusion Hb should be monitored regularly to maintain an optimal level (>9 g/dl) to prevent some complications such as hepatosplenomegaly and growth retardation (Wahidiyat & Iskandar, 2018).

**Transfusion Frequency**

The findings of the studies in this review showed that transfusion frequency was significantly related to physical function, psychosocial health, and life quality of life; the higher transfusion frequency per year, the lower the score on the PedsQL and both dimensions. Ismail et al (2013) proved that children with thalassemia who received transfusions more often had lower psychosocial health scores than those who received transfusions less frequently. Children with thalassemia major require blood transfusions at least once a month, which demand them to be in hospital for the whole day. This condition makes children often absent from school, and as a result, it indirectly affects the quality of life of children. This condition requires cooperation among parents, schools, health services, and the government to facilitate the education of children with thalassemia. One possible solution is to provide a blood transfusion service on weekends to reduce the number of children’s absences from school.

**Age during the First Transfusion**

The age during the first transfusion was significantly correlated with physical function; the older the children received the first transfusion, the better the physical function. Hamdy et al. (2021) found similar results, in which the age when received the first transfusion was significantly correlated with children’s quality of life score. Sazlina et al. (2015) proved that children who received their first transfusion before four years old had a lower quality of life total score than those who received their first transfusion after four years old. It means that the younger the child received the first transfusion, the earlier the onset of anemia, which requires the body to receive external supplies of red blood cells.

**Age’s child**

The two studies analyzed in this review showed that the younger the children, the significantly better the quality of life, emotional function, social function, and academic function compared to the older children. Moreover, children aged 2-7 years had a better quality of life than children aged 8-12 years. It is supported by a study of children with thalassemia aged 2-18 years conducted by Surapolchai et al. (2010), which proved that children aged 8-18 years had a lower quality of life than children aged less than eight years. A study involving 73 children with thalassemia major and 27 children with thalassemia intermedia in Saudi Arabia also showed that the children’s quality of life decreases with the increasing age (Mikael & Al-Allawi, 2018). At the age above seven years, children are in a transition period from *preschool* to *school*. 
Thus, they start to worry about their academic abilities and their absence from school. Moreover, the children will naturally become more aware of their illness as they grow older. Children are increasingly aware of their physical differences and dependence on blood transfusions. These factors cause them to have negative self-esteem, feel sad and frustrated towards their illness which then causes them to withdraw from the environment. These findings emphasize the importance of psychosocial support for children with thalassemia to improve their psychosocial well-being and quality of life.

Hepatomegaly

The study conducted by Hakeem et al. showed that significant hepatomegaly was correlated with physical function. Hepatomegaly is the most common complication in patients with thalassemia major aged 2-18 years (Hashemizadeh, Noori, & Kolagari, 2012). The main part that produces blood cells is in the bone marrow, precisely at the spongy dark part in the central of the bone. However, the red blood cells produced by the bone marrow are not sufficient because lysis happens to the cells every time they are produced, which destroys large numbers of red blood cells. This condition causes the spleen and liver to work harder than usual and become enlarged. Hepatomegaly causes the liver to be unable to work harder to destroy toxins, filter blood, and fight infection. The presence of hepatomegaly will contribute to an increase in morbidity in children with thalassemia, which can further affect their physical function.

Family Income

Some studies in this review revealed that family income was significantly correlated with physical function; low family income was correlated with children’s low physical function. The low economic status of families with thalassemia children causes the inability to provide a more decent life for the children who need special care. On the other hand, a better economic status can help parents meet all the needs of their children, which can support the children’s health needs optimally. Haghpanah (2013), in a study of 101 patients with thalassemia major, stated that better financial ability allowed patients to deal efficiently with the problems of their illness.

Parents’ Education

In addition to the family income as the factor, Adam et al., in their study, revealed that parents’ education, especially the mother, was significantly correlated with the quality of life and social function of children. A child with an educated mother had a better quality of life than a child with an uneducated mother. It is supported by research conducted by Thiyagarajan et al. (2019), which found that parents’ education was correlated with the quality of life of children with thalassemia.

Educated parents tend to have awareness and concern for the children’s disease and the care needed for them, and they can motivate the child to comply with the treatment. A study conducted by Ankush et al. further strengthens the vital role of parents as the factor to improve the welfare of children with chronic diseases such as thalassemia. It was found that children whose parents were knowledgeable about the disease and had information about bone marrow transplantation had a better physical function. Parents who have a good knowledge of the disease will have a high awareness regarding the importance of health care for sick children. Parents will also have the motivation and strength to provide regular care for their children to promote their physical function optimally. Based on these findings, the local health services are expected to provide health education programs to parents every time they visit the health facility. Thus, the parents get the appropriate knowledge about the disease and the care needed by the children.

Body Mass Index

A study conducted by Bazi et al. found that the Body Mass Index (BMI) had a significant correlation with social function, in which children with low BMI had the lowest
social function. Meanwhile, children with normal BMI had the highest social function scores. A study of 328 children with beta-thalassemia major conducted by Biswas et al. (2021) proves that malnutrition negatively impacts the quality of life. Maltreated children with thalassemia had lower quality of life, physical function, and emotional function scores than those who were not maltreated.

In these studies, however, malnutrition showed no relation with social function, as those maltreated often have a higher score of quality of life. In thalassemia, hemolysis occurs, which causes chronic anemia, resulting in tissue hypoxia. Chronic hypoxia causes disorders in nutrient usage at the cellular level, resulting in impaired growth. Adequate nutrition can be used as a modality in long-term treatment and prevent nutritional disorders, growth disorders, developmental disorders, and immune deficiencies. The author assumes that better physical endurance, as an effect of adequate nutritional intake, can reduce stigmatization and increase the patient’s will to be more involved in social interactions, which results in better social functioning.

Serum Ferritin Level

In the studies reviewed, high serum ferritin levels were significantly associated with low social function. This finding is supported by the research of Khoshavan et al. (2015), which proved that thalassemia children with serum ferritin level of 2500 ng/dl had lower social function than those who had serum ferritin level of <2500 ng/dl. Ansari et al. (2014) also showed that children with thalassemia who had low level of serum ferritin had better quality of life. Serum ferritin level reflects the iron level in the body. High serum ferritin level can increase the risk of organ damage and are associated to high morbidity and mortality. Complication due to high serum ferritin level will cause the patient’s ability to interact with the environment to be more limited, thus affecting the patient’s social function.

Numerous factors affect the quality of life of children with thalassemia major. It is expected that the results of this study will be the foundation to determine strategies in improving the quality of life of children with thalassemia that involves parents, health services, schools, and the government.

CONCLUSION

Factors contributed to quality of life among children with thalassemia major according to this review were chelation therapy, pretransfusion hemoglobin, age during the first transfusion, frequency of transfusion, child’s age, family income, parents’ education, hepatomegaly, body mass index, and serum ferritin levels.

This review notes the necessity of developing strategies in improving the quality of life of children with thalassemia major that involves parents, health services, schools, and the government.

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DECLARATION OF CONFLICTING INTEREST

The authors have no conflict interest.

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AUTHOR CONTRIBUTION

Lailil Fatkuriyah: Main author of the literature review, identifying the articles, and writing the manuscript.

Ainul Hidayati: Identifying the articles and writing the manuscript.

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