RESEARCH ARTICLE

Quality of life in patients with chronic hepatitis C infection: Severe comorbidities and disease perception matter more than liver-disease stage

Sabrina Cossais1*, Michaël Schwarzinger1,2, Stanislas Pol3,4, Hélène Fontaine3,4, Dominique Larrey5, Georges-Philippe Pageaux5, Valérie Canva6, Philippe Mathurin6,7, Yazdan Yazdanpanah1,8, Sylvie Deuffic-Burban1,7

1 Inserm, IAME, UMR 1137, Paris, France; Université Paris Nord, Sorbonne Paris Cité, Paris, France, 2 THEN (Translational Health Economics Network), Paris, France, 3 Unité hépatologie, Groupe Hospitalier Cochin Hôtel-Dieu, Paris, France, 4 Inserm U1223, Institut Pasteur; Université Paris Descartes, Paris, France, 5 Service des maladies de l’ appareil digestif, Hôpital Saint Eloi, IBR- Inserm Montpellier, France, 6 Service des Maladies de l’Appareil digestif et de la Nutrition, Hôpital Huriez, Lille, France, 7 Université Lille, Inserm, CHU Lille, U995—LIRIC—Lille Inflammation Research International Center, Lille, France, 8 Service des Maladies Infectieuses et Tropicales, Hôpital Bichat Claude Bernard, Paris, France

* sabrina.cossais@outlook.fr

Abstract

Background and aims
This study evaluated the clinical and non-clinical determinants of health-related quality of life (HRQoL) associated with untreated chronic hepatitis C (CHC) in France.

Methods
From 01/2014 to 01/2015, untreated CHC patients were invited to complete a questionnaire including EQ-5D utility instrument and two visual analogue scales (VAS) measuring overall health and fatigue in three French centers (Paris, Lille and Montpellier). Answers were analyzed in mixed models (taking into account the clustering effects of centers and physicians).

Results
Five hundreds and five patients were enrolled: 52% males; the mean age was 54; 41% had BMI>25; 64% had genotype 1; 36% were at the stage of severe fibrosis (F3-F4); 38% had severe comorbidities other than liver-related. In the univariate analysis, EQ-5D utility was associated with socio-demographic variables as age, place of birth, education, and employment; CHC-related variables as conditions of HCV screening and severity of fibrosis; CHC-unrelated variables as comorbidities other than CHC, being overweight, and psychiatric disorders; feelings about CHC disease as perception of progression, lack of information on CHC and its treatments, and entourage’s feeling. In multivariate analysis, EQ-5D utility was affected by not being in employment (0.72 vs. 0.80), having severe comorbidities other than
CHC (0.72 vs. 0.79), being overweight (0.73 vs. 0.78), and feeling worried about CHC progression (0.66 vs. 0.72–0.84). Similar results were found for the VAS.

Conclusions
The presence of severe comorbidities and worrying about CHC progression, but not stage of fibrosis, seem to alter significantly EQ-5D health utility in CHC French patients.

Introduction
The impact of chronic hepatitis C (CHC) infection on health-related quality of life (HRQoL) has received increasing interest over the past ten years [1,2]. HRQoL has been especially shown to be impaired in patients with CHC [3–6]. With the advent of highly effective, and well tolerated, new direct-acting antivirals (DAAs), clinicians and patients emphasize that all those with HCV should receive these new treatments, not only to decrease HCV morbidity and mortality and/or HCV transmission, but also to improve patients’ HRQoL. Indeed, higher HRQoL has been found after a sustained virological response [7,8]. The hypothesis is that, because of the impact of these treatments on HRQoL, and despite their high costs, they could be cost-effective even in those patients who are at the early stages of the disease. However, few studies have measured HRQoL [7,9,10].

HRQoL may be affected in a subgroup of HCV-infected patients although not all of them. A recent study conducted in France, the UK, and Germany generated a utility value set for CHC patients, stratified by stage of liver disease [8]. Patient characteristics such as male gender [11,12], being unemployed, being an intravenous drug user, comorbidities, a liver disease stage above F2 [4,13–15], genotype 3, and not having achieved sustained virological response (SVR), decreased HRQoL. Associations were also found between HRQoL and knowledge of diagnosis [16,17] and or being naïve to treatment or not (in relation to adverse events of previous treatment) [18–20].

Beyond the level of disease severity, HRQoL for CHC patients may be impaired by the difficulty of accepting the disease and its social impacts. These non-clinical aspects had not been widely assessed. The availability of new DAAs may change not only the HRQoL of CHC patients, but also their perception of the disease.

The objective of the present study was to evaluate the HRQoL and their determinants in untreated patients with CHC, before the initiation of new DAAs in France, in a period during which patients were aware of DAAs availability.

Methods

Study design and participants
The French ethics committee, Commission nationale de l’informatique et des libertés de France (CNIL) approved by written the study (N/Ref.: MMS/FLR/AR146546). A cross-sectional study was conducted between January 2014 and January 2015 in three reference centers (Paris, Lille and Montpellier). Patients with CHC were eligible for this study if they were 18–70 years old, had not received a liver transplant, and were not receiving treatment for CHC. All patients meeting the inclusion criteria were invited by their physician to participate. The individual in this manuscript has given written informed consent (as outlined in PLOS consent form) to publish these case details.
All participants completed a questionnaire administered face to face by a clinical research fellow, except at Lille, where it was self-administered. The questionnaire proposed 50 questions including measures of HRQoL and patients’ characteristics: comorbidities, circumstances of HCV discovery, CHC clinical history and its evolution, information and perception of CHC (using four-point Likert scales [21]), impact of CHC on daily life including dependence on alcohol (according to a CAGE (Cut-down, Annoyed, Guilty, Eye-opener) questionnaire [22]), and positioning in relation to HCV treatments. Fibrosis stage and genotype were obtained from medical records.

Measure of quality of life
HRQoL was assessed using EQ-5D, for which a time trade-off (TTO) French utility value set is available [23]. This questionnaire contains five generic questions on mobility, self-care, habitual activities, pain/discomfort and anxiety/depression that were declined on three levels (EQ-5D-3L): no problems, some problems, and extreme problems.

HRQoL was also evaluated through two visual analogue scales (VAS), a vertical line of 100 mm: one assessing overall health [24] defined between 0 (worst) and 100 (best imaginable health), and one assessing overall fatigue [25] defined between 0 (none) and 100 (worst fatigue). The patient placed a mark between these two extremities according to his overall health and his level of fatigue felt the day of the interview.

Statistical analysis
Chi-square tests were used to compare patients’ characteristics according to their stage of fibrosis (F0-F1, F2 and F3-F4). HRQoL was evaluated through the estimation of mean EQ5D utility index [23], and mean VAS values on general health [24] and fatigue [25]. Determinants of the EQ-5D utility index, overall health, and overall fatigue, were analyzed with mixed models taking into account the cluster effect (hepatology centers and physicians). Variables associated with the outcome in the univariate analysis (p < 0.20) were introduced in the multivariate analysis. To avoid the inclusion of highly correlated variables in the multivariate analysis, we performed a principal component analysis on all 12 subjective Likert scales on knowledge, attitude, belief, and perception. Accordingly, four variables added little information and were removed: perceived future progression of CHC, severity of CHC disease, knowledge about the availability of new treatments, and knowledge about the chances of healing using older treatments. Next, a step-by-step backward elimination procedure with a significance threshold of 0.05 was used to identify the variables independently associated with each outcome studied, while four socio-demographic variables (gender, age, place of birth, education) were forced in all multivariate models. Data were analyzed using SAS version 9.4.

Results
Demographic characteristics and clinical data
A total of 505 HCV-mono-infected patients were enrolled in the study (Table 1); 481 had complete records. The detailed socio-demographic and clinical characteristics of patients are presented according to fibrosis stage. Forty-one percent of patients had minimal fibrosis (F0-F1), whereas 35% were at an advanced stage F3-F4. Overall, 52% were men; the majority of patients were over 50 years old (72%), born in France (74%), had a bachelor’s degree level of education (54%), were in employment (55%), and had children (75%). The distribution of gender, age, education and parenthood varied according to fibrosis stage. In particular, women represented 58% of F0-F1, 46% of F2 and 36% of F3-F4 (p < 0.0001).
| Variable                  | Class          | Total  | F0–F1        | F2            | F3–F4         | P value |
|---------------------------|----------------|--------|--------------|---------------|--------------|---------|
| Gender                    | Male           | 252 (52.4) | 81 (41.5) | 62 (53.5) | 109 (64.1) | < .0001 |
|                           | Female         | 229 (47.6) | 114 (58.5) | 54 (46.5) | 61 (35.9)  |         |
| Age                       | 18–49          | 133 (27.7) | 75 (38.5)  | 22 (19.0)  | 36 (21.2)  | 0.006   |
|                           | 50–54          | 102 (21.2) | 36 (18.5)  | 25 (21.6)  | 41 (24.1)  |         |
|                           | 55–59          | 104 (21.6) | 39 (20.0)  | 26 (22.4)  | 39 (22.9)  |         |
|                           | 60–64          | 76 (15.8)  | 23 (11.8)  | 22 (19.0)  | 31 (18.2)  |         |
|                           | 65–70          | 66 (13.7)  | 22 (11.3)  | 21 (18.1)  | 23 (13.5)  |         |
| Place of birth            | France         | 354 (73.6) | 136 (69.7) | 88 (75.9)  | 130 (76.5) | 0.284   |
|                           | Abroad         | 127 (26.4) | 59 (30.3)  | 28 (24.1)  | 40 (23.5)  |         |
| Education                 | No bachelor level | 223 (46.4) | 75 (38.5)  | 58 (50.0)  | 90 (52.9)  | 0.015   |
|                           | Bachelor level | 258 (53.6) | 120 (61.5) | 58 (50.0)  | 80 (47.1)  |         |
| Work                      | Yes            | 263 (54.7) | 111 (56.9) | 69 (59.5)  | 83 (48.8)  | 0.148   |
|                           | No             | 218 (45.3) | 84 (43.1)  | 47 (40.5)  | 87 (51.2)  |         |
| Children                  | Yes            | 361 (75.1) | 134 (68.7) | 96 (82.8)  | 131 (77.1) | 0.016   |
|                           | No             | 120 (24.9) | 61 (31.3)  | 20 (17.2)  | 39 (22.9)  |         |
| Centers                   | Paris Cochin   | 221 (45.9) | 104 (53.3) | 52 (44.8)  | 65 (38.2)  | 0.001   |
|                           | Lille          | 112 (23.3) | 52 (26.7)  | 26 (22.4)  | 34 (20.0)  |         |
|                           | Montpellier    | 148 (30.8) | 39 (20.0)  | 38 (32.8)  | 71 (41.8)  |         |
| Physician                 | A              | 28 (5.8)   | 19 (9.7)   | 2 (1.7)    | 7 (4.1)    | < .0001 |
|                           | B              | 72 (14.9)  | 31 (15.9)  | 22 (19.0)  | 19 (11.2)  |         |
|                           | C              | 12 (2.5)   | 2 (1.0)    | 2 (1.7)    | 8 (4.7)    |         |
|                           | D              | 17 (3.5)   | 7 (3.6)    | 5 (4.3)    | 5 (2.9)    |         |
|                           | E              | 24 (4.9)   | 15 (7.7)   | 1 (0.9)    | 8 (4.7)    |         |
|                           | F              | 121 (25.2) | 54 (27.7)  | 37 (31.9)  | 30 (17.7)  |         |
|                           | G              | 45 (9.4)   | 21 (10.8)  | 8 (6.9)    | 16 (9.4)   |         |
|                           | H              | 14 (2.9)   | 7 (3.6)    | 1 (0.9)    | 6 (3.5)    |         |
|                           | I              | 148 (30.8) | 39 (20.0)  | 38 (32.8)  | 71 (41.8)  |         |
| Screening context         | Health check-up| 259 (54.1) | 107 (54.9) | 61 (52.6)  | 91 (54.2)  | 0.271   |
|                           | Medical follow-up | 40 (8.4)   | 19 (9.7)   | 12 (10.3)  | 9 (5.4)    |         |
|                           | Blood donation  | 106 (22.1) | 46 (23.6)  | 26 (22.4)  | 34 (20.2)  |         |
|                           | Persistent fatigue | 74 (15.6)  | 23 (11.8)  | 17 (14.7)  | 34 (20.2)  |         |
| Genotype                  | 1              | 311 (64.7) | 127 (65.1) | 82 (70.7)  | 102 (60.0) | 0.416   |
|                           | 2.3            | 94 (19.5)  | 39 (20.0)  | 17 (14.7)  | 38 (22.4)  |         |
|                           | 4.5 6          | 76 (15.8)  | 29 (14.9)  | 17 (14.7)  | 30 (17.7)  |         |
| Treatment history         | Naïve          | 240 (49.9) | 131 (67.2) | 51 (44.0)  | 58 (34.1)  | < .0001 |
|                           | Non-naïve      | 241 (50.1) | 64 (32.8)  | 65 (56.0)  | 112 (65.9) |         |
| Severe comorbiditiesa     | Yes            | 180 (37.4) | 67 (34.4)  | 42 (36.2)  | 71 (41.8)  | 0.329   |
|                           | No             | 301 (62.6) | 128 (65.6) | 74 (63.8)  | 99 (58.2)  |         |
| Overweightb               | Yes            | 200 (41.6) | 66 (33.9)  | 57 (49.1)  | 77 (45.3)  | 0.014   |
|                           | No             | 281 (58.4) | 129 (66.1) | 59 (50.9)  | 93 (54.7)  |         |
| Psychiatric disorders     | Yes            | 53 (11.0)  | 16 (8.2)   | 14 (12.1)  | 23 (13.5)  | 0.247   |
|                           | No             | 428 (89.0) | 179 (91.8) | 102 (88)   | 147 (86.5) |         |
| Injection or nasal drug use| Yes          | 201 (41.8) | 64 (32.8)  | 50 (43.1)  | 87 (51.2)  | 0.002   |
|                           | No             | 280 (58.2) | 131 (67.2) | 66 (56.9)  | 83 (48.8)  |         |
| Alcohol Use Disordersc    | Yes            | 152 (31.6) | 41 (21.0)  | 28 (24.1)  | 83 (48.8)  | < .0001 |
|                           | No             | 329 (68.4) | 154 (79.0) | 88 (75.9)  | 87 (51.2)  |         |

(Continued)
### Table 1. (Continued)

| Variable                                           | Class                      | Total       | F0-F1       | F2          | F3-F4        | P value |
|----------------------------------------------------|----------------------------|-------------|-------------|-------------|-------------|---------|
| Perceived progression of CHC between infection and today | Very comforting           | 56 (12.2)   | 37 (20.2)   | 10 (8.9)    | 9 (5.6)     | < .0001 |
|                                                    | Rather comforting         | 250 (54.6)  | 115 (62.8)  | 75 (66.4)   | 60 (37.0)   |         |
|                                                    | Rather worrying           | 112 (24.3)  | 23 (12.6)   | 22 (19.5)   | 67 (41.4)   |         |
|                                                    | Very worrying             | 40 (8.7)    | 8 (4.4)     | 6 (5.3)     | 26 (16.1)   |         |
| Perceived future progression of CHC                | Very comforting           | 96 (20.1)   | 51 (26.4)   | 21 (18.3)   | 24 (14.1)   | 0.081   |
|                                                    | Rather comforting         | 158 (33.1)  | 62 (32.1)   | 39 (33.9)   | 57 (33.5)   |         |
|                                                    | Rather worrying           | 164 (34.3)  | 56 (29.0)   | 44 (38.3)   | 64 (37.7)   |         |
|                                                    | Very worrying             | 60 (12.6)   | 24 (12.5)   | 11 (9.6)    | 25 (14.7)   |         |
| Level of information                               | Informed                  | 407 (85.2)  | 166 (85.6)  | 96 (83.5)   | 145 (85.8)  | 0.845   |
|                                                    | Uninformed                | 71 (14.9)   | 28 (14.4)   | 19 (16.5)   | 24 (14.2)   |         |
| Personal research on CHC                           | Yes                       | 338 (70.3)  | 142 (72.8)  | 84 (72.4)   | 112 (65.9)  | 0.297   |
|                                                    | No                        | 143 (29.7)  | 55 (27.2)   | 32 (27.6)   | 58 (34.1)   |         |
| Severity of CHC disease                            | Not serious               | 32 (6.7)    | 17 (8.8)    | 11 (9.6)    | 4 (2.4)     | 0.020   |
|                                                    | Rather serious            | 251 (52.6)  | 104 (53.6)  | 64 (55.7)   | 83 (49.4)   |         |
|                                                    | Very serious              | 194 (40.7)  | 73 (37.6)   | 40 (34.8)   | 81 (48.2)   |         |
| Knowledge of the availability of new treatments    | Very knowledgeable        | 103 (21.8)  | 46 (24.0)   | 31 (27.0)   | 26 (15.7)   | 0.119   |
|                                                    | Fairly well informed      | 243 (51.4)  | 93 (48.4)   | 53 (46.1)   | 97 (58.4)   |         |
|                                                    | Uninformed                | 127 (26.8)  | 53 (27.6)   | 31 (27.0)   | 43 (25.9)   |         |
| Knowledge of chances of healing with older treatments | Yes                       | 295 (62.1)  | 118 (61.1)  | 70 (61.4)   | 107 (63.7)  | 0.87    |
|                                                    | No                        | 180 (37.9)  | 75 (38.9)   | 44 (38.6)   | 61 (36.3)   |         |
| Knowledge of chances of healing with new treatments | Yes                       | 341 (71.9)  | 132 (69.1)  | 89 (77.4)   | 120 (71.4)  | 0.291   |
|                                                    | No                        | 133 (28.1)  | 59 (30.9)   | 26 (22.6)   | 48 (28.6)   |         |
| Living with CHC in society                         | Difficult to live in society | 261 (56.7)  | 109 (59.6)  | 66 (57.4)   | 86 (53.1)   | 0.474   |
|                                                    | Easy to live in society   | 199 (43.3)  | 74 (40.4)   | 49 (42.6)   | 76 (46.9)   |         |
| Need to talk with people with CHC                  | Very often                | 9 (1.9)     | 3 (1.6)     | 2 (1.8)     | 4 (2.5)     | 0.722   |
|                                                    | Often                     | 46 (9.9)    | 21 (11.2)   | 10 (8.8)    | 15 (9.2)    |         |
|                                                    | Occasionally              | 141 (30.4)  | 53 (28.3)   | 31 (27.2)   | 57 (35.0)   |         |
|                                                    | Not at all                | 268 (57.8)  | 110 (58.8)  | 71 (62.3)   | 87 (53.4)   |         |
| Speak freely about CHC with friends                | Yes                       | 326 (68.3)  | 123 (64.1)  | 75 (65.2)   | 128 (75.3)  | 0.051   |
|                                                    | No                        | 151 (31.7)  | 69 (35.9)   | 40 (34.8)   | 42 (24.7)   |         |
| Entourage uncomfortable since their knowledge of the CHC | Yes, they are uncomfortable | 73 (15.4)   | 24 (12.6)   | 19 (16.7)   | 30 (17.9)   | 0.032   |
|                                                    | None is uncomfortable     | 307 (64.9)  | 118 (61.8)  | 72 (63.2)   | 117 (69.6)  |         |
|                                                    | No, because nobody knows  | 93 (19.7)   | 49 (25.7)   | 23 (20.2)   | 21 (12.5)   |         |

N = 481 excluding genotype and stage of fibrosis unknown

*Diabetes, non-liver related transplant, psychiatric disorders, drug addiction / alcohol

*BMI > 25 kg/m²

*Patients hospitalized for alcohol dependence or currently receiving substitution treatment

*Uninformed" regroups "rather uninformed" and "very badly informed"

*"Uninformed" regroups "rather uninformed" and "Very badly informed"

*Except the physician’s information

*"Not serious" regroups "Not serious at all" and "Rather not matter"

*"Uninformed" regroups "Rather uninformed" and "Very badly informed"

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Regarding the information about CHC, the majority of patients were in Paris (46%), had been screened for HCV through routine health check-ups (54%), and had a genotype-1 virus (65%). The distribution of centers and physicians, and the treatment history, varied according to fibrosis stage: the majority of F0-F1 and F2 patients were enrolled in Paris (53% and 45%,
respectively), whereas the majority of F4 patients were enrolled in Montpellier (42%) 
\((p = 0.001)\); 67% F0-F1 and 34% of F3-F4 were treatment-naïve \((p<0.0001)\).

Regarding diseases other than CHC, 37% of patients reported severe comorbidities, 42% were overweight \((\text{BMI}>25 \text{ kg/m}^2)\), and 11% had psychiatric disorders. Thirty-two percent of patients had alcohol dependence and 42% reported a personal history of injection or nasal drug use. The percentages of patients who were overweight, patients who engaged in drug use, and especially patients with alcohol dependence, increased with fibrosis stage: 21% of F0-F1 vs. 49% of F3-F4 had alcohol dependence \((p<0.0001)\).

**Perception of the disease, level of information, and living with CHC**

For 67% of patients (Table 1), the perceived progression of CHC between infection and the day of interview was very or rather comforting \((83\% \text{ among F0-F1 vs. 43\% among F3-F4, } p<0.0001)\). When looking ahead to years to come, 53% perceived CHC progression as very or rather comforting \((58\% \text{ among F0-F1 vs. 48\% among F3-F4, } p = 0.08)\). By contrast, the disease was perceived as very serious in 41% of patients \((38\% \text{ among F0-F1 vs. 48\% among F3-F4, } p = 0.02)\). Regarding knowledge of treatments, 73% felt informed about the availability of new treatments, 62% reported having knowledge about the chances of recovery with older treatments \((72\% \text{ with regard to new treatments), without any difference according to stage of fibrosis.})

For 57% of patients it was difficult to live with CHC in society. Thirty-two percent of patients said they spoke freely about their CHC disease with their friends \((36\% \text{ among the F0-F1 vs. 25\% for F3-F4, } p = 0.05)\). Finally, 15% of patients felt that their entourage had been uncomfortable since finding out about their CHC status \((13\% \text{ among the F0-F1 vs. 18\% for F3-F4}), whereas 20% reported that members of their entourage did not know about their CHC \((26\% \text{ for F0-F1 vs. 12\% for F3-F4}).

**Estimation of utilities and their determinants**

The mean EQ-5D utility was 0.80, while mean VAS values were 68.8 for overall health and 44.7 for overall fatigue. In univariate analyses (Table 2), mean EQ-5D utility decreased with: older age \((\geq 0.80 \text{ before 65 years old vs. 0.72 at 65–70 years old})\); lower levels of education \((0.85 \text{ in patients with bachelor level vs. 0.75 in those without}); being unemployed \((0.86 \text{ for those working vs. 0.73 for those not working}); having children \((0.84 \text{ in patients without children vs. 0.79 in those with children}). Mean EQ-5D utility also varied according to reference center, according to physician, and according to screening context. It also decreased both as the stage of fibrosis advanced \((0.83 \text{ in F0-F1 and 0.82 in F2 vs. 0.76 in F3-F4})\) and in the presence of other diseases.

Mean EQ-5D utility decreased along with worse perceptions of CHC progression between infection and the day of enrollment \((0.88 \text{ when very reassuring to 0.66 when very worrying}), and of future progression of CHC \((0.87 \text{ when very reassuring to 0.66 when very worrying}). Moreover, it also decreased both when patients were not informed about CHC \((0.82 \text{ in F0-F1 and 0.72, and with a worse perception of CHC disease from 0.80 to 0.77). Mean EQ-5D utility also increased with the level of knowledge of the availability of new treatments \((0.75 to 0.83)\) and of the chances of healing with new treatments \((0.76 to 0.82); the utilities were higher when patients were informed. Finally, mean EQ-5D was lower when the perception of life in society with CHC was difficult \((0.77 vs. 0.83 \text{ when easy}, and also when the feeling of the entourage was uncomfortable \((0.71 vs. 0.83 when no one was uncomfortable).}
Table 2. Determinants of HRQoL: Univariate analysis.

| Variable                  | Class       | EQ-5D | P value | VAS Health | P value | VAS fatigue | P value |
|---------------------------|-------------|-------|---------|------------|---------|-------------|---------|
| Gender                    | Male        | 0.81  | 0.197   | 69.0       | 0.947   | 42.9        | 0.226   |
|                           | Female      | 0.79  |         | 68.8       |         | 46.1        |         |
| Age                       | 18–49       | 0.81  | 0.028   | 68.2       | 0.747   | 44.8        | 0.717   |
|                           | 50–54       | 0.81  |         | 68.1       |         | 47.2        |         |
|                           | 55–59       | 0.84  |         | 69.3       |         | 43.7        |         |
|                           | 60–64       | 0.80  |         | 71.7       |         | 41.2        |         |
|                           | 65–70       | 0.72  |         | 67.4       |         | 44.5        |         |
| Place of birth            | France      | 0.80  | 0.922   | 70.2       | 0.019   | 45.2        | 0.339   |
|                           | Abroad      | 0.80  |         | 65.0       |         | 42.3        |         |
| Education                 | No bachelor | 0.75  | < .0001 | 65.7       | 0.003   | 47.5        | 0.038   |
|                           | Bachelor    | 0.85  |         | 71.6       |         | 42.0        |         |
| Work                      | Yes         | 0.86  | < .0001 | 72.9       | < .0001 | 41.6        | 0.017   |
|                           | No          | 0.73  |         | 64.0       |         | 47.9        |         |
| Children                  | Yes         | 0.79  | 0.029   | 68.2       | 0.202   | 45.7        | 0.090   |
|                           | No          | 0.84  |         | 71.2       |         | 40.3        |         |
| Centers                   | Paris       | 0.86  | < .0001 | 72.3       | 0.005   | 39.4        | 0.002   |
|                           | Lille       | 0.75  |         | 65.4       |         | 49.3        |         |
|                           | Montpellier | 0.76  |         | 66.2       |         | 48.6        |         |
| Physician                 | A           | 0.83  | 0.002   | 66.3       | 0.173   | 51.1        | 0.009   |
|                           | B           | 0.73  |         | 65.4       |         | 47.2        |         |
|                           | C           | 0.70  |         | 64.0       |         | 58.5        |         |
|                           | D           | 0.86  |         | 70.0       |         | 40.0        |         |
|                           | E           | 0.87  |         | 75.8       |         | 30.0        |         |
|                           | F           | 0.86  |         | 72.1       |         | 42.8        |         |
|                           | G           | 0.83  |         | 72.2       |         | 35.5        |         |
|                           | H           | 0.91  |         | 72.4       |         | 32.5        |         |
|                           | I           | 0.76  |         | 66.2       |         | 48.6        |         |
| Screening context         | Health check-up | 0.82 | 0.015   | 69.2       | 0.050   | 42.6        | 0.076   |
|                           | Medical follow-up | 0.87 |         | 76.0       |         | 39.2        |         |
|                           | Blood donation | 0.75 |         | 68.4       |         | 46.6        |         |
|                           | Persistent fatigue | 0.79 |         | 64.5      | 51.0   |         |
| Fibrosis stage            | F0-F1       | 0.83  | 0.019   | 73.3       | 0.002   | 42.0        | 0.316   |
|                           | F2          | 0.82  |         | 66.4       |         | 46.4        |         |
|                           | F3-F4       | 0.76  |         | 65.8       |         | 45.9        |         |
| Genotype                  | 1           | 0.81  | 0.576   | 70.0       | 0.227   | 44.2        | 0.961   |
|                           | 2.3         | 0.78  |         | 67.7       |         | 44.9        |         |
|                           | 4.5.6       | 0.80  |         | 65.6       |         | 45.1        |         |
| Treatment-naïve           | Naïve       | 0.81  | 0.299   | 70.3       | 0.153   | 41.6        | 0.029   |
|                           | Non-naïve   | 0.79  |         | 67.5       |         | 47.3        |         |
| Severe comorbidities*     | Yes         | 0.75  | < .0001 | 65.3       | 0.007   | 46.9        | 0.175   |
|                           | No          | 0.83  |         | 70.9       |         | 43.1        |         |
| Overweight²               | Yes         | 0.77  | 0.007   | 68.0       | 0.432   | 47.8        | 0.039   |
|                           | No          | 0.82  |         | 69.5       |         | 42.2        |         |
| Psychiatric disorders     | Yes         | 0.73  | 0.01    | 59.2       | 0.001   | 58.3        | 0.001   |
|                           | No          | 0.81  |         | 70.1       |         | 42.8        |         |
| Injection or nasal drug use | Yes     | 0.82  | 0.173   | 68.3       | 0.623   | 45.9        | 0.354   |
|                           | No          | 0.79  |         | 69.3       |         | 43.4        |         |

(Continued)
Regarding VAS, similar associations were found (Table 2) except that age was not associated either with general health and fatigue, or with the severity of the CHC disease. Moreover, as general health and fatigue deteriorated, the need to talk with people with CHC increased.

![Table 2.](https://doi.org/10.1371/journal.pone.0215596.t002)
Finally, genotype, drug use and alcohol dependence did not affect either mean EQ-5D utilities or mean VAS values for overall health and fatigue.

In multivariate analysis (Table 3), after adjustment on socio-demographic variables (gender, age, place of birth, education) and cluster effects (center and physician), EQ-5D utility remained significantly associated with being unemployed (0.80 for patients working vs. 0.72 for those not working), with the presence of severe comorbidities (0.79 without vs. 0.72 with comorbidities), with being overweight (0.78 without vs. 0.73 with overweight), and with a CHC progression perceived as rather or very worrying (from 0.84 for patients feeling CHC progression was very reassuring, to 0.66 for patients feeling it was very worrying).

Regarding VAS for health and fatigue, similar results were found, except that VAS deteriorated significantly in the presence of psychiatric disorders and for patients feeling that their entourage felt uncomfortable since finding out about their CHC status. Moreover, general health was significantly lower for patients in F2 (56.9) compared to those in F0-F1 (62.7) and F3-F4 (61.2).

Discussion

This is the first study conducted in France to assess QoL in a large sample of patients affected by CHC. We found that EQ-5D utility values, as well as overall health and fatigue assessed by VAS, were mainly influenced by socio-demographic characteristics (unemployment), by comorbidities (including overweight), and by individual perceptions about CHC progression, rather than by the clinical characteristics of CHC (fibrosis stage, genotype, treatment-naïve status).

Although the stage of fibrosis significantly affects EQ-5D in univariate analysis, it was not found to be an independent factor of HRQoL. Similarly, Hsu et al [17,18] did not find an association between HRQoL and the stage of fibrosis, and emphasized the greater impact of socio-demographic variables on HRQoL.

It was not surprising to find that unemployment, overweight, psychiatric disorders, and comorbidities decrease HRQoL. Unemployment was also found to be significantly associated with decreased HRQoL by Pol et al [13]. Multiple studies found an association between each of those comorbidities and decreased HRQoL [26–28]. In our study, over a third of patients reported comorbidities such as diabetes, arterial hypertension, chronic kidney disease, or hemophilia. During the interview, patients reporting comorbidities were systematically asked to directly compare the severity of CHC with that of other comorbidities (N = 222). Forty-four percent felt that CHC was more severe than their other comorbidities, 36% felt CHC was as severe, but 20% felt CHC was less severe than other comorbidities (not shown). These results suggest that the eradication of HCV after treatment will not necessarily improve the HRQoL of those patients with comorbidities and emphasize a need for active therapeutic interventions regarding these comorbidities.

Patients perception on CHC disease was found to be associated with HRQoL. This perception was principally related to the stage of fibrosis. Patients who saw their disease progress to F3-F4 at the moment of this study were obviously more worried than those at F0-F2. However, despite minimal fibrosis, F0-F1 patients were also found to be worried (17% seeing CHC disease as rather or very worrying). Indeed, as stated by others, HRQoL also decreases along with patients’ anxiety regarding the evolution of their disease [29] which may be unrelated to fibrosis stage. For example, we found that HRQoL was also impacted by the feeling of the entourage. In a large proportion of patients, the entourage was unaware of the CHC status or, when knowing it, felt uncomfortable. In these cases, these feelings may contribute to a sense of isolation on the part of the patient; again regardless to the fibrosis stage.
| Variable                              | Class                        | EQ5D (N = 420) | P value | VAS health (N = 416) | P value | VAS fatigue (N = 416) | P value |
|--------------------------------------|------------------------------|----------------|---------|----------------------|---------|-----------------------|---------|
| Gender                               | Male                         | 0.78 (0.73–0.82) | 0.022   | 60.9 (56.7–65.1)     | 0.512   | 50.1 (42.1–58.2)      | 0.059   |
|                                      | Female                       | 0.74 (0.69–0.78) |         | 59.6 (55.8–63.5)     |         | 55.0 (47.5–62.6)      |         |
| Age                                  | 18–49                        | 0.74 (0.70–0.79) | 0.617   | 57.8 (53.4–62.2)     | 0.155   | 53.4 (45.3–61.6)      | 0.573   |
|                                      | 50–54                        | 0.74 (0.69–0.80) |         | 57.7 (53.1–62.3)     |         | 56.2 (47.9–64.6)      |         |
|                                      | 55–59                        | 0.78 (0.73–0.83) |         | 58.6 (53.7–63.4)     |         | 52.5 (43.7–61.3)      |         |
|                                      | 60–64                        | 0.76 (0.71–0.82) |         | 62.9 (57.4–68.5)     |         | 49.8 (40.3–59.3)      |         |
|                                      | 65–70                        | 0.75 (0.69–0.81) |         | 64.3 (58.3–70.4)     |         | 50.9 (41.1–60.7)      |         |
| Place of birth                       | France                       | 0.75 (0.71–0.79) | 0.528   | 62.8 (59.2–66.3)     | 0.017   | 53.9 (46.5–61.4)      | 0.350   |
|                                      | Abroad                       | 0.76 (0.71–0.81) |         | 57.8 (53.2–62.4)     |         | 51.2 (42.8–59.6)      |         |
| Education                            | No bachelor level            | 0.74 (0.69–0.78) | 0.041   | 59.9 (55.9–63.9)     | 0.689   | 53.3 (45.5–61.1)      | 0.567   |
|                                      | Bachelor level               | 0.78 (0.73–0.82) |         | 60.7 (56.6–64.7)     |         | 51.8 (44.0–59.7)      |         |
| Work                                 | Yes                          | 0.80 (0.75–0.84) | 0.001   | 63.8 (59.5–68.0)     |         | 0.001                 |         |
|                                      | No                           | 0.72 (0.67–0.76) |         | 56.8 (52.9–60.7)     |         |                      |         |
| Fibrosis stage                       | F0–F1                        | 62.7 (58.2–67.1) | 0.039   |                      |         |                      |         |
|                                      | F2                           | 56.9 (52.3–61.5) |         |                      |         |                      |         |
|                                      | F3–F4                        | 61.2 (57.0–65.4) |         |                      |         |                      |         |
| Severe comorbidities\a               | Yes                          | 0.72 (0.67–0.77) | < .0001 | 57.7 (53.7–61.8)     | 0.008   |                      |         |
|                                      | No                           | 0.79 (0.75–0.84) |         | 62.8 (58.9–66.7)     |         |                      |         |
| Overweight\b                        | Yes                          | 0.73 (0.69–0.78) | 0.017   | 55.3 (47.6–63.1)     | 0.031   |                      |         |
|                                      | No                           | 0.78 (0.74–0.82) |         | 49.8 (41.9–57.7)     |         |                      |         |
| Psychiatric disorders                | Yes                          | 57.0 (51.2–62.7) | 0.023   | 58.3 (48.6–67.9)     | 0.004   |                      |         |
|                                      | No                           | 63.6 (60.8–66.4) |         | 46.9 (40.1–53.7)     |         |                      |         |
| Perceived progression of CHC between infection and today | Very comforting | 0.84 (0.78–0.90) | < .0001 | 71.2 (65.2–77.1) | < .0001 | 41.6 (31.4–51.8) | < .0001 |
|                                      | Rather comforting            | 0.82 (0.77–0.86) |         | 64.8 (61.2–68.4)     |         | 50.5 (43.0–58.0)      |         |
|                                      | Rather worrying              | 0.72 (0.67–0.77) |         | 54.2 (49.6–58.7)     |         | 61.1 (53.0–69.3)      |         |
|                                      | Very worrying                | 0.66 (0.59–0.73) |         | 51.0 (44.4–57.5)     |         | 57.1 (46.6–67.6)      |         |
| Need to talk with people with CHC    | Very often                   | 57.4 (38.6–76.1) | 0.027   |                      |         |                      |         |
|                                      | Often                        | 47.2 (37.9–56.6) |         |                      |         |                      |         |
|                                      | Occasionally                 | 56.7 (49.7–63.7) |         |                      |         |                      |         |
|                                      | Not at all                   | 49.1 (42.9–55.3) |         |                      |         |                      |         |

(Continued)
Our study has some limitations. First, it was conducted in only three reference centers. These were deliberately chosen to yield a geographically comprehensive representation of patients in France. Despite this limitation, patients’ characteristics were representative of CHC patients in France, with a majority of men, an average age of around 54, and two-thirds of patients with genotype 1 [30]. Second, we used the EQ-5D instrument to assess the self-reported HRQoL of patients because it is a commonly used generic measure of health that is recommended for analyzing cost-effectiveness [31,32]. However, it was reported not to be very sensitive to variations in HRQoL [32–33]. Therefore we added more sensitive measurement instruments with two visual analogue scales on overall health and fatigue. As in previous studies, the main results based on EQ-5D utility were similar to those obtained with the more sensitive VAS scores. Finally, our study took place over the year 2014; one may consider that the patients knowledge of new DAA at that time where less than today. Thus, a study conducted today may in particular result into patients with higher quality of lives.

In conclusion, factors such as the perceived progression of CHC, the need among patients to share the experience of their disease by talking with other CHC sufferers, and a patient’s entourage being uncomfortable in the knowledge of their CHC diagnosis, significantly impact HRQoL, but not the fibrosis stage. These variables should be considered when providing care to HCV patients and deciding which subgroup of patients should be treated. The presence of comorbidities, frequent in patients with HCV disease, was also associated with HRQoL. This may imply that the eradication of HCV does not necessarily improve the HRQoL of patients who continue to live with other diseases.

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Author Contributions

Conceptualization: Michaël Schwarzinger, Stanislas Pol, Hélène Fontaine, Dominique Larrey, Valérie Canva, Philippe Mathurin, Yazdan Yazdanpanah, Sylvie Deuffic-Burban.

Data curation: Sabrina Cossais.

Formal analysis: Sabrina Cossais, Michaël Schwarzinger.

Investigation: Sabrina Cossais.

Methodology: Michaël Schwarzinger, Hélène Fontaine, Dominique Larrey, Valérie Canva, Yazdan Yazdanpanah, Sylvie Deuffic-Burban.

Table 3. (Continued)

| Variable | Class | EQ5D (N = 420) | P value | VAS health (N = 416) | P value | VAS fatigue (N = 416) | P value |
|----------|-------|---------------|---------|---------------------|---------|-----------------------|---------|
| Entourage uncomfortable since their knowledge of CHC | Yes, they are uncomfortable | 57.1 (51.8–62.3) | 0.003 | 59.5 (50.4–68.7) | 0.001 |
| | No one is uncomfortable | 64.7 (61.0–68.3) | | 46.7 (39.2–54.1) | |
| | No, because nobody knows | 59.1 (54.2–64.0) | | 51.5 (42.6–60.4) | |

aDiabetes, non-liver related transplant, psychiatric disorders, drug addiction / alcohol

bBMI >25 kg/m²

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Project administration: Sabrina Cossais, Sylvie Deuffic-Burban.

Resources: Stanislas Pol, Hélène Fontaine, Dominique Larrey, Valérie Canva, Philippe Mathurin, Yazdan Yazdanpanah.

Software: Sabrina Cossais, Michaël Schwarzinger.

Supervision: Sabrina Cossais, Michaël Schwarzinger, Yazdan Yazdanpanah, Sylvie Deuffic-Burban.

Validation: Sabrina Cossais, Michaël Schwarzinger, Yazdan Yazdanpanah, Sylvie Deuffic-Burban.

Visualization: Sabrina Cossais, Sylvie Deuffic-Burban.

Writing – original draft: Sabrina Cossais, Michaël Schwarzinger, Yazdan Yazdanpanah, Sylvie Deuffic-Burban.

Writing – review & editing: Stanislas Pol, Hélène Fontaine, Dominique Larrey, Georges-Philippe Pageaux, Valérie Canva, Philippe Mathurin.

References

1. Strauss E, Dias Teixeira MC. Quality of life in hepatitis C. Liver Int. sept 2006; 26(7):755–65.

2. Miller ER, McNally S, Wallace J, Schlichtorst M. The ongoing impacts of hepatitis c—a systematic narrative review of the literature. BMC Public Health. 2012; 12:672. https://doi.org/10.1186/1471-2458-12-672 PMID: 22900973

3. Thein HH, Maruff P, Krahn MD, Kaldor JM, Koorey DJ, Brew BJ, et al. Improved cognitive function as a consequence of hepatitis C virus treatment*. HIV Med. 2007; 8(8):520–528. https://doi.org/10.1111/j.1468-1293.2007.00505.x PMID: 17944685

4. Wright M, Grieve R, Roberts J, Main J, Thomas HC. Health benefits of antiviral therapy for mild chronic hepatitis C: randomised controlled trial and economic evaluation [Internet]. Gray Publishing; 2006 [cité 15 mai 2014]. Disponible sur: http://www.hta.ac.uk/pdfexecs/summ1021.pdf

5. Siebert U, Sroczynski G, Wasem J, Greiner W, Ravens-Sieberer U, Adelsburger P, et al. Using competence network collaboration and decision-analytic modeling to assess the cost-effectiveness of interferon α-2b plus ribavirin as initial treatment of chronic hepatitis C in Germany. Eur J Health Econ. juin 2005; 6(2):112–23. https://doi.org/10.1007/s10198-005-0280-7 PMID: 15902546

6. Deuffic-Burban S, Deltenre P, Buti M, Stroffolini T, Parkes J, Mühberger N, et al. Predicted effects of treatment for HCV infection vary among European countries. Gastroenterology. oct 2012; 143(4):974–985.e14. https://doi.org/10.1053/j.gastro.2012.05.054 PMID: 22863764

7. Dan AA, Kallman JB, Srivastava R, Younoszai Z, Kim A, Younossi ZM. Impact of chronic liver disease and cirrhosis on health utilities using SF-6D and the health utility index. Liver Transpl. mars 2008; 14(3):321–6. https://doi.org/10.1002/lt.21376 PMID: 18306365

8. Thein H-H, Krahn M, Kaldor JM, Dore GJ. Estimation of utilities for chronic hepatitis C from SF-36 scores. Am J Gastroenterol. mars 2005; 100(3):643–51. https://doi.org/10.1111/j.1572-0241.2005.40976.x PMID: 15743364

9. El Khoury AC, Vietri J, Prajapati G. The burden of untreated hepatitis C virus infection: a US patients’ perspective. Dig Dis Sci. nov 2012; 57(11):2995–3003. https://doi.org/10.1007/s10620-012-2233-1 PMID: 22674399

10. Vietri J, Prajapati G, El Khoury AC. The burden of hepatitis C in Europe from the patients’ perspective: a survey in 5 countries. BMC Gastroenterol. 2013; 13:16. https://doi.org/10.1186/1471-230X-13-16 PMID: 23324473

11. Pol S, Chevalier J, Branchoux S, Perry R, Milligan G, Gaudin A-F. P0747: Health related quality of life and utility values in chronic hepatitis C patients: A cross-sectional study in France, the UK and Germany. J Hepatol. 1 avr 2015; 62:S06.

12. Dalgaard O, Egeland A, Skaug K, Villimas K, Steen T. Health-related quality of life in active injecting drug users with and without chronic hepatitis C virus infection. Hepatology. janv 2004; 39(1):74–80.

13. Zickmund S, Ho EY, Masuda M, Ippolito L, LaBrecque DR. « They treated me like a leper ». Stigmatization and the quality of life of patients with hepatitis C. J Gen Intern Med. oct 2003; 18(10):835–44. https://doi.org/10.1046/j.1525-1497.2003.20826.x PMID: 14521647
14. Chong CAKY, Gulamhussein A, Heathcote EJ, Lilly L, Sherman M, Naglie G, et al. Health-state utilities and quality of life in hepatitis C patients. Am J Gastroenterol. mars 2003; 98(3):630–8. PMID: 12650799

15. Hsu PC, Krajdén M, Yoshida EM, Anderson FH, Tomlinson GA, Krahn MD. Does cirrhosis affect quality of life in hepatitis C virus-infected patients? Liver Int. mars 2009; 29(3):449–58. https://doi.org/10.1016/j.liver.2008.11.010 PMID: 19267865

16. Hsu PC, Federico CA, Krajdén M, Yoshida EM, Bremner KE, Anderson FH, et al. Health utilities and psychometric quality of life in patients with early- and late-stage hepatitis C virus infection: Quality of life in HCV infection. J Gastroenterol Hepatol. janv 2012; 27(1):149–57. https://doi.org/10.1111/j.1440-1746.2011.06813.x PMID: 21679248

17. Schwarzsinger M, Dewedaw S, Rekaciewicz C, Abd Elaziz KM, Fontanet A, Carrat F, et al. Chronic hepatitis C virus infection: does it really impact health-related quality of life? A study in rural Egypt. Hepatol Baltim Md. de ´ c 2004; 40(6):1434–41.

18. Rodger AJ, Jolley D, Thompson SC, Lanigan A, Crofts N. The impact of diagnosis of hepatitis C virus on quality of life. Hepatology. 1999; 30(5):1299–1301. https://doi.org/10.1002/hep.510300504 PMID: 10534353

19. Evon DM, Simpson KM, Esserman D, Verma A, Smith S, Fried MW. Barriers to accessing care in patients with chronic hepatitis C: the impact of depression. Aliment Pharmacol Ther. janv 2012; 34(3):205–17. https://doi.org/10.1111/j.1365-2036.2011.04460.x PMID: 21039678

20. Pavlović Z, Delić D, Marić NP, Vuković O, Jašović-Gašić M. Depressive symptoms in patients with hepatitis C treated with pegylated interferon alpha therapy: a 24-week prospective study. Psychiatr Danub. déc 2011; 23(4):370–7. PMID: 22075738

21. Likert R. A technique for the measurement of attitudes. Arch Psychol. 1932; 22:140.

22. Ewing JA. Detecting alcoholism. The CAGE questionnaire. JAMA. 12 oct 1984; 252(14):1905–7. PMID: 6471323

23. Chevalier J, Pouvoüville G. Valuing EQ-5D using Time Trade-Off in France. Eur J Health Econ. févr 2013; 14(1):57–66. https://doi.org/10.1007/s10198-011-0351-x PMID: 21935715

24. Brooks R, Group E. EuroQol: the current state of play. Health policy. 1996; 37(1):53–72. PMID: 11190005

25. Kleinman L, Zodet M, Hakim Z, Aledort J, Barker C, Chan K, et al. Psychometric evaluation of the fatigue severity scale for use in chronic hepatitis C. Quality of Life Research. 2000; 9(5):499–508. PMID: 11190005

26. Hussain KB, Fontana RJ, Moyer CA, Su GL, Sneed-Pee N, Lok AS. Comorbid illness is an important determinant of health-related quality of life in patients with chronic hepatitis C. Am J Gastroenterol. sept 2001; 96(9):2737–44. https://doi.org/10.1111/j.1572-0241.2001.04133.x PMID: 11569704

27. Kuwashiro T, Mizuta T, Kawaguchi Y, Iwane S, Takahashi H, Oza N, et al. Impairment of health-related quality of life in patients with chronic hepatitis C is associated with insulin resistance. J Gastroenterol. 16 mars 2013; 49(2):317–23. https://doi.org/10.1007/s00535-013-0781-6 PMID: 23503838

28. Afsar B, Elsurer R, Sezer S, Ozdemir NF. Quality of life in hemodialysis patients: hepatitis C virus infection makes sense. Int Urol Nephrol. déc 2009; 41(4):1011–9. https://doi.org/10.1007/s11255-009-9576-3 PMID: 19430922

29. Chen EY, North CS, Fatunde O, Bernstein I, Salari S, Day B, et al. Knowledge and attitudes about hepatitis C virus (HCV) infection and its treatment in HCV mono-infected and HCV/HIV co-infected adults. J Viral Hepat. oct 2013; 20(10):708–14. https://doi.org/10.1111/jvhe.12095 PMID: 24010645

30. Dhumeaux D. Prise en charge des personnes infectées par les virus de l’hépatite B ou de l’hépatite C: rapport de recommandations 2014 [Internet]. 2014 [cité 19 févr 2017]. Disponible sur: http://search.elsevier.com/login.aspx?direct=true&scope=site&db=nlebk&db=nlabk&Jid=AN&doi=811786

31. Torrance GW. Measurement of health state utilities for economic appraisal. J Health Econ. mars 1986; 5(1):1–30.

32. Grieve R, Grishchenko M, Cairns J. SF-6D versus EQ-5D: reasons for differences in utility scores and impact on reported cost-utility. Eur J Health Econ HEPAC Health Econ Prev Care. févr 2009; 10(1):15–23.

33. Chevalier J. Mesure de l’utilité attachée aux états de santé: valorisation de l’indice d’utilité EQ-5D et évolution de l’échelle actuelle en France. Measurement of health state utilities: Valuation of the EQ-5D and improvement of the descriptive system in the French context [Internet]. févr 2010 [cité 2 févr 2016]. Disponible sur: https://basepub.dauphine.fr/handle/123456789/5598