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Analysis of the Clinical Factors Affecting the Quality of Life in Children with Hemophilia A

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ABSTRACT

Background: Utilization of a specified questionnaire to measure the Health-related quality of life (HRQoL) in children with hemophilia is unusual especially in a country with resources limited settings. The objective of this study is to analyze the quality of life (QoL) of children with hemophilia A and the clinical factors that affect them.
Methods: A cross-sectional study was conducted in September 2021. The participants were children with hemophilia A who were registered at the Indonesian Hemophilia Society Association (IHSA) in Surabaya. Inpatients, children with cognitive impairment, mental health disorder, aged 8 to 16 years old and cannot read, and declined to participate are not included. The questionnaires are using Hemophilia-Specific Quality of Life (Haemo-QoL) which have been validated in Bahasa Indonesia. HRQoL was assessed for 3 age groups (I: 4 to 7; II: 8 to 12; and III: 13 to 16 years).
Results: All participants (21 children) were male with a median age of 148 months. More than half (52.4%) of the children had mild hemophilia, followed by moderate hemophilia. The mean total Haemo-QoL score was 38.57 (+9.52). The youngest age group are experienced the highest disturbance in the family dimension, followed by the sports school dimension; children in the second and third age group were impaired in friends and sports school dimension. There was no significant correlation between clinical factors studied and the QoL of children with hemophilia A.
Conclusion: The QoL of the youngest age groups must be prioritized due to susceptibility to the family dimension. Appropriate and prompt treatment plays a major role because the treatment of this disease does not depend on the severity of the patient's clinical factors.

Keywords: hemophilia; quality of life; Haemo-QoL; children

INTRODUCTION

Hemophilia A is a blood clotting disorder with sex-linked recessive, characterized by the deficiency of clotting factor VIII, which occurs in 1 per 10.000 male births per year. The symptoms such as spontaneous bruising, mucosal, joint bleeding, epistaxis, and severe bleeding events that occur frequently such as intracranial hemorrhage (1-3). Repeated joint bleeding causes severe joint damage and pain that causes disability (4). Regular visits to the hospital, repeated injections, and activity restrictions are common disorders in hemophiliacs in addition to feelings of anxiety about recurrent bleeding and the risk of permanent disability that will affect the quality of life (5). The fact that until now there is no definitive cure for hemophilia and lifelong therapy is required, assessment of the patient's quality of life becomes an important parameter (6, 7).

Throughout the literature search, studies on the assessment of the quality of life of children with hemophilia using a specific quality of life instrument for hemophilia in Indonesia have not been widely studied. A precise quality of life assessment instrument has been developed that makes them more sensitive to the problems of hemophiliacs including the impact of specific therapy and disease outcomes, which provide detailed patterns of hemophilia-related symptoms and disorders (8). Validated instruments developed in the last 2 decades include the Hemophilia-Specific Quality of Life Index (Haemo-QoL) and Canadian Hemophilia Outcomes – Kids Life Assessment Tool (CHO-KLAT) (9, 10).

The Haemo-QoL instrument assessed the average quality of life of children with hemophilia was 45.1±14.7 (10.4-73.4), with the most influencing factors being 'family, treatment, and physical healths' factors (11). A study conducted by Gringeri in 2004 on 318 children with hemophilia found that the quality of life was quite satisfactory, namely scores far below 50 in the range 0-100, with higher scores indicating the worse quality of life disorders; the youngest age group experienced the impaired quality of life in the dimensions of 'family' and 'treatment', which was associated with overprotection of the family.

Children in the older age group are impaired on 'social' dimensions, such as 'perceived support' and 'friends'; whereas the adolescent age group has problems in the dimension of 'facing hemophilia' (8). The QoL of children with hemophilia and the factors that influence it are different in each country, not only due to differences in the number of participants but also cross-cultural issues between countries (12)

The quality of life in patients with chronic diseases such as asthma, diabetes mellitus, and leukemia has received increasing attention in recent years. However, the QoL of children with hemophilia is still largely neglected (13). The assessment of the QoL aims to detect children who have difficulties related to their hemophilia disease, estimate the problems associated with hemophilia, and determine a holistic and satisfactory treatment. Therefore, it is necessary to study and analyze whether the degree of bleeding, the severity of hemophilia, the age at diagnosis, and the age at initiation of therapy affect the QoL in children with hemophilia.

METHODS

An analytical cross-sectional study was conducted in September 2021. The data were collected using a questionnaire containing socio-demographic data collection sheets and Haemo-QoL instruments to assess QoL as well as for data on factors affecting QoL in children with hemophilia A. Samples were collected through offline meetings in the office of Indonesian Hemophilia Society Association (IHSA) East Java Branch in Surabaya, by previously filling out a willingness or informed consent to attend and participate in the study. The Haemo-QoL questionnaire was presented in Bahasa Indonesia with permission from Khaerani and colleagues. The Indonesia version of the Haemo-QoL questionnaire has been tested for validity and reliability (14).

HRQoL was assessed for 3 age groups (I: 4 to 7; II: 8 to 12; and III: 13 to 16 years). The score of the Haemo-QoL questionnaire, for each item: a score of 3 for the age group I or 5 for the age group II and III was closely related to poorer QoL; while lower scores (closer to 1) are associated with a better or positive quality of life. The sum results of each dimension were transformed into a transformed scale score (TSS) according to the scoring guidelines, so that a scale of 0 to 100 was obtained to allow comparisons between age groups and QoL disorders of each dimension, with the interpretation of higher scores indicating poorer quality of life (8, 15).

The samples of this study were children with hemophilia A who are members of the IHSA East Java Branch. Parents as guardians fill out socio-demographic questionnaires and know the condition of their children. Especially for the 4-7 age group, parents can help fill out the questionnaires if they do not comprehend them. The inclusion criteria for this study were boys aged 4-16 years with hemophilia A, understood Indonesian language, outpatients, aware, and had a good ability to fill out questionnaires, while the exclusion criteria included inpatients, children with hemophilia A with cognitive impairment and mental health disorders, children aged 8-16 years who could not read and write, and/or refused to participate in the study. Ethical clearance was obtained by the Health Research Ethics Committee, Faculty of Medicine Universitas Airlangga Number 154/EC/KEPK/FKUA/2021.

STATISTICAL ANALYSIS

The data were analyzed using IBM SPSS Statistic Version 24. All variables have undergone the Shapiro-Wilk test to determine whether the data is normally distributed or not. We assessed the degree of bleeding, the severity of hemophilia, age at diagnosis, and age at initiation of therapy with QoL in children with hemophilia A. The analysis carried out among clinical factors affecting the QoL was performed by using Pearson or Spearman analysis. The tables and figures are presented to show the mean or median of each dimension based on age group and severity of hemophilia.

RESULTS

A total of 21 children with hemophilia A who are members of the Indonesian Hemophilia Society Association (IHSA) East Java Branch participated in the study. All participants met the study inclusion criteria, no subjects were excluded. Of the 21 children with hemophilia A, all were boys. The average age of the participants was 148.71 (±37.88) months with the highest age group being 13 -16 years of age as many as 12 children (57.1%). More than half of all participants had mild hemophilia, 11 children (52.4%), followed by 10 children with moderate hemophilia (47.6%), no patients with severe hemophilia were found in this study. The clinical characteristics of the research subjects can be seen in Table 1.

TABLE 1: The clinical characteristic of children with hemophilia A

Characteristic	N (%)	Mean (±SD) / Median (IQR)
Current age (months)		
Age group according to Haemo-QoL		148.71 (±37.88) [a]
• 4-7 years old	2 (9.5)	
• 8-12 years old	7 (33.3)	
• 13-16 years old	12 (57.1)	
Education level		
• Not yet in school	1 (4.08)	
• Kindergarten	0 (0)	
• Primary school	8 (38.01)	
• Junior high school	9 (42.9)	
• Senior high school	3 (14.3)	
Age at diagnosis (years old)		
• 0-1	13 (61.9)	
• 2-3	0 (0)	18 (8-54) [b]
• 3-6	3 (14.3)	
• 6-12	5 (23.8)	
• 12-18	0 (0)	

Characteristic	N (%)	Mean (±SD) / Median (IQR)
Age at the initiation of therapy (years old)		
• 0-1	11 (52.4)	24 (12-84) [b]
• 2-3	1 (4.8)	
• 3-6	4 (19)	
• 6-12	5 (23.8)	
• 12-18	0 (0)	
The severity of hemophilia A		
• Mild	11 (52.4)	
• Moderate	10 (47.6)	
• Severe	0 (0)	
Degree of bleeding		4 (3-5) [b]
• Normal	3 (14.3)	
• Abnormal	18 (85.7)	
The frequency of replacement therapy per month		
• <4 times	5 (23.8)	4 (3.5-4) [b]
• 4-5 times	15 (71.4)	
• > 5 times	1 (4.8)	
Age at first bleeding (months)		7 (3-10) [b]
Age at first joint bleeding (months)		21 (12-84) [b]
Type of bleeding at diagnosis		
• Joints	6 (28.6)	
- Shoulders	1 (16.67)	
- Elbows	2 (33.33)	
- Knees	2 (33.33)	
- Hips	0 (0)	
- Ankle	1 (16.67)	
• Non-Joints	15 (71.4)	
- Mucosal bleeding	2 (13.33)	
- Gum bleeding	2 (13.33)	
- Bruises on the skin	5 (33.33)	
- Intracranial	3 (20)	
- Post circumcision	1 (6.67)	
- Etc.	2 (13.33)	
Number of joint bleeding per year		10 (2.5-11) [b]
Joint targets		
• None	2 (9.52)	
• Shoulders	0 (0)	
• Elbows	2 (9.52)	
• Knees	9 (42.88)	
• Elbows and knees	1 (4.76)	
• Hips	1 (4.76)	
• Ankle	4 (19.04)	
• Elbows and Ankles	2 (9.52)	
Life-threatening bleeding		
• Yes	6 (28.6)	
• No	15 (71.4)	
Comorbidities		
• Yes	2 (9.5)	
• No	19 (90.5)	

[a] Data are normally distributed, shown as Mean (+SD)
[b] Data are not normally distributed, shown as the Median (IQR = interquartile range)

Table 2 and Figure 1 show that the youngest age group experienced the highest disturbance in the family dimension (median 68.75), followed by sports school dimensions with a median Haemo-QoL score of 41.66. In this study, the median dimension of relationship and partnership was 0 (0-43.75).

This is because most of the children answered 'never' with a score of 0, while there were some children who answered 'all the time' with a weight of 5 so an unequal value was obtained on this dimension because the data were not normally distributed. Statistical analysis found no significant difference by age group (p = 0.135).

Children with moderate hemophilia A were more impaired on the sports and school dimensions with a median of 50 (45.31-61.8), followed by the family dimension with a median of 48.43 (42.81-65.62), the friend's dimension with a median of 46.87 (0-70.31), and dimensions of perceived support with a median of 46.87 (23.43-59.37) when compared with children with mild hemophilia (Table 3). The median value of the Haemo-QoL total score based on the severity of hemophilia is not different 39.13 (30.68-47.79) for children with mild hemophilia A and 38.1 (31.24-44.51) in children with moderate hemophilia A.

The results of the statistical analysis found no significant difference between the total Haemo-QoL score and the severity of hemophilia A (p=0.605) (Table 3). Figure 2 showed a graph of the QoL of children with hemophilia A based on the severity of hemophilia A. Table 4 reported that there is no significant correlation between the degree of bleeding, severity of hemophilia, age at diagnosis, and age at initiation of therapy with the quality of life of children with hemophilia A respectively (p = 0.330, p = 0.608, p = 0.516, p = 0.864; r = -0.223, r = -0.119, r = 0.150, r = 0.040).

TABLE 2: Haemo-QoL scores based on the age group

Haemo-QoL Dimensions	Age Group			
	4-7 years old (N=2)	8-12 years old (N=7)	13-16 years old (N=12)	*p**
Physical health	18.75	39.28 (25-50)	32.14 (14.28-45.53)	0.420
Feeling	0	28.57 (0-35.71)	17.18 (6.25-32.81)	0.110
View	0	38.88 (22.22-63.88)	33.75 (18.12-51.87)	0.083
Family	68.75	50 (40-55)	45.31 (31.25-62.5)	0.213
Friends	0	56.25 (43,75-75)	53.12 (34.37-67.18)	0.087
Perceived support	-	50 (25-62)	43.75 (28.12-50)	0.733
Other Persons	12.5	25 (0-37.5)	22.91 (9.37-34.37)	0.732
Sports School	41.66	50 (43.75-53.12)	51.38 (47.22-63.19)	0.509
Dealing	-	46.42 (32.14-50)	32.14 (17.86-49.99)	0.252
Treatment	12.5	25 (14.28-53.57)	20.31 (0.78-33.59)	0.509
Future	-	-	21.87 (18.75-48.43)	-
Relationship/partnership	-	-	0 (0-43.75)	-
Total hemophilia-specific QoL	24.39	47.79 (34.31-51.05)	38.99 (32.42-42.70)	0.135

*The data were not normally distributed; Presented as Median (IQR); Kruskal-Wallis test was used.

TABLE 3: Haemo-QoL scores based on the severity of hemophilia

Haemo-QoL Dimensions	Severity of hemophilia		
	Mild (N=11)	Moderate (N=10)	*p**
Physical health	28.57 (10.71-46.42)	32.14 (25-48.21)	0.468
Feeling	28.57 (6.25-40.62)	17.18 (0-25.78)	0.197
View	40 (22.22-57.5)	28.75 (5.62-42.91)	0.282
Family	43.75 (31.25-65.62)	48.43 (42.81-65.62)	0.468
Friends	56.25 (43.75-68.75)	46.87 (0-70.31)	0.605
Perceived support	43.75 (25-62.5)	46.87 (23.43-59.37)	0.968
Other Persons	25 (8,33-25)	22.91 (3.12-40.62)	0.756
Sports School	47.22 (43.75-53.12)	50 (45.31-61.8)	0.654
Dealing	39.28 (25-53.57)	33.92 (17.86-44.64)	0.545
Treatment	25 (0-34.37)	21.65 (11.49-36.83)	0.756
Future	25 (18.75-50)	18.75 (15.62-46.87)	0.755
Relationship/partnership	0	25 (0-75)	0.202
Total hemophilia-specific QoL	39.13 (30.68-47.79)	38.1 (31.24-44.51)	0.605

*The data were not normally distributed; Presented as Median (IQR); Mann-Whitney test was used.

TABLE 4: Correlation analysis of Haemo-QoL with the clinical characteristics studied.

Characteristics	Correlation Coefficient (r)	*p*-value
Degree of bleeding	-0.223	0.330[a]
Severity of hemophilia	-0.119	0.608[a]
Age at diagnosis	0.150	0.516[b]
Age at initiation of therapy	0.040	0.864[b]

[a] Pearson correlation analysis
[b] Spearman correlation analysis

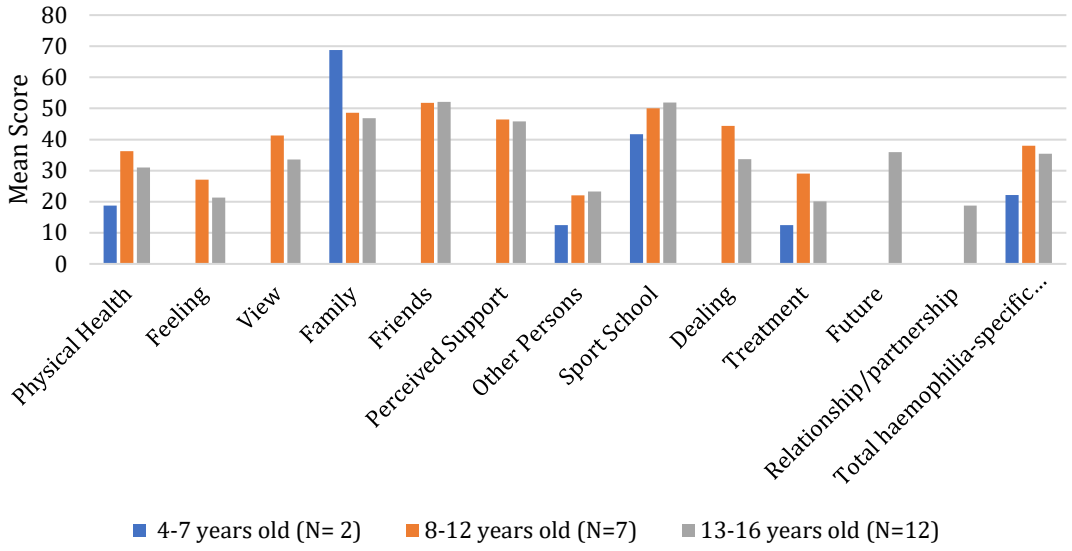

FIGURE 1: Haemo-QoL scores of children with hemophilia A based on age group

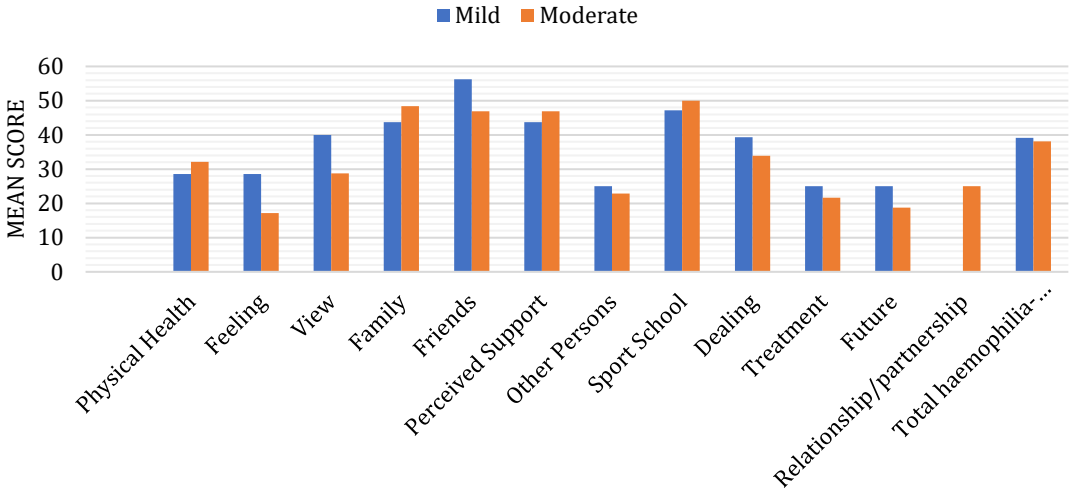

FIGURE 2: Haemo-QoL scores of children with hemophilia A based on the severity of hemophilia

DISCUSSION

The mean total score of Haemo-QoL was 38.57 (±9.52) with the lowest score being 16.7 and the highest being 54.47. El Hawary's research in Egypt (2019) with the same instrument, got a higher mean score of 45.1 (±14.7), with a minimum score of 10.4 to a maximum of 73.4 (11). Not much different from the El Hawary study, another study in Egypt on 60 children with hemophilia from two hemophilia treatment centers found HRQoL scores for the overall Haemo-QoL dimensions above 50 (16). This study obtained a lower mean score, which means it is better when compared to the two studies. A study in the Philippines on 51 pediatric hemophilia patients with the Philippine version of the Haemo-QoL questionnaire obtained a mean total score of 28.39 (±4.76), these results reflect a good quality of life (17).

This study showed that the youngest age group experienced the highest disturbances in the family dimension (median 68.75), followed by sports school dimensions with a median Haemo-QoL score of 41.66. Children in the age group 8-12 years experienced the most disturbances in the dimensions of friends with a median value of 56.25 (43.75-75), followed by three dimensions with the same median, the dimensions of sports school with a median of 50 (43.75-53.12), family dimension with median 50 (40-55), and perceived support dimension with a median 50 (25-62), and dealing dimension with median value 46.42 (32.14-50).

Children in the third age group have similarities with the second age group, experiencing the highest disturbance in the friend dimension with a median of 53.12 (34.37-67.18) and sports school dimension with a median of 51.38 (47.22- 63.19), followed by the family dimension with a median value of 45.31 (31.25-62.5), and the perceived support dimension with a median of 43.75 (28.12-50).

This study is in line with other studies which stated that the youngest age group has a lower QoL on the family dimension, while children with older age groups have a lower QoL on the sports school and perceived support dimensions (8, 10). This can be explained as a result of parental overprotection in the youngest age group, which is listed in the family dimension questions. The age group was not found to be a factor influencing the QoL of children with hemophilia A with p=0.135. The result of this study is contradicting a study in Italy that assessed HRQoL with two generic QoL questionnaires, EuroQoL (EQ-5D) and Short Form-36 (SF), the second result was that the overall quality of life was negatively correlated with age (18).

This study reported that the degree of bleeding was not significantly related to the QoL of children with hemophilia A (p=0.330). Zhang's prospective cohort study in China (2019) on 42 children with hemophilia and parents with the CHO-KLAT instrument showed that the degree of bleeding was negatively correlated with HRQoL.

Children and parents experience decreased HRQoL due to limitations in daily activities, including social and emotional functioning. Faced with the unexpected occurrence of bleeding in their child, the family showed greater concern, as a consequence, it affected the quality of life of the whole family. However, as the child grows, the family worries lessen because the child has gained knowledge about hemophilia and is better prepared for bleeding events (5).

The degree of bleeding score is one of the valuable research parameters that can be applied in clinical practice in assessing the bleeding degree of a patient on a scale of 0 to 4 for each type of bleeding. The degree of bleeding was associated with the presence of hematoma and minor wound bleeding in children with hemophilia A and B; whereas in adult hemophilia patients, the degree of bleeding is related to the incidence of epistaxis, bleeding after tooth extraction, and bleeding due to surgery. The mean score for the degree of bleeding in rare bleeding disorders (RBD) is a disease caused by a genetically inherited deficiency of coagulation factors, including hemophilia A, hemophilia B, hemophilia C, afibrinogenemia, and von Willebrand's disease; significantly higher than the control group (10.97 ±5.65; versus 5.35 ±4.48; $p<0.05$). These data reveal that bleeding grade scores can aid in the diagnosis of bleeding conditions in patients with hemophilia as well as other RBD, and can be considered as a risk predictor or classification of hemophilia grade. This is expected to help reduce the need for supporting examinations for specific coagulation tests, as well as assist in the decision-making and clinical management of patients (19).

This study showed that there was no significant correlation between the degree of hemophilia and the quality of life of children with hemophilia A ($p=0.608$). This is different from a study in Iraq (13) that the degree of hemophilia affects HRQoL in most dimensions. Another study reported that individuals with severe hemophilia generally recorded lower HRQoL levels when compared to individuals with mild or moderate hemophilia, this is associated with high morbidity in individuals with severe hemophilia, especially in the group that did not receive prophylactic therapy. Children with moderate or severe hemophilia have more frequent bleeding, experience arthropathy, joint pain, or more severe limitations of motion, these significantly adversely affect the patient's physical function and quality of life (20). One of the possible differences in results between the existing studies and this study was due to the absence of subjects with severe hemophilia. The median of Haemo-QoL total score based on the degree of hemophilia obtained scores that were not much different in the two groups of the degree of hemophilia, namely 39.13 (30.68-47.79) in the degree of mild hemophilia and 38.1 (31.24-44.51) in the degree of moderate hemophilia. This result from statistical calculations found no significant difference ($p=0.605$).

The next thing that affects the difference in the quality of life is related to the presence of home treatment. Only about half of the children in Turkey were treated at home, while in Europe, 79.2% of children and adolescents were treated at home with 12.6% having a central venous catheter, whereas in Turkey there were no children with a central venous catheter (21). The difference in total Haemo-QoL scores occurs in almost all dimensions, it shows that psychosocial factors including coping mechanisms, social support, and cultural differences between countries also play a role in influencing the QoL of hemophiliacs.

Based on the age at diagnosis, hemophiliacs classified as severe hemophilia experienced important events in the form of diagnosis, first joint bleeding, and first therapy generally in the age period 0-3 years; patients who are classified as moderate grade hemophilia experience a series of these events in the age period of 2-7 years; while people with a mild degree of hemophilia experience it at a greater age, namely when entering elementary school age, around the age of 5-14 years. Although it is easy to distinguish between severe and mild hemophilia, moderate and mild hemophilia are difficult to distinguish. In moderate hemophilia, the sufferer is heterogeneous; age at diagnosis and therapy is almost the same as for mild hemophilia (22). When collecting research participants, age at first bleeding, age at first joint bleeding, and age at diagnosis is not necessarily obtained at the same age. In this study, there was no significant relationship between age at diagnosis ($p=0.516$) and age at the start of therapy ($p=0.864$) with the QoL of children with hemophilia A.

The difference in age at the time of the first bleeding and the age at diagnosis is partly due to the lack of parental education about hemophilia itself, which some parents say that hemophilia is a rare disease, this is shown by the difference in age and type of first bleeding with age and type of bleeding at diagnosis in the majority of patients. Some parents are more aware and aware of their child's hemophilia disease because they immediately take their child for a consultation to the hospital, some because they already have a son who was previously diagnosed with hemophilia, so that the age at diagnosis becomes younger, without considering the degree of hemophilia they have; on the other hand, most parents consider bruising or blue on the skin to be normal because it will go away on its own, so some research subjects have experienced life-threatening bleeding at a young age as a type of bleeding when diagnosed; apart from unexpected events such as trauma that eventually brought the child to the hospital and finally had his blood clotting factor levels checked.

A total of 6 participants (28.6%) experienced life-threatening bleeding episodes in the form of intracranial bleeding and some underwent surgery to bleeding in large quantities and require blood transfusions. Two of the six subjects who experienced life-threatening bleeding had comorbidities, namely epilepsy, one patient had been drug-free for four years, one patient was still on medication, routinely checked into the Outpatient Department of the Children's Neurology Division, Dr. Soetomo General Hospital. In a multicenter study in six Western European countries and a study in Korea, the most common comorbidity reported was hepatitis C infection. Developmental delay was found in four patients and one patient with neuromuscular disease; none of the patients had malignancy (6, 8).

A study in Turkey describes the field situation in the country regarding hemophilia treatment centers. In Turkey there is no hemophilia treatment center, most patients go to the Hematology Unit in university hospitals and several government hospitals with a higher proportion of hematological malignancies than hemophilia and a limited number of hematologists. Some patients in the country still have a long way to go to see a hematologist. Another obstacle is that patients do not have health insurance for a certain period. These things are treatment barriers that cause the age at diagnosis to be quite late, especially in adult hemophilia patients, namely 8.5 ± 10.4 years, and only 32.3% are diagnosed before the age of 24 months (21).

The QoL of patients is not only influenced by clinical characteristics of the disease and therapy, but also by differences in individual characteristics such as coping mechanisms, self-perception, psychosocial, living conditions, and differences in the socioeconomic status background which can explain differences in HRQoL between different countries (10). Several studies report that children with hemophilia have difficulty managing their emotional well-being, including symptoms of depression, anxiety, and low self-perception (23). This has not been studied in this study. Several other factors that affect the quality of life of children with hemophilia that have not been studied in this study include the presence of inhibitors and the type of factor replacement therapy. Inhibitors (neutralizing alloantibodies) are one of the complications that affect the morbidity and quality of life of hemophiliacs caused by multifactor, including genetic and non-genetic factors. Genetic testing and inhibitors are not routinely carried out because it requires high-cost (24).

The next factor is the different types of replacement factor therapy as in existing studies, prophylactic therapy as a factor that affects the quality of life of children with hemophilia. Recurrent joint bleeding can be prevented by giving prophylactic therapy. Children with severe hemophilia with good joint conditions and who received prophylactic therapy could carry out activities like normal children (25). Prophylactic therapy is associated with higher costs of treatment, but it reduces the overall cost of care in children with hemophilia by reducing a significant amount of bleeding episodes, including joint bleeding, pain, joint damage, and disability, compared to patients receiving no prophylactic therapy (8, 20). Indonesia especially Surabaya, has not used prophylactic therapy routinely because of the limited resources.

This is the first study in Indonesia to examine the quality of life of children with hemophilia A using a validated hemophilia-specific quality of life questionnaire, so it is hoped that the use of the Haemo-QoL questionnaire can be carried out routinely to evaluate the QoL of children with hemophilia widely, especially in Tertiary Hospital, Surabaya, Indonesia.

This study has some limitations. First, the parent's report questionnaire was not conducted because it had not been translated and validated into Bahasa Indonesia. Second, the number of participants is too few because of the ongoing COVID-19 pandemic. Third, some of the questions in the questionnaire are difficult to comprehend for the children, potentially causing bias. Further research can be carried out with guidance from the research team who understands the questionnaire and can explain it to participants in a simple way. Finally, the sample size for each age group is not the same so it may not reflect the factual difference in the quality of life among the age groups; the children in the age group of 4-7 years old are struggling to comprehend the questionnaire and the answers are often influenced by the parents, so one could argue that the result is somewhat subjective to the parents. Other confounding factors in the form of differences in medication adherence of each patient, as well as differences in the patient's condition when filling out the questionnaire, were not the same, especially whether the patient had just experienced bleeding or recent injection therapy.

CONCLUSION

We discovered that there is no significant correlation between the clinical factors studied and the QoL of children with hemophilia A. Appropriate and prompt treatment plays a major role in the quality of life because the treatment of this disease does not depend on the severity of the children's clinical factors. The youngest age group experienced the highest disturbance in the family dimension, followed by the sports school dimensions, the second and third age groups experienced disturbances in the friend's dimension, followed by the sports school dimension. In regards to increasing the QoL of the family dimension, parents and relatives must contribute and support their children.

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