

ORIGINAL ARTICLE

Health-related quality of life and productivity impact in haemophilia patients with inhibitors

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Summary. To measure health-related quality of life (HRQL), its determinants, and its association with patient and caregiver productivity among a sample of haemophilia patients with inhibitors in the United States (US). Data on demographical and clinical characteristics, treatment patterns, HRQL (SF-12v2), and productivity outcomes were reported for 53 patients. Mean SF-12v2 domain and mental (MCS) and physical (PCS) component summary scores were assessed and compared with US norms. Regression analyses explored the association of patient and treatment factors with HRQL and productivity. Patients' mean age was 20.7 years (SD = 18.8), 88.5% were type A, and 39.6% received on-demand therapy as their only mode of treatment. Mean PCS was significantly lower than the US norm (PCS, 39.9, $P < 0.01$) and mean MCS showed no significant difference (MCS, 49.9, $P = \text{ns}$). On-demand treatment ($B = -0.336$,

$P < 0.05$) and number of haemorrhages ($B = -0.366$, $P < 0.05$) were negatively associated with PCS; and PCS was associated with patients' missed work or school days [incidence rate ratio (IRR) = 0.93, $P < 0.001$] and perceived impact on daily activities (OR = 0.72, $P < 0.05$). Younger age (IRR = 0.91, $P < 0.01$), lower PCS (IRR = 0.94, $P < 0.01$), more haemorrhages (IRR = 1.05, $P < 0.05$), and surgery (IRR = 2.74, $P < 0.05$) were associated with fewer patients' productive days. Physical functioning among inhibitor patients in the US is compromised and is negatively associated with their daily activities and productivity. These data suggest a positive association of prophylactic and immunotolerance therapy with HRQL, specifically physical impairment.

Keywords: haemophilia, inhibitors, productivity, quality of life

Introduction

Health-related quality of life (HRQL) is increasingly recognized as an important outcome in the care of patients with haemophilia. During the course of the disease, haemophilia patients' HRQL may be compromised because of joint bleeds, chronic pain, and other clinical complications [1]. Variables which have been shown to be associated with reduced HRQL among haemophilia patients include: the severity of the clotting defect [1–5], bleeding frequency [6–8], viral infections [2,5,9] and ortho-

paedic problems [4,5]. As well, treatment may improve patient HRQL. In this regard, evidence suggests that HRQL may be better for haemophilia patients receiving prophylactic treatment compared with on-demand therapy [2,6,10,11].

A subset of haemophilia patients develop inhibitors that inactivate Factor VIII, which compromise the effectiveness of Factor VIII replacement therapy. These patients are often at a greater risk of bleeds, arthropathy, physical disability and mortality [12]. Several studies have noted the connection between inhibitor development and reduced HRQL in haemophilia patients. Gringeri *et al.* [13] evaluated the HRQL of Italian haemophilia patients with inhibitors and observed physical HRQL deficits as compared with the general population. In a subsequent assessment among Italian haemophilia patients with inhibitors, Scalone *et al.* [14] found orthopaedic status to be a significant determinant of HRQL.

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Inhibitor development can also affect the productivity of haemophilia patients and their caregivers (e.g., absenteeism from school or work). In particular, a study by Woolf concluded that school absenteeism was problematic for paediatric haemophilia patients, with an average of 18 school days missed in an academic year [15]. Others have suggested a strong positive relationship between the age of starting prophylaxis treatment and its duration to reduced absenteeism [16,17].

This study was designed to measure HRQL among haemophilia patients with inhibitors in the United States. Furthermore, the study explores clinical and treatment factors associated with HRQL and the relationship between HRQL and productivity, as measured by absenteeism.

Materials and methods

Study sample

Educational patient summits for haemophilia patients with inhibitors and their caregivers were held in 2006 (Anaheim, CA; Baltimore, MD; Chicago, IL; and Dallas, TX). Patients may have become aware of these summits from their clinicians, patient support associations, or the summit website. Upon approval by the Abt Associates Institutional Review Board, this study was initiated. Consent was obtained from 90 patients and caregivers in summit attendance to participate in future research. In 2007, these 90 consenting patients and caregivers were mailed survey questionnaires. Caregivers completed surveys for all patients under the age of 18 and for patients with physical limitations precluding their direct completion.

Data collection

The paper-pencil survey instrument included questions related to patient and caregiver demographics, patient clinical information, treatment, patient HRQL, and patient and caregiver absenteeism and productivity loss in school or work. The survey required approximately 20–25 min for respondents to complete.

Clinical and treatment information

A variety of questions were asked related to disease manifestation and treatment. For example, questions were asked about the number of haemorrhages the patient has experienced, and whether or not the patient has had any surgery, both within the previous 12 months. Patients were also asked to indicate their

current treatment mode across three types of therapies: (i) On-demand treatment (the patient uses treatment when he/she bleeds); (ii) In prevention treatment (the patient uses a product on a regular basis to prevent dangerous bleeds); and (iii) In immunotolerance therapy (the patient uses replacement therapy with the goal of desensitizing his/her immune system to the treatment).

HRQL assessment

Quality of life data were collected using the SF-12v2 survey instrument [18], a general, non-disease-specific 12-item instrument validated in multiple languages. The SF-12 measures eight domains of physical and mental quality of life: physical functioning, role physical, bodily pain (BP), general health, vitality, social functioning, role emotional and mental health. The first four domains comprise physical components of HRQL, while the other four comprise mental components. For each patient, scores were calculated for each domain and for the physical component score (PCS) and mental component score (MCS). A shorter version of the SF-36 [19], the SF-12 is commonly used to assess HRQL among patients with different diseases as well as among the general population, making it useful for comparison between different cohorts. Study results were compared with SF-12 US norms [18].

Patient and caregiver productivity assessment

The number of school or work days patients and caregivers missed in the past 12 months because of illness (or for caregivers, to fulfill their duties related to the illness), as well as the number of days perceived as lower in productivity were obtained. Patients were also asked to what degree they believed that their health limited their activities ('a lot', 'a little bit' and 'not at all').

Statistical methods

Descriptive analysis was conducted using proportions for categorical data, mean and/or median as central tendency parameters for continuous data, with standard deviation (SD), minimum (min), and maximum (max) values as dispersion parameters.

Ordinary least squares (OLS) regression analyses were performed to test the association between the SF-12v2 scales and demographical and clinical characteristics. For example, patient age, number of haemorrhages in the past 12 months, surgery in the past 12 months, and on-demand treatment were considered in the multiple regression analyses as potential determinants of HRQL. Regressions were

also conducted for each SF-12v2 scale, also accounting for factors such as surgery and on-demand, preventive or immunotolerance treatment.

Negative binomial regression analyses were conducted to test the incidence rate ratio (IRR) as a measure of increase (IRR > 1) or decrease (IRR < 1) in the number of missed and low-productive days attributable to the demographical and clinical characteristics. Logistic regressions were run to estimate the odds ratio (OR) as a measure of risk increase (OR > 1) or decrease (OR < 1) of perceived impact on daily activities.

In all analyses, confidence intervals (CI) of 95% and *P*-values <0.05 (two-tailed tests) were considered. All analyses, except the negative binomial regressions, were performed using SPSS, version 12.0.1 (SPSS Inc., Chicago, IL, USA). Negative binomial regressions were performed using STATA version 9/0 (StataCorp, College Station, TX, USA).

Results

Among the 90 surveys mailed to consenting patients and caregivers, 53 were returned (58.8% response rate). Certain analyses involved smaller sample sizes as a result of incomplete and/or missing data, and some statistical analyses involved sub-cohorts. These are highlighted accordingly.

Patient demographical and clinical characteristics

Patients' demographical and clinical characteristics are shown in Table 1. Among the patient sample, 58.8% were children under the age of 18 years. Significantly more children than adult patients were receiving haemophilia prophylaxis (62.1% and 28.6%, *P* < 0.05) and immunotolerance (46.7% and 10.0%, *P* < 0.01) and fewer children received only treatment on-demand (26.7% and 61.9%, *P* < 0.05). No other clinical characteristics were significantly different between adults and children.

Caregivers (70% being mothers of patients, 16.7% fathers of patients, and 13.3% other) completed 64.7% of the survey questionnaires on behalf of patients, including all children (100%) and three adults (14.3%). Among caregivers, 73.5% work, 8.8% attend school, 5.9% work and attend school, and 11.8% neither work nor attend school. Among the caregivers who work, 70.4% work full-time.

Patient HRQL

Patient mean scores on the SF-12 and their comparison with US norms [18] are shown in Table 2. No

Table 1. Sample demographical and clinical characteristics.

	All patients (<i>n</i> = 53), %
Gender	
Male	96.1
Female	3.9
Age, mean (SD)	20.7 (18.8)
Haemophilia type	
A	85.5
B	11.5
Student and employment status	
No work, school, or daycare	32.1
Only work	5.7
Only school or daycare	49.1
Both work and school	13.2
Family annual income (\$US)	
<\$20 000	18.9
\$20 000–\$49 000	20.8
\$50 000–\$74 000	28.3
\$75 000–\$100 000	5.7
>\$100 000	17.0
Would rather not respond	9.4
Health insurance status	
Medicaid	37.7
Medicare	17.0
Through employer	58.5
Self-pay/private	5.7
None	3.8
Treatment mode*	
On demand	77.4
Prevention (prophylaxis)	48.1
Immunotolerance	32.7
On demand only†	39.6
Patient surgery in last 12 months (yes)	32.7
No (0) haemorrhages (last 12 months)	14.0
# Haemorrhages (last 12 months)	
Mean (SD)	11.6 (12.2)
Median (min/max)	8.0 (0.0–50.0)

*Multiple treatment modes were reported.

†Patients reporting on-demand treatment with no use of preventive or immunotolerance therapies.

statistical difference was observed between SF-12v2 scores for children under 18 years of age and adult patients.

Factors associated with HRQL

Patients with more haemorrhages in the past 12 months (*P* < 0.05) and those who received treatment with on-demand therapy (*P* < 0.05) were associated with lower PCS levels. The number of haemorrhages was also negatively associated with physical function (*P* < 0.01). No other significant determinants, such as surgery and age, were observed for MCS, or any specific SF-12v2 domain. Patient age was associated with on-demand treatment (*B* = 0.422, *P* < 0.01, *n* = 51) with older

Table 2. SF-12v2 scores as compared with general US population norms.

Scale Scores	All patients				
	<i>n</i>	Min	Max	Mean	SD
Physical functioning (PF)	50	22.1	56.5	42.6**	13.5
Role physical (RP)	50	20.3	57.2	41.2**	11.6
Bodily pain (BP)	50	16.7	57.4	42.0**	12.7
General health (GH)	47	18.9	62.0	46.5*	11.6
Vitality (VT)	48	27.6	67.9	51.7	10.9
Social functioning (SF)	49	16.2	56.6	43.6**	12.7
Role emotional (RE)	50	11.3	56.1	46.0**	12.5
Mental health (MH)	48	21.9	64.5	49.9	10.4
Physical component summary (PCS)	45	12.9	57.8	39.9**	12.5
Mental component summary (MCS)	45	19.7	65.4	49.9	12.1

Comparison with US population norms [18].

* $P < 0.05$.

** $P < 0.01$.

patients having received more on-demand therapy than younger patients. No other inter-correlations were significant and the relationships between age and SF-12v2 scores were not significant. Age as a unique determinant of HRQL was not significant in any of the analyses. Full model findings include number of haemorrhages as a factor significantly associated with PCS ($B = -0.366$, $P < 0.05$), physical functioning (PF) ($B = -0.403$, $P < 0.01$), and BP ($B = -0.393$, $P < 0.01$). On-demand treatment, along with the number of haemorrhages, also predicted PCS ($B = -0.336$, $P < 0.05$) and BP ($B = -0.371$, $P < 0.05$). Surgery was not significantly related to any of the SF-12v2 scores. Full model regression analysis coefficients for each SF-12v2 scale are shown in Table 3.

Productivity and impact on daily activities

Table 4 shows all productivity and absenteeism results. No difference between adult and paediatric patients for productivity and absenteeism was observed. Patients reported the degree to which their health limited their daily activities as 'a lot', 26.4%; 'a little bit', 45.3%; and 'not at all', 28.3%. No significant difference was observed between adult and paediatric patients for the degree of health limitation.

Associations with productivity and impact on daily activity

Patient surgery was associated with more caregiver missed days (IRR = 3.70, CI = 1.33–10.34,

Table 3. Regression analyses predicting SF-12v2 scales.

Dependent variable	Independent variable	Regression coefficient (<i>B</i>)
Physical functioning (PF) ($n = 46$)	Haemorrhages	-0.403**
	Surgery	-0.075
	On-demand	-0.249
Role physical (RP) ($n = 46$)	Years	-0.139
	Haemorrhages	-0.282
	Surgery	-0.147
Bodily pain (BP) ($n = 46$)	On-demand	-0.193
	Years	-0.031
	Haemorrhages	-0.393**
General health (GH) ($n = 43$)	Surgery	-0.114
	On-demand	-0.371*
	Years	0.140
Vitality (VT) ($n = 44$)	Haemorrhages	0.006
	Surgery	-0.172
	On-demand	-0.314
Social functioning (SF) ($n = 45$)	Years	-0.094
	Haemorrhages	-0.169
	Surgery	-0.078
Role emotional (RE) ($n = 46$)	On-demand	0.013
	Years	-0.215
	Haemorrhages	-0.168
Mental health (MH) ($n = 44$)	Surgery	-0.212
	On-demand	-0.218
	Years	0.043
Physical component summary (PCS) ($n = 41$)	Haemorrhages	-0.110
	Surgery	-0.011
	On-demand	0.103
Mental component summary (MCS) ($n = 41$)	Years	-0.079
	Haemorrhages	-0.227
	Surgery	-0.045
Physical component summary (PCS) ($n = 41$)	On-demand	-0.105
	Years	-0.101
	Haemorrhages	-0.366*
Mental component summary (MCS) ($n = 41$)	Surgery	-0.141
	On-demand	-0.336*
	Years	-0.062
Physical component summary (PCS) ($n = 41$)	Haemorrhages	-0.024
	Surgery	-0.036
	On-demand	0.190
Mental component summary (MCS) ($n = 41$)	Years	-0.081

* $P < 0.05$.

** $P < 0.01$.

$P < 0.05$) and more caregiver low-productive days (IRR = 8.99, CI = 3.60–22.41, $P < 0.001$). Lower patient MCS was associated with more caregiver low-productive days (IRR = 0.96, CI = 0.93–0.99, $P < 0.01$) (see Fig. 1).

Lower patient PCS was associated with higher numbers of patients' missed days (IRR = 0.93, CI = 0.89–0.97, $P < 0.001$) and low-productive days (IRR = 0.94, CI = 0.89–0.98, $P < 0.01$). More haemorrhages (IRR = 1.05, CI = 1.00–1.11, $P < 0.05$), surgery (IRR = 2.74, CI = 1.06–7.12, $P < 0.05$), and younger age (IRR = 0.91, CI = 0.85–0.98,

Table 4. Patient and caregiver productivity.

	All patients, %		Caregivers	
	Mean (SD)	Median (min/max)	Mean (SD)	Median (min/max)
Productivity and absenteeism				
Low-productive days	20.2 (27.0)	(<i>n</i> = 35) 12.5 (0 to 135.0)	19.1 (27.8)	(<i>n</i> = 26) 10.0 (0–100.0)
Missed days (work/school)	25.7 (47.0)	(<i>n</i> = 38) 17.5 (0–292.0)	19.1 (24.9)	(<i>n</i> = 29) 10.0 (0–100.0)

Fig. 1. Negative binomial regression model predicting caregiver productivity outcomes with PCS and MCS (continuous), prophylaxis treatment, haemorrhages (continuous), surgery in the past 12 months, and age (continuous). Missed days, *n* = 21, Low-product days, *n* = 18. Gray boxes denote significant relationships/Z-scores ($P < .05$).

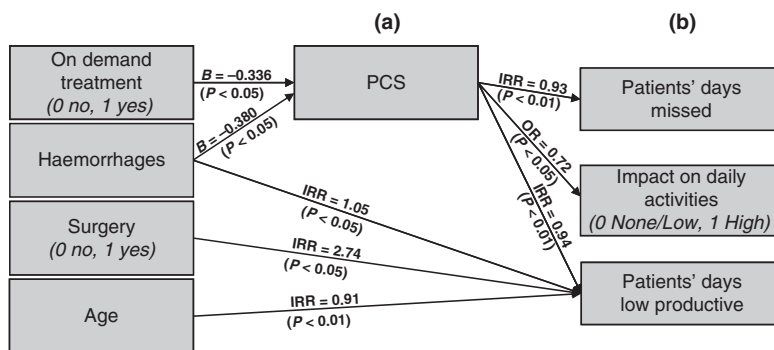
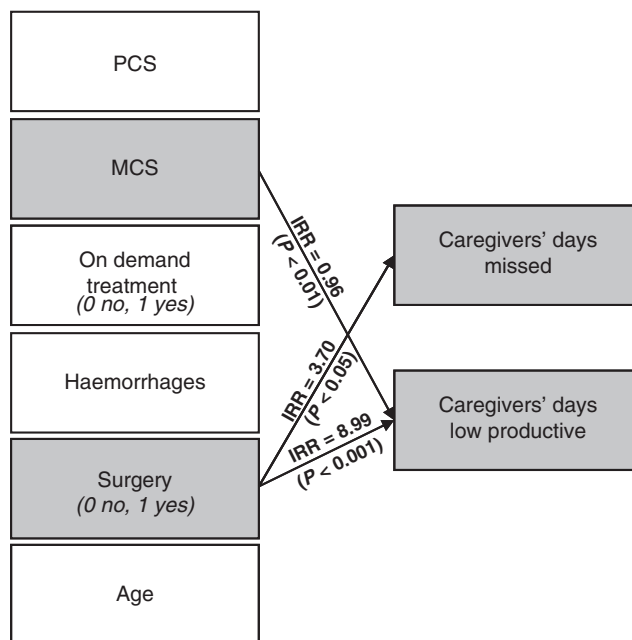


Fig. 2. Conceptual reduced model of significant associations with PCS and patient productivity. Only significant regression coefficients (*B*), Z-Scores (negative binomial regression), and odds ratios (OR) are shown from predicting (a) SF-12v2 MCS and PCS with on-demand treatment, haemorrhages (continuous), surgery in the past 12 months, and patient age (continuous); and (b) patient productivity/activity with SF-12v2 MCS and PCS, on-demand treatment, # of haemorrhages, surgery in the past 12 months, and patient age. Patients' days missed, *n* = 26; Impact in daily activities, *n* = 41; Patients' days low productive, *n* = 24.

$P < 0.01$) were associated with more patient-low-productive days. Lower PCS was also associated with higher levels of patient-perceived impact on daily

activities (OR = 0.72, CI = 0.55–0.93, $P < 0.05$). Figure 2 shows the significant determinants of PCS and associations with patient productivity.

Discussion and conclusion

The purpose of this study was to measure HRQL, its determinants, and its association with patient and caregiver productivity among US haemophilia patients with inhibitors. HRQL was measured with the SF-12v2 and productivity was measured by the number of missed and low-productivity days. This sample of haemophilia patients with inhibitors, and their caregivers, was one of convenience as these participants were recruited from multiple patient summits conducted in the US.

Data suggest that the most impaired aspects of HRQL are physical domains: physical functioning (PF) and role physical (RP). The mean patient PCS of 39.9, is well below the general US population of 49.6 [18], whereas, the mental component score (MCS = 49.2) was comparable with general US norms (49.4). Scales relating to social and emotional functioning (SF and RE), which result in social, work, and daily activity limitations, also showed relative impairment as compared with US population norms. HRQL results are comparable with those observed in the Gringeri *et al.* study [13] among Italian haemophilia patients with inhibitors; researchers obtained a PCS of 36.9 and MCS of 50.2 using the SF-36 scale [19,20].

Findings are consistent with past research among haemophilia patients without inhibitors suggesting the negative association of on-demand treatment (vs. prophylaxis) with HRQL [6,11,12]. Though on-demand therapy was more prevalent among adult than paediatric patients in this study (61.9% vs. 26.7, $P < 0.05$), the negative association between on-demand treatment and physical quality of life (PCS) was maintained whether or not age was included in the prediction equation. The number of haemorrhages was also negatively associated with PCS. Past work among haemophilia patients without inhibitors has suggested different HRQL determinants based on the severity of clotting defect [1–5] as well as the frequency of bleeding episodes [6–8].

Despite potential improvements in HRQL for haemophilia patients with inhibitors related to new treatment methods and disease management [10,13,21], impairments related to physical HRQL (PCS) and their association with patients' daily activities and productivity is suggested by this study. Patients with lower PCS scores missed more work and school days and also had more days with compromised productivity. Aledort *et al.* [17] found that haemophilia patients on long-term prophylaxis missed fewer days annually from work or school as

compared with patients not receiving any specific prophylaxis (1.43 days vs. 6.89 days). Though this study did not include questions related to the start or duration of prophylaxis treatment, we found a positive association between treatment for prevention and immunotolerance and physical HRQL; higher physical HRQL was associated with greater patient productivity.

Work and school days missed or that are less productive for either patients or caregivers contribute to the economic burden of haemophilia with inhibitors. Approximately half of the adult patients did not report current employment. Among those who did, substantial work-time was missed or compromised, and this was associated with physical HRQL deficits. We did not collect data on specific reasons why patients and caregivers were not working or going to school. It is possible that the associations observed between productivity and PCS are conservative.

The non-experimental design of this study, sample selection, and possible response bias limit the causal references that can be drawn from these data. The patient sample is not necessarily representative of US haemophilia patients with inhibitors. Patients were self-selected from many participants attending a conference involving those interested in learning more about their disease. We are unable to assess the demographical and clinical characteristics of patients who did not consent, or those who did not return a completed survey. Thus, we are unable to identify how this study sample may differ from the universe of patients at large. Another limitation of these survey results is sample size. Although this sample of inhibitor patients is relatively large as compared with the total US population of inhibitor patients, it was inadequate for sub-group analyses, for example, those by age or number of bleeds.

In conclusion, findings from this study provide further support of compromised physical functioning among inhibitor patients and the positive association of prophylaxis and immunotolerance therapy with physical HRQL. Reducing disease severity, or the number of haemorrhages, could possibly improve physical functioning and increase patient productivity. Given the high cost and effort associated with prophylaxis and immunotolerance treatments, more research is necessary involving both direct and indirect costs and HRQL. Our findings reinforce the necessity of taking a broader, patient-centered approach, mindful of caregiver concerns, in caring for patients with haemophilia and inhibitors.

Disclosures

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