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Health-Related Quality of Life Assessment in Iranian Hemophilia Patients (Single Center); A Cross-Sectional Study

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Abstract

Objectives: Hemophilia affects the patients' life in many aspects. The major concerns are restriction on physical activities, life-threatening bleeding, arthropathy, etc., and worsening mental issues like anxiety. This study aimed to evaluate the health-related quality of life in hemophilia patients.

Methods: In this cross-sectional study, 147 patients with hemophilia had been referred to special patients' clinic at Kermanshah province (IRAN) for comprehensive medical care services. The patients who met the criteria of this study were selected using counting sampling method and were assessed with the quality of life in hemophilia patients' questionnaire (A36 Hemofilia-QoL® questionnaire).

Results: Out of 147 patients with hemophilia, 139 were male and 8 were female. The mean age of the subjects was 25.85 years ± 15.54 years. The results demonstrate that the total score of 65 patients (44.2%) had poor quality, 60 patients (40.8%) had moderate quality and 22 patients (15.0%) had good quality of life. Although there was no significant correlation between hemophilia A & B with health-related quality of life, there was a good connection between age, gender, level of education, and the severity of disease with health-related quality of life.

Conclusion: According to the low quality of life in relation to health in hemophilia patients, different interventions should be administrated to increase health-related quality of life in these patients.

Keywords: Hemophilia A;, Hemophilia B; Psychosocial factors; Health-related quality of life; Narcotics; Hematology; Physical activities

Abbreviations: HRQOL: Health-Related Quality of Life; ABR: Annual Bleeding Rate; ALT: Alanine Aminotransferase; EU: European Union

Introduction

Over the past two decades, quality of life has been one of the most important issues in clinical research and effective aspects of patient care [1]. Health-Related Quality of Life (HRQOL) has become an important indicator of health and has been considered as one of the most important factors in many clinical trials. Health-related circumstances focus on factors that play a major role in the person's well-being like welfare and performance [2].

Hemophilia is a bleeding disorder and characterized by coagulation factor deficiency mostly factor VIII (hemophilia A), and IX (hemophilia B) deficiency. These two diseases are similar in inheritance and clinically undetectable [3].

The world hemophilia federation estimates that about 400,000 people suffer from hemophilia all around the world [4]. According to the statistics presented by the Iran Hemophilia

Association, 6,500 of 12,000 patients suffer from hereditary disorders are hemophiliac.

The joint damage by frequent hemarthrosis and chronic pain reduce the patients' daily performance and mobility in hemophilia patients. This disease affects all the aspects of the patients and their families' life. Depending on the nature of the disease, recurrent bleeding occurs spontaneously or by the slightest trauma can damage the patients' psychiatric and physical health. In the past, the safety of blood products especially coagulation factors which can seriously expose the patient and their family to a variety of viral diseases or other issues that hemophiliac patients encounter is the expenses of treatment [5-8].

Nowadays, the advances in the treatment of hemophiliac patients and the deduction in their physical complications have contributed to improving their quality of life. An important method for evaluating the health of hemophilia patients is to assess their HRQOL, which is dependent on physical, psychological, social, behavioral, and functional factors that are described either by the patient or their families. Not only, assessment of the HRQOL can be influenced by the disease severity and its treatment, but also it can affect the patients' personality, life conditions, and socioeconomic status [9].

Evaluating the HRQOL can help us to assess the benefits of new therapies from the patients' perspective. Furthermore, it can assist to evaluate the quality of care for hemophilia patients by dividing them into groups sorted by age, sex, type, and severity of hemophilia, and also the impact of their education on their quality of life to improve standard local and international care [10].

In addition, the evaluation of pharmaceutical economy is an essential part of the assessment of HRQOL. Many human and financial resources are being spent on the treatment of hemophilia disease, and it directly affects the evaluation of patients' HRQOL. The design of the treatment methods for patients should be based on the analysis of clinical cost indicators and their impact on HRQOL assessment. Assessing HRQOL is one of the most important tools that can balance cost and profitability [11].

The patients' perception of their health not only aids in assessing the degree of profitability but also promotes correction and improvement of the overall quality of hemophilia care system and structures. In addition, the assessment of HRQOL compares health systems with hemophilia care centers across countries to encourage governments and communities to align with the world health service [12].

The aim of this study was to evaluate the HRQOL in hemophilia patients.

Material and Methods

Study design

The present research was a cross-sectional study performed to evaluate the HRQOL in hemophilia patients. The studied population included all patients with hemophilia who had been referred to the special patients' clinic of Kermanshah province (IRAN) from March 2018 to August 2019 and were eligible for inclusion in the study using the counting sampling method. The population size was 147 patients with hemophilia (139 males and 8 females (symptomatic carriers)) and 91 people had severity of diseases which were selected based on the inclusion and exclusion criteria.

Human rights were respected in accordance with the Helsinki Declaration 1975, as revised in 1983. The ethical committee of the Iran University of Medical Sciences (Ethical code; IR.KUMS.REC.1394.412) approved the study. The informed consent was taken from parents and first relatives.

Inclusion criteria

All patients were over 5 years old with hemophilia A and B with an Annual Bleeding Rate (ABR) ≥ 2 on at least one-year standard half-life FVIII prophylaxis

Exclusion criteria

Patients who have had a history of Factor VIII inhibitors, patients who have other hemostatic disorders, or patients participating in interventional studies.

Statistical analysis

The collected data was entered in SPSS18 software by a statistical expert and it was analyzed by relevant analytical methods.

Levan test, independent t-test, ANOVA, U-Mann-Whitney, and Kruskal-Wallis tests were used for data analysis.

Health-Related Quality of Life Questionnaire (HRQOL) in Hemophilia patients

This questionnaire (A36 Hemofilia-QoL® questionnaire) was developed in 2005 by Arranz [13] to assess HRQOL in hemophilia patients. The Quality of Life section has 9 parts with 36 questions. H 1 depicts the inquiry categories asked in the mentioned questionnaire (Table 1).

Section #	Inquires
1	8 questions related to physical health
2	4 questions are related to daily activities

3	3 questions are related to joint injury
4	2 questions are related to pain
5	2 questions are related to treatment satisfaction
6	4 questions are related to treatment difficulties
7	5 questions are related to emotional related function
8	3 questions are related to mental health
9	5 questions related to communication and social activity

Table 1: Health-Related Quality of Life Questionnaire (HRQoL) for the hemophilia patients. Different categories were asked to fully understand their quality of life and their concerns.

Its overall reliability is determined by Cronbach's alpha coefficient of 0.95 and 0.88, 0.88, 0.79, 0.78, 0.66, 0.58, 0.74, 0.74 and 0.85 respectively. Nine aspects of quality of life have been reported. The scores of each variable such as physical health, daily activities, joint injury, pain, and mental health are obtained by summing up the ranks of 0 to 4. The scores of the variables of treatment satisfaction, treatment difficulties, and emotional-related function are obtained by inverting the rank of the questions (0=4, 1=3, 2=2, 3=1, and 4=1) and then summarizing them. The overall score of the quality of life variable is also obtained by summing up the scores of the nine variables above. The minimum possible value for this score is zero and the maximum value is 144. Among these, a score of less than 25.0% is considered as low-quality level, between 25.0% to 50.0% as average quality level, between 50.0% to 75.0% as good quality level, and more than 75.0% as excellent quality level. To determine the distribution of age, sex, education, and also the type of hemophilia, disease severity, descriptive statistics were used in frequency and statistical analysis.

Results

Out of 147 patients with hemophilia, 139 (94.6%) were male and 8 (5.4%) were female. The majority of the subjects were in the age range of 21 years-30 years 51 (34.7%) and 39 (26.5%) had high school education. In terms of the type of hemophilia, 115 patients (78.2%) had hemophilia type A, 24 Patients (16.3%) had hemophilia B, and 8 patients (5.4) were symptomatic carriers and most of them 90 patients (61.2%) were severely ill which had low quality of life compared to people who had a mild or moderate form of the disease.

The results showed that HRQOL levels in the study sample were 65 patients (44.2%) with poor HRQOL, 60 patients (40.8%) with moderate, and 22 patients (15.0%) with good HRQOL (Table 2) (Figure 1).

Variable	**Levels**	**Frequency (%)**	
Sex	Male	139 (94.6)	
	Female	8 (5.4)	
Age(year)	10-May	23 (25.6)	
	20-Nov	31 (21.1)	
	21-30	51 (34.7)	
	31-40	24 (16.3)	
	41-50	5 (3.4)	
	51-60	5 (3.4)	
	>60	8 (5.4)	
Education	Academic	37 (25.2)	
	High school	39 (26.5)	
	Middle school	11 (7.5)	
	Elementary	40 (27.2)	
	Illiterate	20 (13.6)	

Type of hemophilia	A	115 (78.2)	
	B	24 (16.3)	
	Symptomatic carrier A	8 (5.4)	
Severity of disease	5-50%(Mild)	27 (18.4)	
	1-5%(Moderate)	30 (20.4)	
	Less than 1%(Severe)	90 (61.2)	
Health-related quality of life levels	Poor	65 (44.2)	
	Average	60 (40.8)	
	Good	22 (15)	

Table 2: Demographic characteristics of the studied patients.

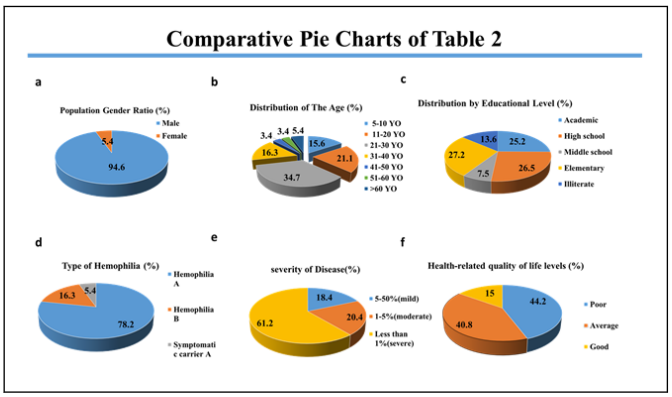

Figure 1: Comparative pie charts of table 2. Pie charts as a circular statistical graphic chart, demonstrate the numerical proportion clearly. a) The population gender ratio. As it is obvious the male patient is very frequently. b) Distribution of the age. The results show the most crowded period is 21-30 YO (YO stands for years old). c) The distribution of the education level in the referenced patients. As it is obvious, the more educated people have highest proportion. Authors believe that the high percentage in more academic people is due to their care about the health and disease symptoms. Illiterate people are the lowest income population; hence, their low income does not allow them to refer to the health centers or other health screening stations. d) Type of hemophilia proportion. The results illustrate that hemophilia type A is significantly dominant type in the studied population. e) Severity of disease chart. The pie chart shows that the bold severity level in the studied population is the severe cases (less than 1.0%). f) HRQL levels in references population. It shows that most of the hemophilia patients have poor quality of life and they demand further care and support to have a better quality of life.

The results showed that most people with poor HRQOL were in the age range of 21 years-30 years (11 people (21.6%)), most people with average quality of life were in the age range of 31 years-40 years (14 people (58.3%)) and Most people with good quality of life were in the age range of 11 years-20 years (11 people (35.0%)). The results showed that there was a significant difference between age groups and HRQOL levels (P<0.01).

In males, 55 (39.6%) of them had poor level, 63 (45.3%) had moderate level and 21 (15.1%) had good level of HRQOL, and in females, 4 patients (50.0%) had moderate and 4 (50.0%) had good levels of HRQOL. The results showed that there was a significant difference between gender and HRQOL levels (P<0.05). As the severity of factor FVIII deficiency is less in females (symptomatic carriers) the disease is milder in them and they have a better quality of life than males, and the usage of factor FVIII in Iranian males is about 1.56 IU per capita which is higher than the global per capita mean [14].

In terms of education level, most people with poor HRQOL had primary education (19 people), most people with moderate quality of life had academic education (20 people) and most people with good quality of life had high school education (8 people). The results showed that there was a significant difference between education level and HRQOL levels (P <0.05).

In people with hemophilia type A, 29 (23.6%) patients had poor quality of life, 65 (52.8%) had moderate and 29 (23.6) had good quality of life, and in people with hemophilia type B, 6 (0.25%) had poor quality of life, 15 (62.8%) had moderate and 3 (12.5) had good quality of life. The results showed that there was no difference between two types of hemophilia (A, B) and HRQOL levels (P>0.05).

In people with severe disease 25 patients (27.8%) had poor quality of life, 47 people (52.2%) were average and 18 people (20.0%) had good HRQOL. The results showed that there was a significant difference between disease severity and HRQOL levels (P <0.05) (Table 3) (Figure 2).

Variable	Levels	Health-related quality of life levels (%)			Mean and standard deviation	Significance level
		Poor	Average	Good		
Age (year)	10-May	6 (26.1)	13 (56.5)	4 (17.4)	35.17 ± 20.78	0.004

	20-Nov	8 (25.8)	12 (38.8)	11 (35.5)	43.19 ± 27.05	
	21-30	11 (21.6)	13 (60.8)	9 (17.6)	42.68 ± 27.88	
	31-40	6 (25)	14 (58.3)	4 (16.7)	47.58 ± 25.61	
	41-50	0 (0)	0 (0)	5 (100)	52.60 ± 29.11	
	51-60	3 (60)	1 (20)	1 (20)	35.80 ± 32.67	
	>60	1 (12.5)	4 (50)	3 (37.5)	65.87 ± 27.62	
Sex	Male	55 (39.6)	63 (45.3)	21 (15.1)	42.58 ± 26.18	0.02
	Female	0 (0)	4 (50)	4 (50)	64.62 ± 31.28	
Education	Academic	11 (29.7)	20 (54.1)	6 (16.2)	45.72 ± 26.73	0.04
	High school	13 (33.3)	18 (46.2)	8 (20.5)	53.02 ± 26.78	
	Middle school	5 (45.5)	5 (45.5)	1 (9.1)	38.18 ± 26.53	
	Elementary	19 (47.5)	16 (40)	5 (12.5)	40.17 ± 26.30	
	Illiterate	9 (45)	8 (40)	3 (15)	33.00 ± 24.42	
Hemophilia type	A	29 (25.2)	62 (53.9)	24 (20.8)	42.90 ± 24.21	0.39
	B	6 (25)	15 (62.5)	3 (12.5)	48.08 ± 31.27	
	Symptomatic carrier A	0 (0)	3 (37.5)	5 (62.5)	35.40 ± 27.67	
Severity of disease	5%-50% (Mild)	2 (7.4)	17 (63)	8 (29.6)	81.25 ± 16.47	0.01
	1%-5% (Moderate)	8 (26.7)	16 (53.3)	6 (20)	43.96 ± 23.76	
	Less than 1% (Severe)	25 (27.8)	47 (52.2)	18 (20)	32.47 ± 19.05	

Table 3: HRQL levels based on demographic, medical, and clinical records in hemophilia patients.

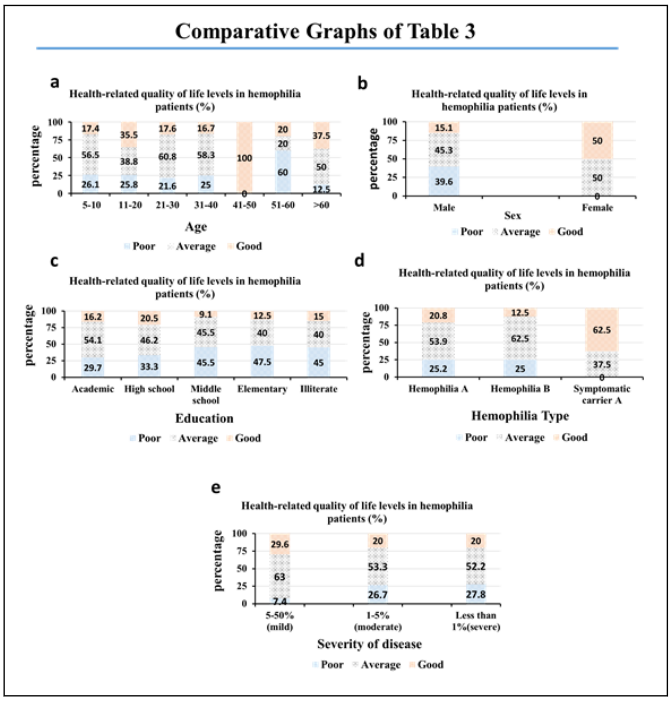

Figure 2: Comparative bar charts of table 3. Health-related quality of life levels versus a) age, b) sex, c) education, d) hemophilia type, e) severity of disease. Authors believe that the good quality of life for the patients of 41-50 YO in graph a, is due to the lack of data which means few reference patients in that range.

Discussion

In this study, a specific HRQOL assessment questionnaire was used in patients with hemophilia. According to the results of the study, 65 patients (44.2%) had poor quality of life, 60 patients (40.8%) had moderate quality and 22 patients (15.0%) had good quality of life.

Mahlangu and colleagues [15], performed their study on 152 participants who were divided into three separate groups. Group A received 1.5 mg/kg of Emicizumab, group B received 3 mg/kg of emicizumab and group C had no prophylaxis. In group c which had no prophylaxis, their ABR was 68.0% lower than the two groups which received emicizumab. The results of the study demonstrated that emicizumab therapy led to a significantly lower ABR than previous factor VIII prophylaxis.

The only Hemophilia A gene therapy was studied by Biomarin [16], on 15 patients. They used AAV5-FVIII-B-domain, with identical primary sequences as current factor products. In the low dose and mid-dose cohort, they used 6 × 1012 vg/kg and 2 × 1013 vg/kg, respectively. Increasing in factor VIII levels was only seen in 1 patient, up to 2.0%. In the high-dose cohort of 6 ×

1013 vg/kg, factor VIII levels, surprisingly, ranged from 40.0% to 150.0% over 8-month period. The results declared that in patients who stopped prophylaxis, their ABR was reduced by 97.0% and their Alanine Aminotransferase (ALT) enzyme increased in 10 out of 15 patients and no immune response to factor VIII was reported.

In the other study conducted by Schramm [17], 1400 patients (84.3% were suffering from hemophilia A and 15.7% with hemophilia B) were evaluated and enrolled by 42 centers between 2004 and 2006. About 70.0% of patients had severe factor deficiency. Patients were divided into 3 regions based on clotting factor per capita which was more than 5 IU in region 1, 2 to 5 IU in region 2, and less than 2 IU in region 3. In region 3, prophylactic therapy was conducted in 31.3% of children and 8.9% adults with severe hemophilia in comparison to region 1 which consisted of 93.7% children and 54.1% adults. This study revealed that regions with low factor consumption were the most prominent risk factor for joint disease. 20 European Union (EU) member states reported that the median use of factor VIII was 5.4 IU per capita with a mean of 4.94 IU per capita. Also, the data collected from the 12 non-EU countries demonstrated that the median factor VIII use was 1.50 IU per capita with a mean of 1.83 IU per capita.

The data gathered by Dorgalaleh [15], depicted that 5369 patients suffer from hemophilia A and hemophilia B in Iran which 4438 of them have hemophilia A. Genes of approximately one-fifth of the hemophilia A patients were analyzed and their defects were detected. The patients mostly exhibited clinical complications such as post-dental extraction bleeding, epistaxis, hemarthrosis, and ecchymosis. Bleeding management for hemophilia A patients was performed by replacement therapy with concentrates of factor VIII and factor IX or cryoprecipitate and in hemophilia B patients fresh frozen plasma. In hemophilia A patients mean per capita is for factor VIII is 1.56 IU. On the other hand, the mean per capita for factor IX is lower than the global mean and is 0.24 IU, yet is highest among eastern Mediterranean countries. The results conducted that in Iran 223 hemophilia A and 6 hemophilia B patients developed inhibitors and are substantially treated by recombinant factor VII and concentrate of activated prothrombin-complex.

In this study, the results showed that there is a significant difference in HRQOL in males and females, which females have a mild factor deficiency (symptomatic carrier) and have better HRQOL compare to males. Also, the results showed that there was a difference between the scores of HRQOL in the educational groups. Tukey test showed that the two illiterate and high school educated groups had a significant difference and people with high school education had higher scores of HRQOL.

The present study's limitations were only included patients with hemophilia in Kermanshah province (IRAN), therefore, generalizing the findings to patients in other geographical areas should be done more cautiously. Also, incomplete control over bothersome variables such as personality, physical and psychological factors as well as social, economic, and cultural variables of patients was another limitation. Outcomes pertaining to HRQOL in hemophilia patients can be used in developing comprehensive care for these patients and to improve and enhance their HRQOL.

Conclusion

The findings of this study indicated a low HRQOL in hemophilia patients and also showed that there is a connection between age, gender, and level of education, and severity of disease with HRQOL. It is suggested that to improve HRQOL in hemophilia patients, considerations should be made around providing educational and psychosocial support so that they can have a more effective adaptation to their disease. As mentioned above, HRQOL increased in developed countries due to the use of cutting-edge treatment methods such as gene therapy, long-acting factor replacement, and also some drugs like emicizumab, whereas in Iran, patients do not have any access to these facilities; so their HRQOL is lower as a consequence.

Declarations

Ethics approval and consent to participate

Human rights were respected in accordance with the Helsinki Declaration 1975, as revised in 1983. The ethical committee of the Iran University of Medical Sciences (Ethical code; IR.KUMS.REC.1394.412) approved the study. The informed consent was taken from parents and first relatives.

Consent for publication

All authors gave their consent for submission of this manuscript in this journal.

Availability of data and materials

The data that support the finding of this study are available from the corresponding author on request.

Disclosure

The authors declare no potential conflicts of interest related to this study.

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Authors' contributions

Mohammad Faranoush: Main conceptual idea and correspond

Mohammad Reza Golpayegani: Developed the theory and performed the computations

Mohammad Reza Foroughi-Gilvaee: Developed the theory and performed the computations, Manuscript preparation

Mohammad Reza Tohidi: Critical revision of article

Pooya Faranoush: Data analysis, Manuscript preparation

Fariba Kakery: Data gathering

Negin Sadighnia: Data gathering

Afsoon Zandi: Data interpretation

Ashkan Zandi: Final approval version to publish

S Mohamad Sadegh Mousavi-Kiasary: Final approval version to publish

Zahra Safaei: Data interpretation

All authors discussed the results and commented on the manuscript.

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