Clinical and Applied Thrombosis/Hemostasis
2018, Vol. 24(5) 815-821

DOI: 10.1177/1076029617733041
journals.sagepub.com/home/cat
SAGE

Health-Related Quality of Life and Association With Arthropathy in Greek Patients with Hemophilia

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Abstract

Health-related quality of life (HRQoL) is increasingly implicated in contemporary hemophilia management. This study focuses on the assessment of HRQoL in Greek patients with hemophilia and the comparison with normative data from the general population, as well as on the extent arthropathy may affect the patients' HRQoL. One hundred and nine adult patients completed the Greek social functioning (SF-36) and Haem-A-QoL questionnaires. Arthropathy was assessed by both the World Federation of Hemophilia clinical score and Pettersson radiological score. The most impaired domains of Haem-A-QoL were sports/leisure (SL) and physical health (PH; mean scores 61.2 and 42.2, respectively). The patients experienced statistically significant lower mean scores in all SF-36 domains than the normative sample, especially in role physical (RPH), bodily pain (BP), and general health (GH) subscales. Among Haem-A-QoL subscales, SL and PH were found strongly associated with severity of arthropathy using both orthopedic scores ($P < .001$), and maintained the statistical significance after adjustment for age ($P < .05$). A poor orthopedic status was also negatively associated with certain SF-36 subscales. However, none of these correlations remained after adjustment with age. Compared to normative data from Greece, patients with hemophilia showed deterioration in all HRQoL subscales, with a more pronounced effect in RPH, BP, and GH subscales. Health-related quality of life was strongly influenced by arthropathy, mainly in the physical aspects of HRQoL. The use of the disease-specific Haem-A-QoL tool can capture additional associations between HRQoL and hemophilic arthropathy.

Keywords

arthropathy, health-related quality of life, hemophilia, orthopedic score, Haem-A-QoL

Introduction

Hemophilia is an X-linked recessive bleeding disorder, caused by deficiency or complete absence of coagulation factors VIII (FVIII) or IX (FIX), causing hemophilia A or B, respectively. It is estimated that approximately 400 000 patients with hemophilia are living worldwide. Today in Greece, about 1000 patients are diagnosed with hemophilia A or B, according to the levels of coagulation factor activity.[1-3] Hemophilia A is more common than hemophilia B, accounting for 80% to 85% of total hemophilia. The current standard treatment for hemophilia is intravenous replacement therapy with concentrates of coagulation factors, either in a preventive way (prophylaxis) or in case of a bleeding episode (on demand). Patients with hemophilia have recurrent bleeding episodes, either spontaneously or following trauma, that occur within joints, usually ankles, knees, or elbows. Recurrent bleeding into the same joint leads to hemophilic arthropathy, which represents the most common clinical manifestation of hemophilia, with significant effect on the patients' quality of life.[4-12]

In addition to clinical measurements, such as bleeding frequency and joint range of motion, evaluation of health-related quality of life (HRQoL) is increasingly used as a significant health outcome measure in hemophilia. Assessment of HRQoL

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in patients with hemophilia has been performed in several studies, using generic questionnaires, such as social functioning (SF-36) and EQ-5D,[13,14] or validated disease-specific instruments, such as Hemo-QoL-A, Hemophilia-QoL, Hemolatin-QoL, and Haem-A-QoL.[5,15-18] In a number of studies, it has been suggested that HRQoL is diminished in patients with hemophilia, when compared to healthy controls or to normative data from corresponding male populations.[8,10,14,19,20] Age, severity of disease, and coinfections are some of the significant factors with a negative relationship to perceived health that have been identified in the literature.[8,13,14,21,22] Haem-A-QoL has been used in 2 recent studies that measure quality of life among patients with hemophilia.[23,24]

The severity of arthropathy in patients with hemophilia is thought to play a major role in their HRQoL. A strong negative association between arthropathy and HRQoL has been documented in a number of previously published reports. The presence and severity of arthropathy, measured either clinically via the World Federation of Hemophilia (WFH) score or radiologically via the Pettersson score, was correlated mainly with the physical subscales of general questionnaires, such as SF-36.[8-11,21]

In Greece, there is only one report in which HRQoL was assessed in patients with hemophilia with a generic instrument.[25] Recently, a Greek version of the disease-specific questionnaire Haem-A-QoL was validated in a number of patients with hemophilia, and it was found to be reliable and valid.[26] The objectives of this study were (1) to assess the level of HRQoL in Greek patients with hemophilia with a disease-specific and a generic instrument and compare it with the norm data from the general population of Greek males and (2) to determine to what extent arthropathy may affect the patients' HRQoL.

Patients and Methods

Patients and Data Collection

The study was conducted in the National Reference Center for Congenital Bleeding Disorders in Laiko General Hospital of Athens, where 40% of patients of the country are followed. Data were collected between September 2011 and March 2012. The study sample consisted of 109 patients with hemophilia A or B of all severities, who visited the center during recruitment period and agreed to provide an informed consent. All patients included in the study completed both SF-36 and the Greek version of the Haem-A-QoL instruments, along with a short questionnaire regarding their sociodemographic characteristics. The patients' clinical data were obtained from their medical records. The hospital's review board granted ethical approval for this study. All procedures performed were in accordance with the ethical standards of the Helsinki Declaration of 1975, as revised in 2008.

HRQoL Instruments

Health-related quality of life was assessed using 2 questionnaires; (a) the generic instrument SF-36, a self-administered generic HRQoL questionnaire for adults,[27] consisting of 36 items pertaining to 8 dimensions of HRQoL (PF, physical functioning; RPH, role physical; BP, bodily pain; GH, general health; VT, vitality; SF, social functioning; RE, role emotional functioning; MH, mental health; PCS, physical summary component score; MCS, mental summary component score). The validated Greek version[28] of the generic SF-36 Health Survey was used as the "gold standard" for HRQoL assessment in this study. (b) the disease-specific instrument Haem-A-QoL, designed for adult patients with hemophilia, which consists of 46 items comprising 10 dimensions (PH, physical health; FL, feelings; VW, view; SL, sport and leisure time; WS, work and school; DL, dealing; TR, treatment; FU, future; FP, family planning; RP, relationships/partnership) and a scale representing total score.[18,29] Scoring ranges from 0 to 100, with 0 representing best and 100 the worst HRQoL. The Greek version of Haem-A-QoL has been validated in a recent report.[26]

Assessment of Arthropathy

The severity of arthropathy was assessed in all patients in the 6 major joints—knees, elbows, and ankles—using the clinical score (WFH score), as described by the Orthopedic Advisory Council of the WFH.[6,30] The degree of arthropathy was graded between 0 and 12 for knees and ankles and from 0 to 10 for elbows. A score of zero corresponds to normal joints and a score of 68 indicates the worst level of arthropathy. The Pettersson score for joints was assessed on plain radiographs.[31] The 6 major joints were scored from 0 to 13 on the extent of radiological deterioration, with a maximum possible score of 78. All patients included had a joint score evaluation at least 12 months before the completion of the QoL questionnaires.

Data Analysis

Data are expressed as median with interquartile range, mean, and standard deviation or percentage as appropriate. Student *t* test for unpaired data was applied, when testing differences between groups. Associations between Haem-A-QoL and SF-36 scales and between WFH and Pettersson scores were evaluated with Pearson or Spearman correlations. Univariable but also multivariable regression models were fit to address the associations between different scales of quality of life and orthopedic status for possible confounders. Two-tailed *P* values $<.05$ were considered to indicate statistical significance. All analyses were performed using SPSS software, version 20.0 (SPSS Inc, Chicago, Illinois).

Results

Patient Characteristics

The sociodemographic and clinical characteristics of the study participants are shown in Table 1. The patients' age varied between 18 and 75 years, with a median age of 39 and mean age 39.7 ($\pm$12.9). The majority of the patients in our study sample had hemophilia A (77.1%) and 63.3% of the individuals

Table 1. Sociodemographic and Clinical Characteristics of the Sample.[a]

Variables	Value
Age (years)	
Mean (SD)	39.7 (12.9)
Median (IQR)	39 (28.5-47)
Hemophilia, n (%)	
A (Factor VIII deficiency)	84 (77.1)
B (Factor IX deficiency)	25 (22.9)
Severity, n (%)	
Severe	69 (63.3)
Moderate	16 (14.7)
Mild	24 (22.0)
Inhibitor, n (%)	
Yes	9 (8.3)
No	100 (91.7)
Prophylaxis, n (%)	
No	86 (78.9)
Constant	14 (12.8)
Interrupted	9 (8.3)
WFH score	
Mean (SD)	21.34 (20.0)
Median (IQR)	18.0 (3-35.5)
Pettersson score	
Mean (SD)	25.43 (23.7)
Median (IQR)	18.0 (0-46)

Abbreviations: IQR, interquartile range; n, number of patients; SD, standard deviation; WFH, World Federation of Hemophilia.
[a]N = 109.

had severe hemophilia. Only 9 (8.3%) patients had developed high titer inhibitors, but none of them have been treated with an Immune Tolerance Induction (ITI) protocol. All inhibitor patients were treated on demand with bypassing agents, and 4 of the 9 have currently a negative titer. Most of the patients received either treatment on demand (78.9%) or interrupted prophylaxis treatment (8.3%), and only 12.8% of the cohort was in constant prophylaxis treatment. The overall median Pettersson score was 18 (range: 0-78) and mean score of 25.43 ($\pm$23.7), with 29 patients (26.6%) having score of zero. World Federation of Hemophilia clinical score had a mean value of 21.34 ($\pm$20.0), with a median score of 18 (range: 0-68;Table 1).

Quality of Life Assessment

Mean scores of Haem-A-Qol subscales and the total score are shown in Table 2. The highest scores were observed in SL and PH (61.2 and 42.2, respectively), suggesting reduced quality of life in these dimensions. In contrast, the least impaired dimensions were DL, FP, and RP, with mean scores 25.6, 25.6, and 24.8, respectively. The instrument's reliability was assessed with Cronbach α coefficient for each subscale and for total score. As shown in Table 2, Cronbach α for the questionnaire overall was .94 and almost all subscales met the .70 internal consistency criterion. Only 1 dimension (DL) had lower internal consistency coefficient, but still borderline (.585).

Table 2. Mean Scores and Internal Consistency of Haem-A-QoL Scales.[a]

	Mean (SD)	Cronbach α
PH	42.25 (22.68)	.865
FL	35.09 (23.29)	.863
VW	40.46 (20.34)	.773
SL	61.19 (21.19)	.803
WS	30.96 (18.68)	.795
DL	25.61 (18.69)	.585
TR	30.85 (16.83)	.758
FU	38.81 (19.10)	.783
FP	25.63 (22.84)	.879
RP	24.85 (29.94)	.953
Total	33.21 (13.73)	.943

Abbreviations: DL, dealing; FL, feelings; FP, family planning; FU, future; n, sample size; PH, physical health; RP, relationship/partnership; SD, standard deviation; SL, sports/leisure; Total, total Haem-A-QoL score; TR, treatment; VW, view; WS, work/school. [a] N = 109.

Moreover, mean scores of all SF-36 subscales were assessed and compared with a reference male population from Greece. Normative data from a healthy age and gender-matched population, consisting of 469 male Greek individuals with similar age to our study population (mean age 45 years), were used to compare these results.[32] As anticipated, patients with hemophilia had lower mean scores, and differences were statistically significant in all SF-36 subscales ($P < .001$). RPH, BP, GH, and PCS had the most pronounced negative effect on patients' quality of life. Social functioning, RE, MH, and MCS were the least affected quality of life domains. Mean scores of the study group in RPH, BP, and GH subscales were decreased by >20 points compared to mean values of the reference population. The biggest difference (35 points) between the study and the reference group was observed in dimension RP, whereas the lowest difference (7.55 points) was observed in MH scale (data not shown).

HRQoL and Orthopedic Status

In an attempt to evaluate possible associations of patients' arthropathy with quality of life in our study sample, a correlation analysis between the clinical and radiological orthopedic scores and all Haem-A-QoL subscales was performed. Three dimensions, PH, SL, and WS, showed relatively strong correlations, both with WFH score and Pettersson score (r ranging from 0.216 to 0.380, $P < .005$), while VW, FP, and Total score correlated relatively strongly only with WFH score ($r = 0.192$, 0.205, and 0.201, respectively). Since it is generally accepted that both QoL and hemophilic arthropathy deteriorate with age,[13,14,33] a partial correlation between Haem-A-QoL subscales and both orthopedic scores was conducted, in which age was introduced as a confounder. In the age-adjusted analysis, the only subscales that maintained statistically significant strong correlations, both with WFH and with Pettersson scores, were PH and SL (Table 3).

Similarly, PF, SF, and PCS of SF-36 were inversely correlated with WFH orthopedic score ($r = –0.264$, –0.193,

Table 3. Correlations and Partial Correlations With Age as a Confounder of Haemo-A-QoL and SF-36 Subscales With WFH and Pettersson Score.[a]

		WFH		WFH (Controlling for Age)		Pettersson Score		Pettersson Score (Controlling for Age)	
		r	*P* Value	*r*	*P* Value	*r*	*P* Value	*r*	*P* Value
Haem-A-QoL	PH	**0.380**[b]	**.000**	**0.291**[b]	**.002**	**0.340**[b]	**.000**	**0.239**[b]	**.013**
	FL	0.051	.600			–0.036	.709		
	VW	**0.192**[b]	**.046**	0.103	.289	0.120	.214		
	SL	**0.305**[b]	**.001**	**0.218**[b]	**.024**	**0.282**[b]	**.003**	**0.186**[b]	**.050**
	WS	**0.216**[b]	**.024**	0.125	.196	**0.186**[b]	**.053**	0.087	.370
	DL	–0.068	.481			–0.034	.723		
	TP	–0.010	.917			–0.041	.672		
	FU	0.096	.321			–0.047	.626		
	FP	**0.205**[b]	**.033**	0.181	.620	0.120	.216		
	RP	0.034	.727			0.044	.649		
	Total	**0.201**[b]	**.036**	0.091	.347	0.142	.140		
SF-36	PF	**–0.264**[b]	**.006**	–0.17	.860	**–0.243**[b]	**.011**	–0.004	.966
	RPH	–0.029	.769			0.019	.844		
	BP	–0.049	.614			–0.031	.752		
	GH	–0.119	.216			–0.074	.443		
	VT	0.043	.658			0.105	.276		
	SF	**–0.193**[b]	**.045**	–0.138	.156	–0.143	.138		
	RE	0.122	.205			0.158	.101		
	MH	0.072	.458			0.128	.185		
	PCS	**–0.181**[b]	**.053**	0.048	.623	–0.161	.094		
	MCS	0.102	.289			0.164	.088		

Abbreviations: BP, bodily pain; DL, dealing; FL, feelings; FU, future; FP, family planning; GH, general health; MCS, mental summary component score; MH, mental health; PCS, physical summary component score; PF, physical functioning; PH, physical health; RE, role emotional; RP, relationship/partnership; RPH, role physical; SF, social functioning; SL, sports/leisure; Total, total Haem-A-QoL score; TR, treatment; VT, vitality; VW, view; WFH, World Federation of Hemophilia; WS, work/school.

[a]Numbers in boldface indicate statistically significant correlations.

[b]Correlation is significant at the .05 level.

and –0.181) and only PF exhibited a relative strong correlation ($r = –0.243$) with the Pettersson score. However, none of these statistically significant correlations remained after adjustment with age (Table 3).

The significance of the aforementioned relationships between orthopedic scores and Haem-A-QoL or SF-36 domains was confirmed with a regression analysis. In five dimensions (PH, SL, WS, FP, and Total Haem-A-QoL score), orthopedic status as measured by WFH score was identified as a statistically significant predictor of decreased HRQoL (Table 4). However, in the age-adjusted linear regression analysis, only PH and WS remained significant predictors of HRQoL deterioration. Age and WFH score together accounted for 21% of PH score variance and 14.4% of SL score variance (Table 4). Likewise, when Pettersson score was used as a measure of arthropathy, it was also recognized as a significant predictor of diminished HRQoL in 3 Haem-A-QoL domains (PH, SL, and WS). In the age-adjusted linear regression analysis, age and Pettersson score together accounted for 18.6% of PH and 13.3% of SL score variance, respectively, in a statistically significant manner (Table 4).

When SF-36 was used in a linear regression analysis, only WFH score was identified as statistically significant predictor of decreased HRQoL in just two dimensions (SF and PCS). However, in the age-adjusted linear regression analysis, none of them maintained their significance as predictors (Table 4).

Discussion

In this study, we assessed for the first time the HRQoL in Greek patients with hemophilia, using a disease-specific (Haem-A-QoL) and a generic instrument (SF-36), and the results were compared with normative data from corresponding male population of the country. The psychometric properties of the Greek version of Haem-A-QoL instrument were evaluated in a previous study, and the instrument was found to be reliable and with good construct validity.[26] The results of this study showed impaired HRQoL, especially in the domains that affect PH, expressing mainly the inability of patients to participate in different activities and sports. Similar to our results, SL in Haem-A-QoL was the most affected domain in 2 recent studies.[23,24] Physical health followed as the second affected domain in both our study and in the study by Ferreira et al, whereas FU was the second worst subscale in the study by Mercan et al. RP was among the least affected Haem-A-QoL scales in all 3 studies. Dealing was among the least impaired dimension in our study and in the study by Mercan

Table 4. Unadjusted and Adjusted for Age Linear Regression Analysis of Certain Haem-A-QoL and SF-36 Subscales With WFH and Pettersson Score.[a]

		WFH Score							
		Unadjusted Linear Regression Analysis				Adjusted for Age Linear Regression Analysis			
		B Coefficient	*P* Value	95% CI	Adjusted R^2	B Coefficient	*P* Value	95% CI	Adjusted R^2
Haem-A-QoL	PH	**0.431**	**.000**	**0.230, 0.631**	**.136**	**0.321**	**.002**	**0.118, 0.524**	**.210**
	SL	**0.323**	**.001**	**0.130, 0.516**	**.085**	**0.229**	**.024**	**0.031, 0.426**	**.144**
	WS	**0.201**	**.024**	**0.027, 0.376**	.038	0.117	.196	–0.061, 0.296	.099
	FP	**0.234**	**.033**	**0.020, 0.448**	.033	0.216	.062	–0.011, 0.444	.026
	Total	**0.138**	**.036**	**0.009, 0.266**	.031	0.061	.347	–0.068, 0.194	.129
		Pettersson score							
	PH	**0.325**	**.000**	**0.153, 0.497**	**.107**	**0.224**	**.013**	**0.049, 0.399**	**.186**
	SL	**0.252**	**.003**	**0.087, 0.416**	.071	**0.166**	**.054**	**–0.003, 0.335**	**.133**
	WS	0.146	.053	–0.002, 0.295	.026	0.419	.370	–0.083, 0.221	.091
		WFH score							
SF-36	PF	–0.210	.081	–0.446, 0.026	.019	–0.020	.860	–0244, 0.204	.210
	SF	**–0.233**	**.045**	**–0.460, –0.005**	.028	–0.172	.156	–0.410, 0.066	.041
	PCS	–0.090	.053	–0.184, 0.004	.024	–0.023	.623	–0.114, 0.068	.175
		Pettersson score							
	PF	–0.174	.087	–0.373, 0.026	.018	–0.004	.966	–0.194, 0.186	.210

Abbreviations: FP, family planning; PCS, physical summary component score; PF, physical functioning; PH, physical health; SF, social functioning; SL, sports/leisure; Total, total Haem-A-QoL score; WFH, World Federation of Hemophilia; WS, work/school; 95% CI, 95% confidence interval.
[a]Boldface values indicate significant associations.

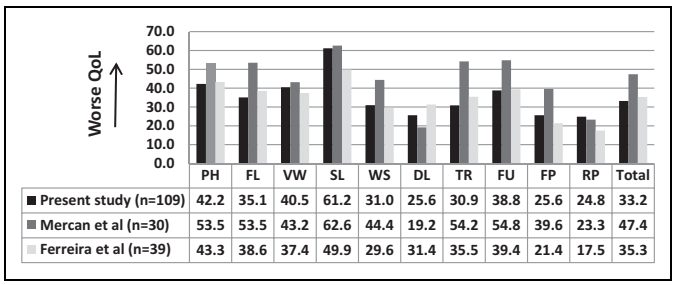

Figure 1. Comparison of Haem-A-QoL subscales mean scores between the present and recent studies using the same instrument. Mean values for each subscale are indicated. DL indicates dealing; FL, feelings; FP, family planning; FU, future; PH, physical health; RP, relationship/partnership; SL, sports/leisure; Total, total Haem-A-QoL score; TR, treatment; VW, view; WS, work/school.

et al, but not in the study by Ferreira et al.[23,24] These differences can be attributed to some extent to the different sizes of the study populations in the 3 studies (Figure 1).

The use of the generic QoL instrument suggests that the patients perceived a worse quality of life in all the parameters measured by SF-36 questionnaire. Several previous studies assessed HRQoL using SF-36 generic instrument and performed comparisons with the population norms. In all these studies, consistent with our results, patients with hemophilia had statistically significant reduced HRQoL in all physical-related dimensions of SF-36.[8,10,14,19,20] Although reduced scores in MH-related subscales of SF-36 compared to normative data have been observed in several studies, these differences were either small or not statistically significant. Contrary to this, we detected statistically significant differences in the RE, MH, and SF domains of SF-36 compared to healthy population, with the highest difference in RE and SF.[8,14,19,20,34] This difference might be ascribed in part to the fact that our patients exhibited elevated orthopedic scores and their subsequent orthopedic deformities might have affected their social function in general.

Several studies in the literature have addressed the issue of HRQoL with regard to patients' orthopedic status. In the majority of them, assessment of HRQoL was performed with the generic instrument SF-36 and evaluation of arthropathy was realized either with the radiological Pettersson score and/or with the clinical WFH score. A strong negative effect of arthropathy mainly on the physical aspects of quality of life has been documented in these reports,[8-11,21,35] which is in line with our results. In addition, Aznar et al reported a statistically significantly strong association of vitality to arthropathy.[8] This finding corresponds relatively well with our results of a moderately strong association between orthopedic status and SF. When the above associations were controlled for age, they were either alleviated or disappeared completely in some studies, indicating that the impact on PH is in essence moderated by age.[9-11] A most recent study by Fischer et al corroborates a statistically deterioration of PF due to arthropathy, mainly in patients with Pettersson scores >21.[36] In agreement with these observations,

the effect on PCS and SF disappeared when age was introduced in our partial correlation and regression analysis, with a marginal effect remaining only on PF.

It is of interest that almost no correlation between orthopedic scores and Haemo-A-QoL or SF-36 subscales was obtained when the analysis was conducted using the subgroup of patients on prophylaxis treatment (n = 14, mean age = 29.2 years; data not shown). Since patients on constant prophylaxis have initiated treatment at a very early age, they have not developed any arthropathies, and have consequently better quality of life. Previous analysis from the authors corroborate this, since they have shown that patients with on demand treatment showed statistically significant higher mean scores (worse quality of life) in Haem-A-QoL PH, WS, DL, and RP compared to patients with transient or constant prophylactic treatment.[26]

Recent reports have utilized Haem-A-QoL, a hemophilia-specific instrument for HRQoL assessment. In a Turkish study, only PH shows a statistically significant strong correlation with the level of arthropathy, without, however, any adjustment for the age factor.[24] Ferreira et al conclude in general that HRQoL in people with hemophilia is influenced by the presence of arthropathy, since the presence of target joints was strongly associated with the Haem-A-QoL total score.[37] Furthermore, patients with a highly impaired orthopedic status had significantly worse HRQoL, as measured by Haem-A-QoL$_{\text{Elderly}}$, compared to those with a less impaired orthopedic status, indicating the important role of the level of arthropathy to the perceived quality of life.[38] Consistent with the aforementioned reports, our results support the general observation of the significant effect of arthropathy on HRQoL of patients with hemophilia. Nevertheless, the current study also provides efficient evidence that the use of a disease-specific questionnaire such as Haem-A-QoL may unveil subtler changes in quality of life in relevance to arthropathy. World Federation of Hemophilia orthopedic score and Pettersson radiological score were strongly associated with 5 and 3 domains of Haem-A-QoL, respectively. Even after controlling for age, the negative influence of arthropathy was evident in PH and SL subdomains of QoL, both with WFH and with the Pettersson score, suggesting that a disease-specific QoL questionnaire can give more accurate and accordingly reliable results, compared to a generic instrument; thus, it should be adopted as an outcome measure in patients with hemophilia.

Conclusion

Overall, this study was one of the first to provide evidence on the HRQoL in patients with hemophilia in Greece, comparing it with normative data from a corresponding male population. People with hemophilia experience considerable diminished quality of life, as measured by the Haem-A-QoL disease-specific instrument, with a higher impact on PH and SL domains. Statistically significant differences were detected in all SF-36 subscales compared with gender-matched general population norms. The current study also provides important evidence that hemophilic arthropathy, measured by both the clinical and radiological orthopedic scores, is associated with reduced HRQoL, mainly on the physical well-being of the patients. The use of the disease-specific Haem-A-QoL seems to be able to recognize subtler changes in HRQoL in patients and is also able to pick up additional associations between HRQoL and hemophilic arthropathy, compared to the generic SF-36 instrument. Even though these associations are markedly moderated with age, the physical aspects of QoL are significantly impaired by the level of arthropathy itself, therefore should be taken into account in routine monitoring of these patients.

Authors' Note

Part of this work was selected for poster presentation in the 9th Annual Congress of the European Association of Hemophilia and Allied Disorders February 3-5, 2016, in Malmo and was published as abstract in Hemophilia 2016, Vol. 22 (Suppl. 2). AV, OK, and NK were involved in conception and design of the study. AV and AK collected data and questionnaires. AV performed statistical analysis and NK and DN helped with interpretation of results. AV and OK were involved in drafting the manuscript. OK and AK participated in critical review of the analyses and clinical input. AK, OK, and DN critically revised the manuscript for important intellectual content. All authors read and approved the final version of the manuscript.

Acknowledgments

The authors would like to express their appreciation to Dr S. von Mackensen and the Haemo-QoL group for granting them permission to use the Greek version of Haem-A-QoL instruments free of charge, for this noncommercial and nonsponsored study. The authors are also thankful to the patients who participated in this research.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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