META-ANALYSIS

Current standard values of health utility scores for evaluating cost-effectiveness in liver disease: A meta-analysis

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Abstract

BACKGROUND
Health utility assessments have been developed for various conditions, including chronic liver disease. Health utility scores are required for socio-economic evaluations, which can aid the distribution of national budgets. However, the standard health utility assessment scores for specific health conditions are largely unknown.
AIM
To summarize the health utility scores, including the EuroQOL 5-dimensions 5-levels (EQ-5D-5L), EuroQol-visual analogue scale, short from-36 (SF-36), RAND-36, and Health Utilities Index (HUI)-Mark2/Mark3 scores, for the normal population and chronic liver disease patients.

METHODS
A systematic literature search of PubMed and MEDLINE, including the Cochrane Library, was performed. Meta-analysis was performed using the RevMan software. Multiple means and standard deviations were combined using the StatsToDo online web program.

RESULTS
The EQ-5D-5L and SF-36 can be used for health utility evaluations during antiviral therapy for hepatitis C. HUI-Mark2/Mark3 indicated that the health utility scores of hepatitis B patients are roughly 30% better than those of hepatitis C patients.

CONCLUSION
The EQ-5D-5L is the most popular questionnaire for health utility assessments. Health assessments that allow free registration would be useful for evaluating health utility in patients with liver disease.

Key Words: Quality of life; EuroQOL 5-dimensions 5-levels; Short from-36; RAND-36; Health Utilities Index-Mark

INTRODUCTION
The quality of health is an important factor when assessing medical management rather than simple survival periods[1,2]. Health utility is an important factor in medical assessments and socio-economic politics[3]. National health budgets have risen steadily in various countries, and governments need to deeply consider the need to maintain a socio-economic balance[4]. Therefore, health benefits should be compared with social costs to avoid national financial collapse.

It is difficult to quantify health quality at regular intervals[5]. We are developing wearable devices that can automatically obtain health data, including data regarding mental health. Some health utility assessments require the use of questionnaires, which are associated with low compliance and involve bothersome calculations[2,6,7]. Before launching our novel health utility assessment tool, we performed this meta-analysis in order to summarize the currently available health utility assessment tools. The most useful questionnaire for evaluating health status depending on liver disease status or sex is unclear. In addition, no universal health utility assessment values for specific liver diseases or the normal population have been reported. Therefore, we conducted a meta-analysis to estimate health utility assessment values for specific populations.

The EuroQOL 5-dimensions 5-levels (EQ-5D-5L) is the simplest instrument for evaluating health utility and has been widely translated into various languages with high reliability and validity[6,8-10]. It only involves five questions and five answering levels. The health utility scores produced by the EQ-5D-5L can be used to calculate quality-adjusted life year (QALY) values[8]. The Health Utilities Index Mark 2/Mark 3 is another instrument for evaluating health utility scores and can also be used to obtain QALY values[11]. However, the Health Utilities Index is complicated, as it involves 45 questions, which take a long time to answer. The short-form 36-item (SF-36) is also widely used to evaluate health quality, although it does not directly involve QALY evaluations[9,12,13].
There are two types of SF-36, and the copyrights to these tools belong to The RAND Corporation (Santa Monica, CA, United States)[14] and QualityMetric (Johnston, RI, United States), respectively[15]. However, most researchers do not actively consider which version they use[12]. Therefore, the exact method and results of such assessments are not always described in the literature (Table 1).

In this meta-analysis, we describe the scores obtained with various health utility indexes (HUIs) in normal healthy populations or patients with different types of liver disease (Table 2)[16-32].

**MATERIALS AND METHODS**

**Literature search**
The PICOS scheme was used to set appropriate inclusion criteria. A systematic literature search of PubMed and MEDLINE, including the Cochrane Library, was performed independently by two authors (Ishunuki T and Ota S). The search was limited to human studies whose findings were reported in English. No restrictions were placed on the type of publication, the publication date, or publication status. The search strategy was based on different combinations of words for each database. For the PubMed database, the following combination was used: (("liver"[MeSH Terms] OR "liver"[All Fields] OR "livers"[All Fields] OR "liver s"[All Fields]) AND "qol"[All Fields]) AND (1990/1/1:3000/12/12[pdat]). For the MEDLINE database, the following combination was used: [quality of life (QOL) and Liver].

**Study selection**
The two independent authors screened the titles and abstracts of the primary studies identified in the database search. Duplicate studies were excluded. The following inclusion criteria were employed for the meta-analysis: (1) Studies that compared QOL in patients who had liver disease; (2) Studies that compared QOL between male and female patients with liver disease; (3) Studies that reported at least one QOL outcome; and (4) If the same institute reported more than one study, only the most recent or the highest-level study was included.

**Data extraction**
The same two authors extracted the following primary data: (1) The questionnaires used for each QOL evaluation; (2) The first author, year of publication, and type of study; (3) The etiology of the disease and the number of times each intervention was performed; and (4) The timing of the evaluations.

**Statistical analysis**
Meta-analyses were performed using the RevMan software (version 5.3.; The Cochrane Collaboration). The mean differences (MD) between groups were calculated for continuous variables. The interquartile ranges of the data were transformed by dividing them by 1.35 to produce alternative standard deviation values. Multiple means and standard deviations were combined using the StatsToDo online web program (https://www.statstodo.com/index.php).

The chi-square test was used to evaluate heterogeneity, and the Cochran $Q$ and $I^2$ statistics were reported. The $I^2$ value describes the percentage variation between studies in degrees of freedom. $P$ values of <0.05 were considered significant.

**RESULTS**

**EQ-5D-5L**
The EQ-5D-5L has been widely investigated as a tool for evaluating general health in normal populations and patients with different stages of liver disease (Table 3)[17,18,22,25-27,30,32]. Health utility indices should be affected by age, sex, ethics, religion, and geography. However, the EQ-5D-5L produced similar utility indices for groups with different health statuses (Table 3), such as normal healthy individuals (0.8413 ± 0.1905) and hepatitis C virus (HCV)-infected patients with compensated or decompensated cirrhosis (0.8113 ± 0.2261 and 0.7903 ± 0.2182), HCV-infected patients exhibiting a sustained virologic response (SVR) (0.846 ± 0.1816), and patients with hepatocellular carcinoma 0.8127 ± 0.2084).

In general, the EQ-5D-5L produces significantly higher scores in males than in females (Figure 1A) (0.8267 ± 0.229 vs 0.7922 ± 0.239; $P$ < 0.001). The mean total EuroQol-visual analogue scale score for the general population was found to be 79.796 ± 17.614 in two independent studies (Table 4)[26,30].

**SF-36**
The SF-36 consists of eight scales, including physical functioning (85.07 ± 15.40); role limitations due to physical health problems (RP)(82.50 ± 25.15); bodily pain (BP) (77.62 ± 17.55); general health perceptions...
Table 1 Current health-related outcome for liver disease

| Questionnaire                        | Total Permission | Company/Organization                      |
|--------------------------------------|------------------|-------------------------------------------|
| EQ-5D-5L                             | Five questions   | The EuroQol Research Foundation.          |
| Health Utilities Index Mark 2 or 3   | 45 questions     | Health Utilities Inc.                      |
| 36-Item Short Form Survey            | 36 questions     | QualityMetric                             |
|                                      | Free             | The RAND Corporation                       |

Table 2 List of previous studies and health utility assessments

| Ref.                  | Subjects and countries                        | EQ-5D-5L | EQ-VAS | HUI-mark | SF-36 | Type of SF-36 | Others  |
|-----------------------|------------------------------------------------|----------|--------|----------|-------|---------------|---------|
| Jenkinson et al[16]   | Normal population from United Kingdom          | O        | Δ      | Δ        | O     | RAND®         |         |
| Ratcliffe et al[17]   | Normal population/Liver transplantation patients from United Kingdom | Δ        | Δ      | Δ        | O     | Not described |         |
| Chong et al[18]       | Normal population from Canada                  | O        | Δ      | Δ        | Δ 1   |               |         |
| Grieve et al[19]      | Population from United Kingdom                | O        | Δ      |           |       |               |         |
| Bondini et al[20]     | Population from United States                 |          | Δ 1   |           | CLDQ  |               |         |
| Dan et al[21]         | Population from United States                 | O        |       |           |       |               |         |
| Björnsson et al[22]   | Population from Sweden                         | O        |       |           |       | SF-6D         |         |
| Hsu et al[23]         | Population from Vancouver                      | O        |       |           |       | v2            | HQLQv2  |
| McDonald et al[24]    | Population from United Kingdom                 | O        | Δ      |           |       |               |         |
| Scalone et al[25]     | Population from United Kingdom                 | O        | Δ      |           |       |               |         |
| Vahidnia et al[26]    | Population from United States                  | O        | Δ      |           |       |               |         |
| Kaishima et al[27]    | Population from Japan                          | O        | Δ      |           |       |               |         |
| Blanco et al[28]      | Population from Spain                          | O        | Δ      |           |       |               |         |
| Kesen et al[29]       | HCV patients from Turkey                       | O        |       |           |       | Not described | HADS    |
| Cortesi et al[30]     | Population from Italy                          | O        |       |           |       |               | HADS    |
| Karimi Sari et al[31] | HCV patients from Iran                         | O        |       |           |       | Not described |         |
| Zanone et al[32]      | HCV patients from Italy                        | O        |       |           |       |               |         |

1Modified scale excluding from the analyses.
O: The eligible study including the analyses; Δ: The excluding outcomes due to different conditions; EQ-5D-5L: EuroQol 5-dimensions 5-levels; EQ-VAS: EuroQol-visual analogue scale; HUI-mark: Health utility index mark; SF-36: Short form-36; CLDQ: Chronic liver disease questionnaire; SF-6D: Short form 6-dimensions; HQLQv2: Hepatitis Quality of Life® survey version 2; HADS: Hospital anxiety and depression scale; HCV: Hepatitis C virus.

Modified scale excluding from the analyses. O: The eligible study including the analyses; Δ: The excluding outcomes due to different conditions; EQ-5D-5L: EuroQol 5-dimensions 5-levels; EQ-VAS: EuroQol-visual analogue scale; HUI-mark: Health utility index mark; SF-36: Short form-36; CLDQ: Chronic liver disease questionnaire; SF-6D: Short form 6-dimensions; HQLQv2: Hepatitis Quality of Life® survey version 2; HADS: Hospital anxiety and depression scale; HCV: Hepatitis C virus.

(GH) (63.37 ± 14.16); vitality, energy, or fatigue (VT) (63.37 ± 14.16); social functioning (SF) (86.97 ± 15.13); role limitations due to emotional problems (RE) (83.94 ± 23.57); and general mental health (63.37 ± 14.16). Although the eligible healthy controls differed among countries and age groups, the health utility scores produced by each scale were similar (Table 5) [16,17,22,23].

**Compensated liver cirrhosis vs sustained virologic response**

Patients with hepatitis C had achieved an SVR exhibited significantly better health utility scores for each SF-36 scale (Figure 2) [22,29,31] and the EQ-5D-5L (Figure 1B) [18,19,22,32] than those with compensated liver cirrhosis (Table 6) [18,19,22,29,31,32]. In particular, significant differences in the scores for RP (61.5 ± 31.6 vs 73.3 ± 27.3), GH (64.8 ± 20.9 vs 74.8 ± 18.5), VT (70.5 ± 24.0 vs 78.1 ± 18.4), RE (56.8 ± 32.0 vs 68.1 ± 27.3), and the EQ-5D-5L (0.6863 ± 0.3065 vs 0.846 ± 0.1816) were seen between these groups. These results indicate that health utility indices improve by 10%-20% after patients with hepatitis C achieve an SVR.
### Table 3 EuroQol 5-dimensions 5-levels

| Ref. | Total | Mean  | SD  |
|------|-------|-------|-----|
| Normal healthy individuals | | | |
| Ratcliffe et al[17] | 3386 | 0.85 | 0.03 |
| Chong et al[18] | 1518 | 0.821 | 0.011 |
| Björnsson et al[22] | 2953 | 0.819 | 0.217 |
| Vahidnia et al[26] | 1565 | 0.94 | 0.1 |
| Cortesi et al[30] | 6800 | 0.915 | 0.107 |
| Total | 42622 | 0.8413 | 0.1905 |
| Compensated cirrhosis with hepatitis C | | | |
| Chong et al[18] | 24 | 0.74 | 0.085 |
| Grieve et al[19] | 40 | 0.55 | 0.34 |
| Björnsson et al[22] | 76 | 0.749 | 0.212 |
| Scalone et al[25] | 222 | 0.736 | 0.259 |
| Kaishima et al[27] | 20 | 0.824 | 0.106 |
| Cortesi et al[30] | 574 | 0.891 | 0.119 |
| Zanone et al[32] | 94 | 0.68 | 0.37 |
| Total | 1050 | 0.8113 | 0.2261 |
| Decompensated cirrhosis with hepatitis C | | | |
| Chong et al[18] | 9 | 0.66 | 0.2 |
| Grieve et al[19] | 64 | 0.45 | 0.24 |
| Björnsson et al[22] | 53 | 0.565 | 0.266 |
| Kaishima et al[27] | 4 | 0.524 | 0.25 |
| Cortesi et al[30] | 523 | 0.859 | 0.14 |
| Total | 653 | 0.7903 | 0.2182 |
| Sustained virologic response | | | |
| Chong et al[18] | 36 | 0.83 | 0.065 |
| Grieve et al[19] | 24 | 0.82 | 0.21 |
| Björnsson et al[22] | 52 | 0.792 | 0.209 |
| Zanone et al[32] | 91 | 0.89 | 0.18 |
| Total | 203 | 0.846 | 0.1816 |
| Hepatocellular carcinoma | | | |
| Chong et al[18] | 15 | 0.65 | 0.21 |
| Grieve et al[19] | 64 | 0.45 | 0.24 |
| Scalone et al[25] | 85 | 0.777 | 0.241 |
| Kaishima et al[27] | 14 | 0.75 | 0.057 |
| Cortesi et al[30] | 545 | 0.867 | 0.146 |
| Total | 723 | 0.8127 | 0.2084 |

**HUI Mark-2/Mark-3**

Hepatitis B and C are the main causes of viral-associated chronic liver disease (Figure 3)[20,21]. The health utility scores of hepatitis B patients were significantly better than those of hepatitis C patients (0.6312 ± 0.2867 vs 0.8186 ± 0.1886); i.e., there was a roughly 30% difference between the scores of these patients.
**Table 4** EuroQol-visual analogue scale in normal healthy individuals

| Ref.          | Total | Mean  | SD   |
|---------------|-------|-------|------|
| Vahidnia et al[26] | 1565  | 87.6  | 10.6 |
| Cortesi et al[30]   | 6800  | 78    | 18.4 |
| Total            | 8365  | 79.796| 17.614|

**Figure 1** EuroQOL 5-dimensions 5-levels. A: Men vs women; B: Compensated liver cirrhosis vs sustained virologic response. EQ-5D-5L: EuroQol 5-dimensions 5-levels.

**DISCUSSION**

Which HUI should be used for normal populations or patients with chronic liver disease?

In this meta-analysis, we summarized the findings of previous studies examining health utility evaluations in patients with chronic liver disease. Various questionnaires have been used to evaluate health utility in different populations at different times. The EQ-5D-5L is the most popular of the questionnaires used to examine health utility scores internationally[17].

One of the concerns regarding the application of health utility scores is their sensitivity[33]. For example, the health utility scores produced by the EQ-5D-5L for patients with compensated cirrhosis and decompensated cirrhosis did not differ significantly (Table 3). On the other hand, the health utility scores for hepatitis C patients with compensated liver cirrhosis and those who achieved an SVR differed significantly according to both the SF-36 and EQ-5D-5L (Table 6). This indicated that both questionnaires are suitable for evaluating health utility in hepatitis C patients after viral elimination. Although the health utility scores derived from the EQ-5D-5L were calculated from 5 questions, the score range of the EQ-5D-5L (123.3%) was greater than that of the SF-36 (105.8%-119.2%). Therefore, the EQ-5D-5L could be suitable for evaluating health utility scores in this specific disease state. On the other hand, EQ-5D-5L-derived health utility scores are based on only five personal factors, mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Therefore, their sensitivity and any ceiling effects should be validated in each language and ethnic group.

It is well known that the prevailing subtype of viral hepatitis differs depending on the geographic region[34]. Hepatitis B is the prevailing subtype in East Asia[13], whereas hepatitis C is the most common in Western countries[35]. Both types of hepatitis can be controlled by nucleic acid analogs[36]. In this meta-analysis, the HUI scores of hepatitis C patients were roughly 30% lower than those of hepatitis B patients. The differences between hepatitis B and hepatitis C need to be investigated using the EQ-5D-5L and SF-36 in future.

The second concern regarding the use of questionnaires for health assessments relates to the number of questions in each questionnaire. The EQ-5D-5L consists of only five questions[5], whereas the other tools consist of 36[14-16] or 45[11] questions. The number of questions affects study compliance, especially in the elderly[37]. If possible, the number of questions should be minimized.
## Table 5: Short form-36: Healthy controls

| Ref.                | Total | Mean | SD  |
|---------------------|-------|------|-----|
| **Physical function** |       |      |     |
| Björnsson et al[22] | 339   | 87   | 19  |
| Jenkinson et al[16] M 60 | 681  | 80   | 22.1|
| Jenkinson et al[16] W 60 | 684  | 74.8 | 23.5|
| Ratcliffe et al[17] | 8883  | 85.4 | 2.55|
| Hsu et al[23]      | 9367  | 85.8 | 20  |
| Total               | 19954 | 85.07| 15.40|
| **Role physical**   |       |      |     |
| Björnsson et al[22] | 339   | 82   | 32  |
| Jenkinson et al[16] M 60 | 717  | 78.8 | 36.1|
| Jenkinson et al[16] W 60 | 757  | 76.8 | 36.9|
| Ratcliffe et al[17] | 9151  | 83.7 | 4.4 |
| Hsu et al[23]      | 9367  | 82.1 | 33.2|
| Total               | 20331 | 82.50| 25.15|
| **Body pain**       |       |      |     |
| Björnsson et al[22] | 339   | 72   | 27  |
| Jenkinson et al[16] M 60 | 724  | 78.8 | 23.6|
| Jenkinson et al[16] W 60 | 779  | 75   | 25.1|
| Ratcliffe et al[17] | 9214  | 80   | 3.05|
| Hsu et al[23]      | 9367  | 75.6 | 23  |
| Total               | 20423 | 77.62| 17.55|
| **General health**  |       |      |     |
| Björnsson et al[22] | 339   | 68   | 24  |
| Jenkinson et al[16] M 60 | 707  | 62.9 | 20.3|
| Jenkinson et al[16] W 60 | 763  | 59   | 21.4|
| Ratcliffe et al[17] | 9089  | 61.1 | 2.75|
| Hsu et al[23]      | 9367  | 65.8 | 18  |
| Total               | 20265 | 63.37| 14.16|
| **Vitality, energy, fatigue** | | | |
| Björnsson et al[22] | 339   | 68   | 24  |
| Jenkinson et al[16] M 60 | 707  | 62.9 | 20.3|
| Jenkinson et al[16] W 60 | 763  | 59   | 21.4|
| Ratcliffe et al[17] | 9089  | 61.1 | 2.75|
| Hsu et al[23]      | 9367  | 65.8 | 18  |
| Total               | 20265 | 63.37| 14.16|
| **Social function** |       |      |     |
| Björnsson et al[22] | 339   | 88   | 21  |
| Jenkinson et al[16] M 60 | 729  | 86.9 | 22.6|
| Jenkinson et al[16] W 60 | 783  | 85.9 | 22.6|
| Ratcliffe et al[17] | 9219  | 87.8 | 2.8 |
| Hsu et al[23]      | 9367  | 86.2 | 19.8|
The last concern is about gaining permission to use such questionnaires for health utility assessments. It takes great effort to develop a questionnaire. However, health utility assessments need to be repeated continuously. In certain human health emergencies, the use of some vaccines has been allowed without patent royalties having to be paid[38]. Commercial companies that own the rights to health assessments should reconsider their policies regarding their use.

**CONCLUSION**

Health assessments that allow free registration would be useful for evaluating health utility in patients with liver disease. Alternatively, a portable QOL tracker could be used to perform QOL evaluations of any patient-reported outcome, and we are currently developing such a tracker.
Ishinuki T et al. Health utility scores in liver disease

Figure 2 Short from-36: Compensated liver cirrhosis vs sustained virologic response. A: Physical function; B: Role physical; C: Body pain; D: General health; E: Vitality; F: Social function; G: Role emotional; H: Mental health.

Figure 3 Health Utilities Index-Mark2 or 3: Hepatitis C vs hepatitis B. HUI: Health Utilities Index.

ARTICLE HIGHLIGHTS

Research background
The most useful questionnaire for evaluating health status depending on liver disease status or sex is unclear.

Research motivation
No universal health utility assessment values for specific liver diseases or the normal population have been reported.

Research objectives
The objective of this study was to conduct a meta-analysis to estimate health utility assessment values for specific populations in the liver disease.

Research methods
A systematic literature search was performed using PubMed and MEDLINE, including the Cochrane Library.

Research results
The short from-36 and EuroQOL 5-dimensions 5-levels (EQ-5D-5L) can be used for health utility evaluations during antiviral therapy for hepatitis C.

Research conclusions
The EQ-5D-5L is the most popular questionnaire for health utility assessments. Health assessments that allow free registration would be useful for evaluating health utility in patients with liver disease.

Research perspectives
Alternatively, a portable quality of life (QOL) tracker could be used to perform QOL evaluations of any patient-reported outcome in future.
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FOOTNOTES

Author contributions: Ishinuki T and Ota S conceptualized and designed the review; Ishinuki T, Harada K, Kawamoto M, and Meguro M searched for and screened the articles; Kutomi G, Tsutumi H, Harada K, and Kato T assessed the articles for eligibility; Miyanishi K and Ohyanagi T carried out the statistical analyses; Hui TT and Mizuguchi T drafted the initial manuscript; Mizuguchi T finalized the manuscript; and all of the authors reviewed and approved the final manuscript as submitted.

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