haematologica 2001; 86:722-728
*http://www.haematologica.it/2001_07/0722.htm*

# Multivariate analysis of factors influencing quality of life and utility in patients with hemophilia

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*Background and Objectives.* Although several studies have determined quality of life (QOL) in patients with hemophilia, generic questionnaires have rarely been used. The objectives of our study were; 1) to measure QOL and utility in patients with hemophilia using the Short Form 36 (SF-36) and the EuroQOL questionnaires; 2) to evaluate the influence of some clinical variables on QOL and utility; 3) to assess the correlation between the two questionnaires.

*Design and Methods.* All consecutive patients with hemophilia were asked to complete the SF-36 and the EuroQOL questionnaires. The following information was recorded from each patient: age, type of hemophilia, severity of disease, HCV and HIV infection, number of bleeding episodes and cumulative dose of coagulation factors over the previous year. These items were entered into a multivariate analysis to assess their effect on QOL. Correlation analyses were conducted to evaluate the relationship between the EuroQOL and SF-36.

*Results.* Fifty-six patients completed the SF-36 and the EuroQOL questionnaires. The mean scores of the SF-36 ranged from 55.2 (general health) to 74.7 (social functioning). The EuroQOL*self-classifier* and the EuroQOL*vas* showed a mean score of 0.67 (SD=0.26) and 0.66 (SD=0.17), respectively. Among the clinical variables, age significantly influenced both the EuroQOL and the SF-36 scores. The EuroQOL indices showed a statistically significant correlation with each dimension of the SF-36.

*Interpretation and Conclusions.* Our study quantified the degree to which QOL is impaired in patients with hemophilia by using both a generic questionnaire and a utility-based approach.

Key words: hemophilia, quality of life, utility

The research on quality of life (QOL) in hemophilia is still at an early stage of advancement.[1-7] Two studies[6,7] have employed well-established generic questionnaires [the Short Form 36 (SF-36)[6,7] or the EuroQOL[7])], but the other studies have generally adopted a merely descriptive approach without using standard QOL instruments.[1-5]

The SF-36 is the most widely used questionnaire for *analytic* QOL assessments;[8-10] this instrument explores 8 domains of QOL and its application to different disease conditions is already very wide. The EuroQOL[11,12] reflects a more *synthetic* approach because, in its application, a single parameter (utility) is assessed for each patient as an aggregate indicator of his or her QOL preferences. Utility measurements are important because they allow a link to economic data about treatments or cost-of-illness and thus represent the basis to construct cost-utility parameters such as the cost per quality-adjusted life year (QALY) gained.

We used the SF-36 and the EuroQOL questionnaires to study QOL in the hemophilia patients referred to our regional Hemophilia Center in Tuscany. Our study had three objectives: 1) to measure QOL and utility in patients with hemophilia using a generic questionnaire (SF-36) and a utility questionnaire (EuroQOL); 2) to analyze the QOL and utility scores in the framework of a multivariate analysis for determining the influence of some clinical variables on these measurements; 3) to assess the correlation between the QOL and the utility measurements produced by the two questionnaires.

## Design and Methods

### Study design and data collection

We studied all consecutive patients with hemophilia who were referred to our regional Hemophilia Center in Tuscany from 1 April, 2000 to 30 June, 2000. The study had a cross-sectional design;

accordingly, patients were included in the study once only (i.e. on the occasion of their first contact with our Center during the study period).

The eligibility criteria for patients' enrollment were the following: a) diagnosis of either hemophilia A or hemophilia B; b) age ≥ 16 years; c) referral as an in-patient or out-patient to the units of Hematology of the Careggi Hospital or to the Regional Hemophilia Center of Careggi; d) no measurable titer of inhibitors at the last visit (determined over the previous 12 months using the Bethesda assay); e) no regular administration of factor VIII or IX for prophylaxis (defined as at least two weekly prophylactic infusions of the deficient factor over the previous six months). The ineligibility of patients with inhibitors and those receiving a regular prophylaxis [criteria (d) and (e)] had the purpose of increasing the homogeneity of our QOL measurements. When the eligibility criteria were met, the inclusion criterion was simply written consent from the patient to participate in the study.

All patients enrolled in the QOL study were asked to complete the SF-36 and the EuroQOL questionnaires. For the purpose of our study, the following information was obtained from each patient:

1. quality of life measurements based on the SF-36 questionnaire (responses to the 36 questions and date of the interview);
2. utility measurements based on the EuroQOL questionnaire [responses to the 5 questions of the EuroQOL*self-classifie*r, response to the EuroQOL*vas* (visual analog scale) and date of the interview];
3. age;
4. type of hemophilia;
5. severity of disease (classified as severe, moderate or mild depending on whether the level of the deficient factor was less than 1%, between 1% and 5%, or greater than 5%, respectively);
6. presence of HCV infection determined by two criteria: a) anti-HCV antibody assayed by EIA (assay manufactured by Roche, Italy); and b) ALT more than 2.5 higher than upper limit of normal in at least two independent samples over a period of 6 months;
7. presence of HIV infection (determined by ELISA assay, Organon, Italy);
8. number of bleeding episodes over the previous year;
9. dosage of coagulation factors over the previous year.

The information of items from 3 to 9 was used as clinical variables for our statistical analysis, and their influence was assessed on the results of both the SF-36 and the EuroQOL questionnaires.

### *Questionnaires and scoring methods*

The SF-36 questionnaire measures 2 main health concepts (physical and mental health) with 36 items and 8 multi-item scales called dimensions or domains (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, mental health). An additional 1-item measure assesses self-evaluated change in health status. Scores are assembled using the method of summated ratings;[10,13,14] the raw scores are then transformed to a 0 to 100 scale (with 0 and 100 assigned to the lowest and highest possible value, respectively). Highest transformed scores indicate better health. Two component summary scores, one concerning the physical dimension (physical component score or PCS) and the other concerning the mental dimension (mental component score or MCS), are also calculated as a result of a weighted combination of the 8 dimensions.[15] The SF-36 health survey has been available in Italian since 1990.

The EuroQOL questionnaire[11,12] consists of 5 questions and contains a visual analog scale (VAS). Two separate utility estimates are calculated, the first (EuroQOL*self-classifier*) from the 5 questions [which are processed through a simple computation algorithm,[11,12]] and the second (EuroQOL*vas*) directly from the VAS. This characteristic of a single-dimension score for both versions of the EuroQOL permits the comparison of utility with costs and the construction of cost-utility ratios where appropriate.

In our study, the two questionnaires were used in the Italian version[9,11] and were self-administered in accordance with current recommendations.[8,12] When necessary, the patient was assisted during the self-administration by his or her clinician. Missing responses were handled according to the procedure indicated by the algorithm of the two questionnaires (cases of missing responses can be inferred from our results when the number of observations was less than 56).

### *Normative data*

To assess the influence of hemophilia on QOL, the results obtained using the SF-36 in our patients were compared with those of 2,031 Italian normal subjects (normative data) reported previously by Apolone *et al.*[9] Since normative data from Italian subjects are lacking for the EuroQOL, no comparison with normative information is presented for this questionnaire.

### *Statistical analysis*

The parameters estimated from the two questionnaires (namely: scores for each of the 8 dimensions of SF-36, summary physical score and summary mental score of SF-36, EuroQOL utility according to the self-classifier algorithm, EuroQOL utility according to the VAS) were presented as means with standard deviation (SD) inclusive of subgroup analyses where appropriate. To determine the influence of the clinical variables on the SF-36 and the EuroQOL measurements, a multivariate regression analysis (SPSS computer program for Windows, Version 8.0, SPSS Inc., 1997) was conducted to test the statistical association between each of the SF-36 and EuroQOL parameters and the clinical variables; this analysis estimated the significance level for each variable and calculated partial correlations and regression coefficients. Categorical variables stratified on more than two levels (e.g. disease severity stratified as severe, moderate, or mild) were handled as dummy variables. A backward stepwise method of variable elimination was used, wherein the variables with $p<0.10$ were eventually retained; the choice of using this $p=0.10$ limit was made to explore not only the associations with clear-cut statistical significance ($p<0.05$), but also those suggested in terms of statistical trends ($0.05<p<0.10$).

A separate analysis tested the inter-relations between the SF-36 and the EuroQOL results (using Spearman's correlation); this analysis, too, was carried out using the SPSS computer program mentioned above.

## Results

Our study recruited a total of 67 patients at their first contact with our Center over the study period. After excluding patients with inhibitors (n=7) and patients receiving prophylaxis (n=4), a total of 56 cases were enrolled in the QOL study; none of these patients refused to participate in the study. The main characteristics of this patient cohort are summarized in Table 1. The age range was very wide (from 16 to 70 years). All patients with severe disease (100%; n=32) and 19 of the 24 patients with moderate/mild disease (79%) were HCV-positive; 11 (34%) of the 32 patients with severe disease and 1 (4%) of the 24 patients with moderate/mild disease were HIV-positive.

The administration of the SF-36 questionnaire to these patients gave the results shown in Table 2. The mean scores for the 8 domains of the SF-36 ranged from 55.2 (general health, SD = 25.2) to 74.7 (social functioning, SD=24.8). The physical and mental summary scores of the SF-36 had an average of 44.7 (SD=10.8, valid cases = 56) and 47.2 (SD=12.5, valid cases = 55), respectively.

**Table 1. Characteristics of the 56 patients with hemophilia included in our study.**

| Patients' characteristics | Values |
|---|---|
| Age (yrs)* | 38.7±15.4 |
| Ratio hemophilia A/B (n/n) | 44/12 |
| Severity of disease | |
| severe | N=32 (57%) |
| moderate | N=15 (27%) |
| mild | N=9 (16%) |
| Presence of HCV infection | N=51 (91%) |
| Presence of HIV infection | N=12 (21%) |
| Median number of bleeding episodes over the previous year (range) | 8 (0 to 80) |
| Median cumulative dose (range) of coagulation factors in units administered over the previous year | 20,000 (0 to >180,000) |

**Mean±SD.*

**Table 2. Quality-of-life scores (mean±SD) obtained by application of the SF-36 in the 56 patients.**

| *Domain** | *N* | *Our study* | *Normative values°* | *Difference between hemophilia patients and normal subjects†* |
|---|---|---|---|---|
| Physical functioning | 56 | 73.6±25.4 | 84.5±23.2 | -13% |
| Role physical | 56 | 64.7±42.6 | 78.2±35.9 | -17% |
| Bodily pain | 56 | 66.3±29.6 | 73.7±27.6 | -10% |
| General health | 56 | 55.2±25.2 | 65.2±22.2 | -15% |
| Vitality | 56 | 62.6±19.6 | 61.8±20.7 | +1% |
| Social functioning | 55 | 74.7±24.8 | 77.4±23.3 | -3% |
| Role emotional | 56 | 65.5±42.6 | 76.2±37.2 | -14% |
| Mental health | 56 | 68.0±21.8 | 66.6±20.9 | +2% |
| Physical component summary score | 56 | 44.7±10.8 | - | - |
| Mental component summary score | 55 | 47.2±12.5 | - | - |

*Abbreviations: N = valid cases . *The responses to the additional 1-item measure of self-evaluated change in health status (question: "compared with one year ago, how would you rate your health in general now?") were the following: first level ("much better now than one year ago"), N=7 (12.5%); second level ("somewhat better now than one year ago"), N=6 (10.7%); third level ("about the same as one year ago"), N=38 (67.9%); fourth level ("somewhat worse now than one year ago"), N=4 (7.1%); fifth level ("much worse now than one year ago"), N=1 (1.8%); no response, N=0 (0%). Values derived from a sample of 2,031 healthy subjects studied by Apolone et al.[9] †Calculated from the ratio of the two respective means.*

The results obtained with the EuroQOL questionnaire were the following: EuroQOL*self-classifier* = 0.68 (SD=0.26, valid cases=56), EuroQOL*vas* = 0.66 (SD=0.17, valid cases=55).

Our comparison of the SF-36 results between hemophilia patients and normal subjects (Table 2)

**Table 3. Results of the multivariate regression analysis to assess the influence of the clinical variables on the domains of the SF-36 and on the two utility estimates based on the EuroQOL.**

| *QOL parameter* | *Variables retained in the analysis** | *Regression coefficient* | *Partial correlation°* | *Statistical significance* | |
|---|---|---|---|---|---|
| SF-36 domains | Physical functioning | Age | -0.823 | -0.499 | *p* <0.001 |
| | Role physical | Age | -1.461 | -0.529 | *p* <0.001 |
| | Bodily pain | Age | -0.828 | -0.384 | *p* =0.004 |
| | | No. of bleeding episodes | -0.484 | -0.251 | *p* =0.065 |
| | General health | Age | -0.961 | -0.593 | *p* <0.001 |
| | | HIV infection | -12.50 | -0.249 | *p* =0.066 |
| | Vitality | Age | -0.423 | -0.359 | *p* =0.008 |
| | | Moderate disease (vs. severe disease)† | -8.71† | -0.392† | *p* =0.003 |
| | | HIV infection | -12.02 | -0.282 | *p* =0.039 |
| | Social functioning | Age | -0.590 | -0.368 | *p* =0.006 |
| | Role emotional | Moderate disease (vs. severe disease)† | -13.08† | -0.290† | *p* =0.032 |
| | | Age | -1.12 | -0.417 | *p* =0.002 |
| | Mental health | Moderate disease (vs. severe disease)† | -7.93† | -0.321† | *p* =0.018 |
| | | HIV infection | -18.11 | -0.361 | *p* =0.007 |
| | | Age | -0.442 | -0.442 | *p* =0.014 |
| SF-36 summary scores | Physical component | Mild disease (vs. severe disease) | -3.016 | -0.231 | *p* =0.090 |
| | | Age | -0.408 | -0.546 | *p* <0.001 |
| | Mental component | Moderate disease (vs. severe disease)† | -4.47† | -0.321† | *p* =0.017 |
| | | Age | -0.220 | -0.282 | *p* =0.037 |
| EuroQOL parameters | EuroQOL*self-classifier* | Age | -0.008 | -0.408 | *p* <0.001 |
| | | HIV infection | -0.180 | -0.314 | *p* =0.020 |
| | EuroQOL*vas* | Age | -0.005 | -0.511 | *p* <0.001 |
| | | HIV infection | -0.167 | -0.434 | *p* =0.001 |

**The cut-off for retaining a variable in the analysis was set at p=0.10. °A negative correlation coefficient indicates that the clinical variable worsens the QOL or the utility parameter and vice versa. †This symbol identifies paradoxical results in that the effect of the variable on QOL was opposite to that expected.*

indicates that the 4 physical domains (physical functioning, role physical, bodily pain, general health) are all consistently affected by hemophilia. Among the mental-related domains, the *role emotional* dimension was worsened while the other 3 were unaffected.

Among the clinical variables that influenced QOL and utility (multivariate regression analysis, Table 3), age had by far the greatest impact because it significantly influenced each of the 8 dimensions of the SF-36, the physical and mental component summary scores of the SF-36, and both utility estimates of the EuroQOL; in fact, all of these indices worsened with increasing age.

HIV infection negatively influenced the mental health domain of the SF-36 and both EuroQOL measurements. Subgroup means (with SD) of all QOL and utility parameters are presented in Tables 4 and 5 according to age and HIV infection, respectively.

In our multivariate analysis (Table 3), a paradoxical positive influence of disease severity (comparison between moderate vs. severe disease) was found in some mental scores of the SF-36 (vitality, role emotional, mental health and MCS). This finding might reflect a patient selection in which subjects with moderate disease were more compromised in some respects than those with severe disease.

Table 6 illustrates our correlation analyses between the EuroQOL and SF-36 domains. Both the EuroQOL*self-classifier* and the EuroQOL*vas* showed a statistically significant correlation with each of the SF-36 domains; the level of this correlation between the two utility measurements and SF-36 was homogeneously strong with no difference between physical-related and mental-related domains. As regards the correlation between the EuroQOL*self-classifier* and the EuroQOL*vas*, Spearman's coefficient was 0.69 ($p<0.001$).

## Discussion

Two studies[6,7] have thus far utilized the SF-36 and/or the EuroQOL in patients with hemophilia (Table 7). The study by Molho *et al.*[6] was a cross-sectional investigation conducted in 116 French patients with severe hemophilia (mean age = 25 years) using the SF-36. The study by Miners *et al.*[7] involved a series of 168 English subjects with

**Table 4. Subgroup values (mean±SD) according to age for the 8 domains of the SF-36, the two summary scores of the SF-36 and the two EuroQOL utility scores.**

| | *Age* | | |
|---|---|---|---|
| | *15 to 30 yrs (N=22)* | *31 to 45 yrs (N=16)* | *45 yrs (N=18)* |
| Physical functioning | 87.0±15.6 | 78.7±23.6 | 52.8±24.0 |
| Role physical | 82.9±29.3 | 78.1±37.5 | 30.6±41.6 |
| Bodily pain | 67.5±32.0 | 84.0±22.7 | 49.1±22.7 |
| General health | 69.9±22.8 | 57.6±19.5 | 35.3±19.3 |
| Vitality | 70.4±16.4 | 62.8±20.1 | 52.8±19.3 |
| Social functioning | 82.5±22.4 | 77.6±24.6 | 61.9±24.1* |
| Role emotional | 78.8±33.4 | 81.2±36.5 | 35.1±43.5 |
| Mental health | 74.7±20.0 | 70.5±19.1 | 57.6±23.4 |
| Physical component summary score | 49.6±9.0 | 48.5±9.8 | 35.5±7.8 |
| Mental component summary score | 50.6±11.8 | 48.7±12.8 | 41.7±11.4 |
| EuroQOL*self-classifier* | 0.81±0.16 | 0.70±0.23 | 0.49±0.30 |
| EuroQOL*vas* | 0.73±0.15 | 0.70±0.16 | 0.54±0.15* |

**N=17. Abbreviations: N = valid cases*

**Table 5. Subgroup values (mean±SD) according to HIV infection for the 8 domains of the SF-36, the two summary scores of the SF-36 and the two EuroQOL utility scores.**

| | *HIV-positive (N=12)* | *HIV-negative (N=44)* |
|---|---|---|
| Physical functioning | 67.1±32.9 | 75.4±23.1 |
| Role physical | 64.6±44.5 | 64.8±42.6 |
| Bodily pain | 66.1±25.0 | 66.4±31.0 |
| General health[§] | 47.7±19.8 | 57.3±26.3 |
| Vitality[§] | 58.7±19.7 | 63.6±19.7 |
| Social functioning | 79.7±25.6* | 73.5±24.7 |
| Role emotional | 83.3±33.4 | 60.6±43.9 |
| Mental health[†] | 59.0±24.0 | 70.4±20.8 |
| Physical component summary score | 42.6±10.1 | 45.3±11.1 |
| Mental component summary score | 47.3±13.3* | 47.2±12.4 |
| EuroQOL*self-classifier* | 0.55±0.32 | 0.71±0.24 |
| EuroQOL*vas* | 0.55±0.21* | 0.69±0.15 |

*[†] According to our multivariate analysis (Table 4), this score was statistically different between the two groups. [§] According to our multi-variate analysis (Table 4), this score was at the limits of statistical significance. (0.05<p < 0.10). *N=11. Abbreviations: N = valid cases.*

**Table 6. Correlation between the various domains of the SF-36 and the two utility estimates based on the EuroQOL.**

| *SF-36 domain* | | *EuroQOL self-classifier* | *EuroQOL vas* |
|---|---|---|---|
| Physical functioning | Spearman's Correlation | 0.64 | 0.61 |
| | *p*-value | <0.001 | <0.001 |
| | N | 56 | 55 |
| Role physical | Spearman's Correlation | 0.57 | 0.57 |
| | *p*-value | <0.001 | <0.001 |
| | N | 56 | 55 |
| Bodily pain | Spearman's Correlation | 0.43 | 0.31 |
| | *p*-value | .001 | 0.021 |
| | N | 56 | 55 |
| General health | Spearman's Correlation | 0.76 | 0.71 |
| | *p*-value | <0.001 | <0.001 |
| | N | 56 | 55 |
| Vitality | Spearman's Correlation | 0.61 | 0.65 |
| | *p*-value | <0.001 | <0.001 |
| | N | 56 | 55 |
| Social functioning | Spearman's Correlation | 0.65 | 0.64 |
| | *p*-value | <0.001 | <0.001 |
| | N | 55 | 55 |
| Role emotional | Spearman's Correlation | 0.55 | 0.58 |
| | *p*-value | <0.001 | <0.001 |
| | N | 56 | 55 |
| Mental health | Spearman's Correlation | 0.65 | 0.65 |
| | *p*-value | <0.001 | <0.001 |
| | N | 56 | 55 |
| Physical component summary score | Spearman's Correlation | 0.59 | 0.51 |
| | *p*-value | <0.001 | <0.001 |
| | N | 56 | 55 |
| Mental component summary score | Spearman's Correlation | 0.59 | 0.63 |
| | *p*-value | <0.001 | <0.001 |
| | N | 55 | 55 |

*Abbreviations: N = valid cases*

hemophilia (mean age = 42.7 years) who completed both the SF-36 and the EuroQOL questionnaires.

As shown in Table 7, the patients of Molho *et al.*[6] showed relatively low scores in the domains of bodily pain, general health, and vitality, while the least affected dimensions were physical functioning and social functioning. These findings were generally similar to ours. As in our study, Molho *et al.*[6] found that age was the main factor influencing QOL measurements. In the case of Miners' investigation,[7] the average scores of SF-36 and EuroQOL were very close to ours (Table 7). Again, as in our study, age was a strong predictor of QOL; in contrast, HIV infection had no significant influence in Miners' patient series.

In comparison with our results, Molho *et al.*[6] reported higher scores in the domains of physical functioning, role physical, general health, social functioning, and role emotional. On the other hand, the results of the two summary scores of the SF-36 were very similar to ours. In the case of Miners' investigation,[7] the average scores of the SF-36 (with the exception of the domain of physical functioning) and of the EuroQOL were higher than ours

**Table 7. Quality-of-life scores (means±SD) of the SF-36 questionnaire: comparison between our study and the two previous studies published by Molho *et al.*[6] and by Miners *et al.*[7]**

| *Domain* | *Our study* | *Molho et al.*[6] | *Miners et al.*[7]* |
|---|---|---|---|
| Physical functioning | 73.6±25.4 | 76.8±22.2 | 62.3 |
| Role physical | 64.7±42.6 | 71.7° | 72.0 |
| Bodily pain | 66.3±29.6 | 60.2±25.2 | 69.2 |
| General health | 55.2±25.2 | 59.3±23.1 | 57.2 |
| Vitality | 62.6±19.6 | 57.8±19.5 | 74.8 |
| Social functioning | 74.7±24.8 | 76.1±23.1 | 76.1 |
| Role emotional | 65.5±42.6 | 73.8° | 81.7 |
| Mental health | 68.0±21.8 | 67.8° | 73.6 |
| Physical component summary score | 44.7±10.8 | 43.3° | 38.7 |
| Mental component summary score | 47.2±12.5 | 47.7° | 52.9 |

**For these scores, Miners et al. reported separate values for the two subgroups of patients with severe disease (n=91) and with mild or moderate disease (n=158); we have recomputed a pooled overall mean by weighting the two means according to the respective sample sizes. °The SD was not reported for these scores.*

(Table 7). Of course, we were unable to make statistical comparisons between our results and those of Miners *et al.* because we lacked patient-level information from the French study.

One drawback to these two studies is that no multivariate analysis was undertaken to assess the joint effect of clinical variables on QOL. Hence, in the light of these two previous studies, the most interesting part of our work is the multivariate analysis. According to our results, age was the main variable affecting QOL because it significantly influenced all measurements of QOL without any exception (Table 4). For example, in the comparison of the 8 domains of the SF-36 between patients aged from 15 to 30 years and those aged over 45 years, the percent reduction ranged from 23% (mental health) to 63% (role physical); this reduction was 28% and 18% for PCS and MCS, respectively, while the EuroQOLself-classifier and the EuroQOLvas showed relative reductions of 40% and 26%, respectively.

One limitation of our analysis is that its statistical power was probably insufficient to explore the effect on QOL of disease severity (split into 3 subgroups of 32 vs 15 vs 9 patients). For example, there was a paradoxical effect for moderate disease which had some scores lower than those found for severe disease. There is plenty of data in the literature on HCV in individuals without hemophilia that suggest HCV decreases QOL. Since in our study all individuals with severe hemophilia were HCV positive, it was impossible to rule this out.

Because many advanced treatments for hemophilia have become available in the last 15 years, the impaired QOL level of our older patients might reflect the negative long-term effect of inadequate treatments received in young age; however, the decline that QOL indices generally show with age in normal subjects and in a variety of disease conditions might also have contributed to this finding.

HIV infection ranked second in our multivariate analysis. As shown in Table 5, its presence caused a relative reduction in the two EuroQOL indices (by 22% for EuroQOL*self-classifier* and 20% for the EuroQOL*vas*) as well as a substantial worsening of the SF-36 domain of mental health (-16% relative change).

The strong agreement between the two utility estimates and each of the 8 domains of the SF-36 (Table 6) is a finding that confirms the good consistency between the EuroQOL and these 8 domains (all correlations were significant or highly significant). On the other hand, the correlation between EuroQOL*self-classifier* and the EuroQOL*vas*, though statistically significant, was not particularly strong (Spearman's correlation coefficient = 0.69). As pointed out in other studies,[16] VAS-scores might not express trade-off measures, whereas the self-classifier instrument is thought to be closer to a traditional trade-off score. Hence, the two utility instruments possibly reflect a somewhat different pattern from one another and do not seem to be mutually interchangeable.

In conclusion, the section of our study based on the SF-36 substantially confirmed the results of previous investigations and provided new information on the critical issue of which variables affect QOL in hemophilia. The section of our study based on the EuroQOL provided original data in terms of utility that could be useful for future cost-effectiveness studies evaluating this disease condition.

Complete information about utility is the prerequisite to translate clinical outcome and cost of hemophilia patients into a cost/utility ratio (e.g. cost per QALY gained) and to place this latter parameter in the framework of those previously calculated for other medical interventions in other disease conditions.[17–19] In fact, while several investigations have already determined the cost per life year gained or the cost per QALY gained for numerous treatments aimed at different disease conditions, the area of hemophilia is still unexplored under this respect, and even the most critical issues (e.g. prophylaxis vs. on-demand treatment) have not yet been examined using this approach.

Finally, because relevant results were obtained in our study using the EuroQOL questionnaire, future controlled studies in hemophilia patients should consider the inclusion of this questionnaire in outcome assessment in order to place the basis for evaluating cost-utility ratios.

### Contributions and Acknowledgments

*SL, GL and MM conducted the interviews with the patients and collected all clinical information. ST, MV, and AM carried out the analyses. All the authors contributed to the interpretation and writing of the manuscript.*

### Disclosures

*Conflict of interest: none.*

*Redundant publications: no substantial overlapping with previous papers.*

### Manuscript processing

*This manuscript was peer-reviewed by two external referees and by Prof. Vicente Vicente, who acted as an Associate Editor. The final decision to accept this paper was taken jointly by Prof. Vicente and the Editors. Manuscript received September 15, 2000; accepted June 6, 2001.*

### Potential implications for clinical practice

This study sheds light on the main factors that influence quality of life in hemophilia. This information can be of benefit to clinicians in order that they interact adequately with individual patients.

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