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The impact of inhibitors on the quality of life in patients with hemophilia

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Abstract

Objective: To investigate the association of health-related quality of life in hemophilia patients with inhibitor and clinical and demographic characteristics.

Methods: In this multi-center cross-sectional study, 41 male patients with hemophilia A were investigated from May to October 2021. All patients were registered at the Hemophilia Clinic affiliated with Shiraz and Zahedan Universities of Medical Sciences in Iran. Health-related quality of life of the patients was evaluated by the Short Form-36 questionnaire.

Results: The patients' mean ± SD of age was 36.9 ± 13.2 (range: 18–76) years. Eleven patients (26.8%) were inhibitor positive. In univariate analysis, physical function, mental health dimension, and total Short Form-36 scores were significantly lower in the inhibitor-positive patients ($p < 0.001$, $p = 0.045$, and $p = 0.035$, respectively). Moreover, patients with severe disease showed significantly lower scores in physical function ($p < 0.001$), physical health dimension ($p = 0.018$), and total Short Form-36 ($p = 0.031$) than those with mild and moderate hemophilia. Also, blood-borne infections showed a significant association with lower score in physical health dimension ($p = 0.038$). In addition, annual bleeding rate showed significant negative correlations with physical health dimension ($r_s = -0.609$, $p < 0.001$), mental health dimension ($r = -0.317$, $p = 0.044$), and total Short Form-36 ($r = -0.455$, $p = 0.003$) scores. In multiple linear regression analysis, disease severity revealed a significant negative relationship with scores in physical function ($p = 0.001$), role physical (RP) ($p = 0.015$), general health (GH) ($p = 0.006$), physical health dimension ($p = 0.006$), and marginally in total Short Form-36 score ($p = 0.054$). Also, age of the patients showed a significant negative association with physical function and GH scores ($p < 0.001$ and $p = 0.015$, respectively).

Conclusion: Disease severity and age were shown as independent factors affecting health-related quality of life, but inhibitor alone was not an independent influencing factor. Reduced health-related quality of life was also observed in hemophilia patients with higher annual bleeding rate and blood-borne infections. Therefore, it is necessary to pay more attention to these subgroups. Further studies with larger sample size are needed for more accurate results.

Keywords

hemophilia, inhibitor, quality of life, SF-36 questionnaire

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Introduction

Hemophilia is an X-linked congenital bleeding disorder caused by a deficiency of coagulation factor VIII (FVIII) (in hemophilia A) or factor IX (in hemophilia B), with a frequency of 1 in 10,000 births which often affects males. Hemophilia usually presents with easy bruising in early childhood, spontaneous bleeding into joints, muscles, and soft tissues, or excessive bleeding after trauma or surgery.[1] Hemophilia A accounts for 80%–85% of all hemophilia patients. The disease severity is classified into three subtypes: severe (<1%), moderate (between 1% and 5%), and mild (up to 40%).[2]

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The basic treatment of hemophilia is a coagulation factor replacement therapy.[3] Replacement therapy has been developing in the last decades from whole blood cell and free fresh plasma transfusion with poor outcome to use the recombinant factors with excellent efficacy. Although some different challenges such as high risk of transmission of hepatitis (hepatitis B virus (HBV) and hepatitis C virus (HCV)) and HIV during transfusion appeared, morbidity and mortality of the patients decreased and their life expectancy increased.[4] The most important challenging issue in factor replacement therapy is developing inhibitory alloantibodies that compromise the mainstay of treatment and make replacement therapy fail in 25%–30% of severe hemophilia cases and causes pain and disability in hemophilia patients.[5] It leads to higher mortality, morbidity, and impairment in their quality of life (QoL).[6]

The emergence of different types of therapy such as factor eight inhibitor bypass activity (FEIBA), recombinant activated FVIIa, and activated prothrombin complex concentrates was efficacious to some extent in patients with inhibitor.[7] Furthermore, emicizumab prophylaxis showed promising results in reducing bleeding symptoms in hemophilia A with inhibitors in recent years.[8] Also, the optimal therapeutic strategy to eradicate inhibitors is immune tolerance induction, defined as repeated administration of FVIII concentrate.[9] However, due to high treatment costs, hemophilia patients with inhibitors are still far from achieving standard care and management, which leads to increased physical and emotional burden and reduced QoL.[10,11]

Health-related quality of life (HRQoL), as a social measurement, has found its way into clinical studies since 1958; the World Health Organization (WHO) recognized QoL as an important component of health, in defining health as "not merely the absence of disease or infirmity, but a state of complete physical, mental and social wellbeing." Then, WHO defined HRQoL as "individuals perceptions of their position in the context of culture and value systems in which they live, and in relation to their goals, expectations, standards and concerns."[12]

It should be considered that disease and its treatments are not the only measures that affect HRQoL; it is a multidimensional outcome which is also influenced by personality characteristics such as the way one deals with her/him problems, socioeconomic status, and access to care and by the physical, mental, emotional, social, and behavioral state of the patient.[12,13]

The assessment of chronic diseases such as hemophilia through HRQoL has been an important and pervasive criterion in medical studies in the last two decades.[12] Hemophilia patients have enough reasons to experience lower QoL in comparison with normal population.[7] They face different problems like recurrent joint and muscle bleeding leading to arthropathy and musculoskeletal dysfunction that can affect their physical activities. Moreover, they might be complicated by some life-threatening bleeding such as intracranial hemorrhage.[13,14] Thus, assessment of HRQoL in hemophilia patients with a valid questionnaire along with treatment plan should be considered as their essential care goal and it can influence policy decisions.[15,16]

Several HRQoL studies have been evaluated in hemophiliacs in the past decades, showing the cost–benefit role of focusing more on the correct and timely management of hemophiliacs.[17,18] Disease severity is one of the important determinants of reduced QoL in patients with hemophilia.[19] On the other hand, hemophiliacs with inhibitors have higher rate of joint damage and disabilities, more difficult management, and long-term extraordinarily high costs.[20,21] Therefore, they could be at a higher risk of poorer QoL compared to non-inhibitor hemophilia patients. However, because inhibitor development is a rare condition, few studies have evaluated this issue with controversial results.[5,22] Bastani et al. compared the HRQoL in six severe hemophilia patients with inhibitor and 52 severe hemophilia patients without it in Iran. They reported significant lower scores in physical components in patients with inhibitor,[22] while Gringeri et al. reported comparable scores in severe Italian hemophilia patients with and without inhibitor, indicating that allocation of high amounts of resources for appropriate management of hemophilia patients with inhibitor provides a satisfactory QoL in these patients.[5] On the other hand, Iranian hemophilia patients face more difficulties due to sanction, shortage of factors, and poor access to specific and expensive medication which can undoubtedly decrease their QoL.[23] Therefore, this study was designed to compare the HRQoL in a group of Iranian patients with hemophilia A with and without inhibitor using the 36 item Short Form (SF-36) questionnaire. Also, we evaluated the relationship of demographic and clinical characteristics with HRQoL in these patients.

Methods

This cross-sectional study was carried out in the Hematology Research centers affiliated with Shiraz and Zahedan Universities of Medical Sciences in Southern and Southeastern Iran between May and October 2021. The study was approved by the Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.MED.REC.1399.422).

The inclusion criteria were male patients with hemophilia A registered at the Comprehensive Hemophilia Treatment Centers, 18 years old or older, and the clotting FVIII level less than 25%. Exclusion criteria were patients with psychiatric disorders or taking any kind of psychiatric medicines and patients who were not willing to participate in the study. All hemophilia patients with inhibitors ($n = 11$) referring to hemophilia centers affiliated to Shiraz or Zahedan University of Medical Sciences were included in the study during the 6-month study period. For each patient with inhibitor, three patients without inhibitor were randomly

selected as controls based on inclusion and exclusion criteria. Three patients were excluded due to incomplete information. Finally, 41 patients (11 with inhibitor and 30 without it) were enrolled.

The participants were asked to fill out the Persian version of SF-36 questionnaire[24] (Supplemental Materials 1 and 2) in an interview time of 45–60 min after obtaining written informed consent. Demographic and socioeconomic data (age, main occupation, sex, height, and weight) were obtained. Furthermore, clinical data and disease characteristics were gathered from their medical records consisting of age at diagnosis, type and severity of hemophilia, presence of inhibitor, number of bleeding episodes in the last 2 years, and blood-borne infections including HBV, HCV, and HIV.

SF-36 is a reliable and valid questionnaire used as a measure of health status in the medical outcome studies. It contains 36 questions that assess eight health concepts: (1) limitations in physical activities because of health problems; (2) limitations in social activities because of physical or emotional problems; (3) limitations in usual role activities because of physical health (PH) problems; (4) bodily pain; (5) general mental health (MH) (psychological distress and well-being); (6) limitations in usual role activities because of emotional problems; (7) vitality (energy and fatigue); and (8) general health perceptions.[25,26]

The items were scored ranging from 0 to 100 with the higher scores representing better health for each domain as well as two summarized dimensions: PH and MH, and total SF-36 score. Acceptable internal consistency (Cronbach's alpha coefficients from 0.77 to 0.90) and construct validities (discriminant and convergent validities above 0.40 ranging from 0.58 to 0.95) have been reported in translated Persian version of SF-36 questionnaire.[24] Also, it was validated previously in patients with bleeding disorders and thalassemia.[27,28]

Statistical analysis

Data analysis was done using IBM SPSS version 23. (IBM Corp., Armonk, NY, USA) Kolmogorov–Smirnov test was used to check the normality of data. Descriptive data were presented as mean, standard deviation (SD), median, interquartile range (IQR), and percentage. Comparison of qualitative variable among different groups was done using chi-square test. Quantitative data were compared by Student's *t*-test or Mann–Whitney test between the two groups and by analysis of variance or Kruskal–Wallis test among three or more groups of patients. Correlation between quantitative variables was measured using Pearson or Spearman Correlation test as appropriate. Multiple linear regression test was conducted to determine the independent factors affecting HRQoL scores of hemophilia patients. In this model, age, disease severity, and inhibitor were entered as independent variables and HRQoL scores as dependent variables. *p* Value less than 0.05 was considered statistically significant.

Table 1. Demographic and clinical characteristics of the patients with hemophilia.

Variables	Value
Age (year), mean ± SD	36.9 ± 13.2
Age at diagnosis (month), median (IQR)	8 (1–20)
BMI, mean ± SD	23.92 ± 6.77
Underweight <18.5 *N* (%)	9 (22)
Normal (18.5 to <25) *N* (%)	13 (31.7)
Overweight (25 to <30) *N* (%)	14 (34.1)
Obese >30 *N* (%)	5 (12.2)
Employment status	
Employed or student/Unemployed or retired	27/14
Disease severity, *N* (%)	
Mild	11 (26.8)
Moderate	9 (22)
Severe	21 (51.2)
Inhibitor (Yes), *N* (%)	11 (26.8)
Blood borne infection (Yes), *N* (%)	
HBV	4 (9.8)
HCV	9 (22.0)
HIV	4 (9.8)
Annual bleeding rate, median (IQR)	20 (2–55)

HIV: human immunodeficiency virus; BMI: body mass index.

Table 2. HRQoL score in patients with hemophilia.

Parameters	Min–Max	Mean	Standard deviation
Physical function	0–100	45.12	35.75
Role physical	0–100	26.21	36.63
Body pain	0–100	43.00	27.30
General health	0–97	53.80	24.72
Vitality	5–100	55.97	23.05
Social functioning	0–100	56.60	28.36
Role emotional	0–100	54.41	41.39
Mental health	4–100	59.31	22.53
Physical health dimension	11–90	44.75	22.39
Mental health dimension	10–90	56.07	21.20
Total SF-36	7–92	49.26	21.57

Results

The patients' mean ± SD of age was 36.9 ± 13.2 (range: 18–76) years. Their median (range) age at diagnosis was 8 (1–20) months. Demographic and clinical characteristics of the patients are summarized in Table 1. Approximately half of the patients (51.2%) had severe hemophilia A and 26.8% were inhibitor positive. All patients with inhibitor had severe type of the disease. Nine patients (22%) had at least one type of blood-borne infections.

Table 2 presents the HRQoL scores in the eight domains and overall, in PH and MH dimensions and the total SF-36. Comparison of these scores among different groups of patients based on the disease severity and the presence of

Table 3. Comparison of HRQoL scores in patients with hemophilia in different groups of disease severity.

Parameters	Mild, $n=11$	Moderate, $n=9$	Severe, $n=21$	p Value
Physical function, mean ± SD	65.45 ± 38.17	63.88 ± 30.28	26.42 ± 26.60	0.001*
Role physical, median (IQR)	50.0 (00–100)	.00 (00–87.5)	.00 (00–25)	0.061
Body pain, mean ± SD	56.63 ± 27.24	38.88 ± 27.73	37.61 ± 25.92	0.153
General health, mean ± SD	65.81 ± 19.63	57.22 ± 20.60	46.04 ± 26.68	0.086
Vitality, mean ± SD	57.72 ± 21.13	59.44 ± 23.90	53.57 ± 24.45	0.789
Social functioning, median (IQR)	63 (38.00–75)	75 (56.5–81.5)	50 (31.5–75)	0.259
Role emotional, median (IQR)	100 (00–100)	100 (33–100)	33 (00–83.5)	0.275
MH, mean ± SD	60.72 ± 21.74	63.11 ± 21.97	56.95 ± 23.93	0.776
PH dimension, median (IQR)	57 (37–77)	43 (31–72.5)	30 (22.5–49)	0.018*
MH dimension, mean ± SD	61.72 ± 22.17	62.55 ± 20.40	50.33 ± 20.39	0.209
Total SF-36, mean ± SD	59.45 ± 23.28	56.55 ± 22.12	40.80 ± 17.54	0.031*

*Statistically significant.

Table 4. Comparison of HRQoL scores in hemophilia patients with and without inhibitor.

Parameters	Inhibitor negative, $n=30$	Inhibitor positive, $n=11$	p Value
Physical function, mean ± SD	54.5 ± 36.15	19.54 ± 18.36	<0.001*
Role physical, median (IQR)	0 (0–56.25)	0 (0–25)	0.761
Body pain, mean ± SD	44.5 ± 27.46	38.90 ± 27.73	0.568
General health, mean ± SD	55.83 ± 24.70	48.27 ± 25.06	0.392
Vitality, mean ± SD	58.83 ± 21.28	48.17 ± 26.85	0.194
Social functioning, median (IQR)	63 (50–75)	50 (13–63)	0.139
Role emotional, median (IQR)	83.50 (33–100)	33 (0–67)	0.057
MH, mean ± SD	62.80 ± 20.23	49.81 ± 26.61	0.103
PH dimension, median (IQR)	45.50 (30.75–66.50)	27 (21–58)	0.057
MH dimension, mean ± SD	60.06 ± 19.68	45.18 ± 22.30	0.045*
Total SF-36, mean ± SD	53.53 ± 20.55	37.63 ± 20.80	0.035*

*Statistically significant.

inhibitor are shown in Tables 3 and 4, respectively. Patients with severe hemophilia showed significantly lower scores in PF ($p<0.001$), PH dimension ($p=0.018$), and total SF-36 ($p=0.031$) than those with mild and moderate hemophilia. Moreover, PF, MH dimension, and total SF-36 scores were significantly lower in the inhibitor-positive compared to the inhibitor-negative groups ($p<0.001$, $p=0.045$, and $p=0.035$, respectively).

Table 5 shows the results of evaluating the relationship between some demographic and clinical characteristics of the patients with PH and MH dimensions and total SF-36 scores. Patients who were employed or student had significantly higher mean or median scores in the PH and MH dimensions compared to the unemployed and retired patients ($p=0.045$ and $p=0.049$, respectively). It should be mentioned that the mean age of the employed and unemployed patients was comparable (34 ± 11 versus 42 ± 15, $p=0.058$). Also, patients who were complicated by blood-borne infections showed a significantly lower median score in PH dimension than those without blood-borne infection ($p=0.038$). In addition, annual bleeding rate showed a significant negative correlation with PH dimension ($r_s=-0.609$, $p<0.001$), MH dimension ($r=-0.317$, $p=0.044$), and total SF-36 ($r=-0.455$, $p=0.003$) scores.

Table 6 summarizes the results of conducting the multiple linear regression analysis considering age, disease severity, and inhibitor as independent variables and HRQoL scores as dependent variables. As shown in this table, the presence of inhibitor alone is not an independent influencing factor on HRQoL in different domains or total score in hemophilia patients. However, disease severity and age were shown to be the independent influential factors on HRQoL of the patients. Based on the results of this model, severe type of hemophilia had a negative significant relationship with scores in PF ($p=0.001$), RP ($p=0.015$), GH ($p=0.006$), PH dimension ($p=0.006$), and marginally in total SF-36 score ($p=0.054$). Also, the patients' age showed a significant negative association with PF and GH scores ($p<0.001$ and $p=0.015$, respectively).

Discussion

Considering the lifelong chronic problems that hemophilia patients face, especially in developing countries, in this

Table 5. Correlation between demographic and clinical characteristics with MH and PH dimensions and total SF-36 scores in hemophilia patients.

Parameters	PH dimension	MH dimension	Total SF-36
Age (year) correlation coefficient	−0.082	−0.023	−0.01
p Value	0.609	0.884	0.951
Age of diagnosis (month) correlation coefficient**	0.161	0.219	0.194
p Value	0.314	0.169	0.225
BMI correlation coefficient	0.089	−0.123	−0.04
p Value	0.582	0.443	0.802
Employment status			
Employed or student	48 (31–66)	60.75 ± 19.05	53.55 ± 18.82
Unemployed or retired	26 (21–58)	47.07 ± 22.92	41.00 ± 24.72
p Value	0.045*	0.049*	0.077
Blood borne infection (Yes)			
Yes	25 (22–47.5)	52.45 ± 19.55	41.65 ± 18.93
No	45.5 (31–61)	57.10 ± 21.85	51.40 ± 22.05
p Value	0.038*	0.568	0.236
Annual bleeding rate correlation coefficient**	−0.609	−0.317	−0.455
p Value	<0.001*	0.044*	0.003*

*Statistically significant.
**r_s.
BMI: body mass index.

study, we examined HRQoL and possible related factors in a group of Iranian hemophilia patients. Also, we hypothesized that inhibitor-complicated hemophiliacs may have a worse health score due to higher rate of disease-related disabilities and more difficult and expensive management. Based on our results, disease severity and aging were identified as independent factors influencing the HRQoL scores. However, the presence of inhibitor alone was not determined as an independent significant factor affecting HRQoL in these patients.

QoL in Iranian hemophilia patients has been evaluated using different questionnaires such as SF-36 and specific HRQoL of hemophilia (Hem-A-QoL) in several studies in the last 10 years.[29–31] In this study, we used SF-36 questionnaire. Based on the results of this study, in univariate analysis, inhibitor-positive hemophilia patients showed a significantly lower score in PF, MH dimension, and total SF-36 scores compared to the none-inhibitor group as previously presented at International Society on Thrombosis and Hemostasis Congress 2022 Congress.[32] Similarly, a significant lower score in physical component of health perception was previously reported in six Iranian severe hemophilia patients with inhibitor (age range: 11–32 years) compared to non-inhibitor patients.[22] It should be taken into account that the number of hemophilia patients studied with inhibitors in both studies was small. However, in our study, this relationship was not confirmed by the linear regression model considering disease severity, age, and inhibitor as independent variables. It seems that inhibitor alone does not affect QoL in our hemophilia patients and the observed significant difference in univariate analysis is majorly related to disease severity. Nevertheless, since inhibitor development in hemophilia is a rare condition, larger multicenter studies are needed for better evaluation and more accurate results. A large multicenter cohort study in 2003 evaluated QoL in 52 hemophilia patients with inhibitor from 11 hemophilia centers throughout Italy. They reported comparable scores of HRQoL in severe hemophilia patients with inhibitors compared to severe hemophilia patients without inhibitor. It is noteworthy that in this study, the physical QoL of hemophilia patients with inhibitors, especially in physical components, was similar to these values in diabetic patients under dialysis, but their MH QoL was similar to the general population. They concluded that allocating high amount of financial resources for proper management of inhibitor-positive patients contributed to a satisfactory QoL.[5] Comparison of the results of our study with those of Gringeri et al.'s study revealed that in most components of the assessed HRQoL, the scores were lower in Iranian compared to Italian hemophilia patients with inhibitor, especially in PF dimension (19.54 ± 18.36 in Iranian versus 59.1 ± 25.5 in Italian patients) and MH dimension (49.81 ± 26.61 in Iranian versus 70.0 ± 20.8 Italian patients).[5] Also, lower scores in different aspects of HRQoL were observed in mild Iranian hemophilia patients compared to Canadian mild hemophilia patients.[33] These differences can be interpreted by not only differences in social determinants of health among different countries, but also by the difference in facilities available for the proper management of hemophilia patients such as prophylactic treatment in developed and developing countries. Moreover, Holstein et al. compared some aspects of HRQoL SF-36 between Scandinavian countries and low-income countries like Iran. They claimed that the majority of hemophilia patients (86%) in Scandinavian countries, despite perceived limitations in sport activities, felt similar chances to

Table 6. Multiple linear regression of factors associated with HRQoL of patients with hemophilia.

Parameters	Unstandardized coefficient B	Standard error	*p* Value	95% CI for B	
				Minimum	Maximum
Physical function					
Constant	123.460	16.732	0.000	89.526	157.395
Age	−1.324	0.337	0.000*	−2.007	−0.640
Moderate hemophilia	−8.238	11.844	0.491	−32.259	15.783
Severe hemophilia	−45.246	11.924	0.001*	−69.428	−21.064
Inhibitor	−16.910	11.412	0.147	−40.054	6.235
Role physical					
Constant	46.669	22.308	0.044	1.427	91.912
Age	−0.028	0.449	0.951	−0.939	0.884
Moderate hemophilia	−9.483	15.791	0.552	−41.509	22.542
Severe hemophilia	−40.743	15.897	0.015*	−72.984	−8.503
Inhibitor	13.130	15.215	0.394	−17.726	43.987
Body pain					
Constant	54.801	17.560	0.004	19.188	90.413
Age	0.042	0.354	0.906	−0.676	0.759
Moderate hemophilia	−17.536	12.430	0.167	−42.745	7.673
Severe hemophilia	−20.000	12.513	0.119	−45.378	5.378
Inhibitor	2.787	11.976	0.817	−21.502	27.076
General health					
Constant	98.164	14.393	0.000	68.974	127.353
Age	−0.738	0.290	0.015*	−1.326	−0.150
Moderate hemophilia	−12.317	10.188	0.235	−32.979	8.346
Severe hemophilia	−29.909	10.256	0.006*	−50.709	−9.108
Inhibitor	3.304	9.816	0.738	−16.604	23.212
Vitality					
Constant	60.931	15.234	0.000	30.036	91.826
Age	−0.073	0.307	0.813	−0.695	0.549
Moderate hemophilia	1.349	10.783	0.901	−20.521	23.218
Severe hemophilia	1.011	10.856	0.926	−21.005	23.027
Inhibitor	−11.454	10.390	0.278	−32.525	9.618
Social functioning					
Constant	58.786	18.439	0.003	21.390	96.182
Age	0.038	0.371	0.919	−0.715	0.791
Moderate hemophilia	6.626	13.052	0.615	−19.845	33.098
Severe hemophilia	−4.958	13.140	0.708	−31.607	21.691
Inhibitor	−9.302	12.576	0.464	−34.807	16.203
Role emotional					
Constant	84.436	26.184	0.003	31.332	137.541
Age	−0.475	0.527	0.374	−1.544	0.595
Moderate hemophilia	0.527	18.535	0.977	−37.064	38.117
Severe hemophilia	−11.982	18.659	0.525	−49.825	25.861
Inhibitor	−24.208	17.859	0.184	−60.426	12.011
Mental health					
Constant	59.632	14.689	0.000	29.843	89.422
Age	0.025	0.296	0.933	−0.575	0.625
Moderate hemophilia	2.510	10.398	0.811	−18.577	23.597
Severe hemophilia	4.333	10.467	0.681	−16.896	25.562
Inhibitor	−14.935	10.018	0.145	−35.253	5.382
PH dimension					
Constant	76.988	12.935	0.000	50.755	103.222
Age	−0.429	0.261	0.108	−0.958	0.099
Moderate hemophilia	−9.345	9.156	0.314	−27.915	9.224
Severe hemophilia	−27.053	9.218	0.006*	−45.747	−8.359

(Continued)

Table 6. (Continued)

Parameters	Unstandardized coefficient B	Standard error	*p* Value	95% CI for B	
				Minimum	Maximum
Inhibitor	−1.851	8.822	0.835	−19.742	16.041
MH dimension					
Constant	72.315	13.358	0.000	45.225	99.406
Age	−0.242	0.269	0.375	−0.787	0.304
Moderate hemophilia	−0.390	9.456	0.967	−19.566	18.787
Severe hemophilia	−8.245	9.519	0.392	−27.550	11.061
Inhibitor	−11.266	9.110	0.224	−29.743	7.211
Total SF-36					
Constant	73.150	12.954	0.000	46.878	99.421
Age	−0.313	0.261	0.239	−0.842	0.217
Moderate hemophilia	−4.474	9.170	0.629	−23.071	14.122
Severe hemophilia	−18.411	9.231	0.054*	−37.132	0.311
Inhibitor	−7.243	8.835	0.418	−25.161	10.675

In the multiple linear regression model, disease severity as a categorical variable was converted into dummy variable and the scores of moderate and severe hemophilia were compared to mild hemophilia. Also, the value of scores in the positive inhibitor group was compared with the negative inhibitor group.
*Statistically significant.

healthy people to choose a job unlike Iranian hemophilia patients. It underscores the negative impacts of hemophilia on different aspects of life in these patients. Also, starting prophylactic treatment, since young age in Scandinavian countries and the younger age of patients investigated (13–25 years), was reported as a responsible factor for this difference.[34]

Another important finding of this study was significant lower scores in PF, PH dimension, and total SF-36 in patients with severe hemophilia compared to mild and moderate hemophilia patients. Moreover, multiple linear regression model showed a negative association of disease severity with PF, RP, GH, and PH dimension and a borderline significant association with total SF-36 score. This issue highlights the impact of disease severity on HRQoL in hemophilia patients; as previously reported, poorer QoL was observed in severe hemophilia compared to mild and moderate hemophilia.[15,19]

Age at diagnosis is one of the characteristics that seems to be different in most of the reports. In our study, the median age of diagnosis was eight and IQR of (1–20) years that seems higher than the reported range for age at diagnosis in the most recent studies from different countries such as Brazil, United Kingdom, France, and Netherlands which is 1 or 2 years after birth.[15,19,35] As known, higher age at diagnosis leads to the higher rate of hemophilic arthropathy and related disabilities. Thus, lower age at diagnosis is very important to start prophylactic treatment as soon as possible in younger age of childhood and prevent disease-related complications.

The mean age of the patients in this study was 36.9 ± 13.2. The results of regression model showed a significant negative association of PF and GH scores with aging. The aging process itself can decrease the QoL in hemophilia patients as it happens in the general population.[36] Besides, older hemophilia patients face more disease-related complications due to the longer duration of disease, especially in developing countries with low financial support and limited required facilities.

Several studies have shown that obese individuals experience significant impairments in QoL that worsens with increasing degrees of obesity.[37] In hemophiliacs, obesity can also impair their QoL by further limiting exercise and daily activities. Based on our results, 34.1% of the participants were overweight and 12.2% were obese. However, no significant correlation was observed between the QoL of hemophilia patients and their body mass index, probably due to small number of patients.

The presence of blood-borne infection is another important risk factor in reducing the HRQoL of hemophilia patients. As in this study, a significantly higher median score of PH dimension was determined in patients without blood-borne infection compared to those affected by blood-borne infection. Similarly, Ferreira et al. showed that HRQol of hemophilia patients could be influenced by infectious diseases transmitted by blood products using a specific hemophilia HRQol questionnaire (Hem-a-QoL).[15] In contrast, Rambod et al. found no significant association between the presence of hepatitis and HRQol previously in Iranian hemophilia patients despite the higher rate of HCV infection compared to our results (37.9% versus 22%).[31]

Another important factor related to QoL in hemophilia patients that was evaluated in this study was annual bleeding rate. The median and IQR 20 (2–55) which was determined for annual bleeding rate in our adult hemophilia population is much higher than that reported by the world federation of hemophilia in 2018 data reports of world bleeding disorders registry 6 (2–16) overall and 6 (2–14) among severe

hemophilia patients.[38] This issue emphasizes paying more attention to close monitoring of hemophilia patients and the use of primary prophylaxis in patients with higher risk of bleeding.[39]

The employment status is one of the other factors that can affect QoL. There is a close relationship between education, employment, and QoL. Employment can affect the QoL not only through increasing life satisfaction and mental well-being of people, but also through increasing income.[40] Various disabilities in hemophilia patients result in a higher rate of unemployment in hemophiliacs than general population. Thus, the unemployment of young people with hemophilia compared to the general population is a major concern from a social point of view.[41] Based on the results of our study, significantly higher QoL scores in the PH and MH dimensions were obtained in employed patients and students compared to the unemployed and retired patients despite the comparable average age in both groups.

This study was limited due to the lack of a control group and the small number of hemophilia patients with inhibitor because inhibitor development is a rare complication. In addition, QoL may also depend on several factors (social determinants of health) that can vary between countries, making accurate comparisons between different countries difficult.

Conclusion

Disease severity and age were determined as independent factors influencing the HRQoL. Reduced HRQoL was also observed in hemophilia patients with higher annual bleeding rate, blood-borne infections, and in unemployed patients. It warrants further attention to these subgroups of patients. Precise attention should be considered in the prevention and management of bleeding symptoms in these patients. On the other hand, improving the social environment of these patients by providing educational facilities and creating a suitable job situation can improve the physical and MH of these patients. Based on the results of this study, the inhibitor alone had no significant impact on HRQoL in hemophilia patients. However, further studies with larger sample sizes are needed for better evaluation and more accurate results.

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Author contributions

S.H. designed the study, performed the data analysis, and edited the manuscript. M.J. edited the manuscript and collected the data. S.K. prepared the original draft and data collection. H.T. and N.J. collected the data. S.P. collected the data and edited the manuscript. M.K. had the concept of article and edited the manuscript.

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Ethics approval

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Informed consent

Written informed consent was obtained from all subjects before the study.

Trial registration

Not applicable.

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Supplemental material

Supplemental material for this article is available online.

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