Health-Related Quality of Life in Patients With Different Diseases Measured With the EQ-5D-5L: A Systematic Review

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Background: The EQ-5D-5L is a generic preference-based questionnaire developed by the EuroQol Group to measure health-related quality of life (HRQoL) in 2005. Since its development, it has been increasingly applied in populations with various diseases and has been found to have good reliability and sensitivity. This study aimed to summarize the health utility elicited from EQ-5D-5L for patients with different diseases in cross-sectional studies worldwide.

Methods: Web of Science, MEDLINE, EMBASE, and the Cochrane Library were searched from January 1, 2012, to October 31, 2019. Cross-sectional studies reporting utility values measured with the EQ-5D-5L in patients with any specific disease were eligible. The language was limited to English. Reference lists of the retrieved studies were manually searched to identify more studies that met the inclusion criteria. Methodological quality was assessed with the Agency for Health Research and Quality (AHRQ) checklist. In addition, meta-analyses were performed for utility values of any specific disease reported in three or more studies.

Results: In total, 9,400 records were identified, and 98 studies met the inclusion criteria. In the included studies, 50 different diseases and 98,085 patients were analyzed. Thirty-five studies involving seven different diseases were included in meta-analyses. The health utility ranged from 0.31 to 0.99 for diabetes mellitus [meta-analysis random-effect model (REM): 0.83 (95% CI = 0.77–0.90); fixed-effect model (FEM): 0.93 (95% CI = 0.93–0.93)]; from 0.62 to 0.90 for neoplasms [REM: 0.75 (95% CI = 0.68–0.82); FEM: 0.80 (95% CI = 0.78–0.81)]; from 0.56 to 0.85 for cardiovascular disease [REM: 0.77 (95% CI = 0.75–0.79); FEM: 0.76 (95% CI = 0.75–0.76)]; from 0.31 to 0.78 for multiple sclerosis [REM: 0.56 (95% CI = 0.47–0.66); FEM: 0.67 (95% CI = 0.66–0.68)]; from 0.68 to 0.79 for chronic obstructive pulmonary disease [REM: 0.75 (95% CI = 0.71–0.80); FEM: 0.76 (95% CI = 0.75–0.77)]; from 0.65 to 0.90 for HIV infection [REM: 0.84 (95% CI = 0.80–0.88); FEM: 0.81 (95% CI = 0.80–0.82)]; from 0.37 to 0.89 for chronic kidney disease [REM: 0.70 (95% CI = 0.48–0.92); FEM: 0.76 (95% CI = 0.74–0.78)].
**Background**

As a quantitative indicator of health-related quality of life (HRQoL), the health utility reflects people's preference for a given health state. The health utility is measured on a scale from zero to one, where zero represents death and one represents full health (1). The worse the perception of the health status is, the lower the utility value. It can be a negative value when a health state is perceived as being worse than death. There are several preference-based measurement tools for health utility, such as the EuroQol 5 dimensions (EQ-5D) family of instruments (2), the Short Form-6 Dimensions (SF-6D) (3), and the Health Utilities Index (HUI) (4). Health utility can be used as quality-of-life weight to calculate QALYs in cost-utility analysis (CUA). Thus, health utility plays an important role not only in the measurement of HRQoL but also in health economics evaluations (5, 6).

The EQ-5D, developed by the European Quality of Life Group (EuroQol Group), is currently one of the most widely used questionnaires in HRQoL research (7). The original version of the EQ-5D was introduced in 1990 and contains five dimensions: Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression (2). For each dimension, there were three levels to describe the severity, namely, have no problems, have some problems, and have extreme problems, which could describe 243 different health states (2). However, there may be some issues when using the EQ-5D-3L to detect small changes in mild conditions, and the EQ-5D-3L had obvious ceiling effects (8). Therefore, in 2005, the EuroQol Group developed a new version of the EQ-5D based on the same five dimensions but with five rather than three severity levels (EQ-5D-5L); this instrument could detect 3,125 unique health states (8). Published studies have shown that compared with the EQ-5D-3L, the EQ-5D-5L was significantly more sensitive, with reduced ceiling effects (9, 10).

To derive health utility from the responses on the EQ-5D instruments, country-specific value sets need to be estimated (11). Since 2016, more than 20 countries and regions have published standard EQ-5D-5L value sets (Europe: 9; Asia: 9; Americas: 3; Africa: 1) (12). In 2012, before any standard EQ-5D-5L value set was established, van Hout et al. (13) developed a crosswalk project to map the EQ-5D-5L to the EQ-5D-3L, enabling researchers to obtain a crosswalk value set for the EQ-5D-5L based on published EQ-5D-3L standard value sets. Besides that, the psychometric properties of the EQ-5D-5L have been validated in both general and disease populations (12).

**Conclusions:** EQ-5D-5L is one of the most widely used preference-based measures of HRQoL in patients with different diseases worldwide. The variation of utility values for the same disease was influenced by the characteristics of patients, the living environment, and the EQ-5D-5L value set.

**Systematic Review Registration:** https://www.crd.york.ac.uk/PROSPERO/, identifier CRD42020158694.

**Keywords:** HRQoL, health utility, EQ-5D-5L, disease, EuroQol

**Method**

**Search Strategy and Study Inclusion Criteria**

This systematic review and meta-analysis was performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (16). The protocol was registered on PROSPERO with ID CRD42020158694 (https://www.crd.york.ac.uk/PROSPERO/). Literature searches were conducted in Medline via Ovid, Embase via Ovid, The Cochrane Library, and Web of Science from January 2012 to October 2019 with combinations of the following search terms: "quality of life," “QoL,” “HRQoL,” “HRQL,” “EQ-5D,” “EQ-5D-5L,” “five level,” “EuroQol,” “five dimensions,” “randomized controlled trial,” “RCT,” and “diseases” (details in Supplementary Table 1).

According to the selection criteria, all studies were original cross-sectional studies reporting EQ-5D-5L utilities for any specific disease with or without comorbidities and using country-specific value sets or the crosswalk method (mapping from EQ-5D-3L). Due to the lack of EQ-5D-5L standard value sets in many countries, the crosswalk method is the most important value set to calculate utility measured by EQ-5D-5L. In addition, the crosswalk method is recommended by the National Institute for Health and Care Excellence (NICE) to perform CUA when EQ-5D-5L is used to measure health outcomes in England. Therefore, it is useful and necessary to include these articles in this review. Studies reported that multiple utility values using value sets from different countries in the same published article were also included. The language of publication was limited to English. This review excluded reviews, protocols, or abstracts;
studies focused on the general population; longitudinal studies or effects evaluation studies of different interventions; studies that reported only synthetic utilities of multiple diseases, non-EQ-5D-5L utilities, or no utilities; and studies unrelated to HRQoL.

Data Collection and Quality Assessment
After removing duplicates, title and abstract screening was conducted by two authors independently. Following the application of the selection criteria, all eligible studies with full-texts were read, and the relevant references were checked manually. Two researchers independently collected the data using a predesigned data extraction table, including author, publication year, country or region, sample size, disease type, mean age, health utility, EQ-5D VAS score, proportions with problems in the five dimensions, value set, and administration method (i.e., face-to-face, telephone survey). When there was any discrepancy between the two researchers, it was resolved by discussion.

Quality assessment was conducted with the 11-item cross-sectional research checklist developed by the Agency for Healthcare Research and Quality (AHRQ) (17). According to the description in the study and the AHRQ checklist, the reviewer selects one of three options (“Yes,” “No,” and “Unclear”) for each item. “Yes” was assigned one point, while “No” or “Unclear” was assigned zero points. The quality level of each study was determined by summing all the item scores. For each assessed study, 0–3 points indicated low quality, 4–7 points indicated moderate quality, and 8–11 points indicated high quality.

Statistical Analysis
This review involved the analysis of the range of mean health utility values of the overall sample (or subgroups when there is no overall utility value reported) among different studies and value sets used in each study for a specific disease with or without comorbidities. In addition, this study reports the ranges in mean EQ-VAS scores and responses on each dimension of the EQ-5D-5L.

Meta-analysis was performed to synthesize utility data when three or more studies reported utility values and standard error/deviation for a specific disease. For any study that reported multiple utility values for the same sample using different EQ-5D-5L value sets, the average value or the utility calculated by using a local country-specific value set was applied in meta-analysis. Heterogeneity was assessed with the $I^2$ statistic. Random-effect (DerSimonian–Laird estimator method) and fixed-effect (inverse variance method) models were both used to calculate the pooled utility for a specific disease. Sensitivity analysis was conducted by removing EQ-5D-5L utility values derived from crosswalk value sets. All analyses were performed with R (version 4.0.5).

RESULTS
A total of 9,500 articles were identified from the four databases, and four additional studies were obtained from the manual search. After eliminating duplicates, 6,409 documents were screened to assess eligibility, of which 98 articles (15, 16, 18–113) were finally included in qualitative analyses and 35 studies were included in meta-analyses (Figure 1). Those 98 articles involved 98,085 patients. The included studies were published between January 2006 and March 2018 (Table 1). Except for three studies (29, 39, 79) that only included male patients and one study (96) that only included female patients, the rest of the studies included patients of both sexes. Twenty studies did not report the mode of administration. Of the remaining 78 studies, 47.4% involved the face-to-face administration of the survey, 47.4% involved self-administered surveys, and 5.2% involved telephone surveys. The AHRQ checklist scores ranged from four to nine points, the median was six points, and the mode was five points (details in Supplementary Table 2). There were no low-quality studies; 87 studies and 11 studies were of moderate and high quality, respectively. The data about the distributions of EQ-5D-5L are summarized in Supplementary Table 3.

In this review, health utility values derived from the EQ-5D-5L were reported for 50 different diseases. Among these, diabetes mellitus, neoplasms, multiple sclerosis, cardiovascular disease, chronic obstructive pneumonia disease (COPD), human immunodeficiency virus (HIV) infection, chronic kidney disease, and fracture were reported in three or more studies and meta-analyses were performed for these diseases (fracture was not included in meta-analysis, because only two of the studies reported standard error/deviation). The sensitivity analysis results (remove all the utility values derived from the crosswalk value set) are presented in Supplementary Figure 1.

Diabetes Mellitus
For patients with diabetes mellitus (Table 2), 12 studies reported health utility values ranging from 0.31 to 0.99 (14, 15, 18–27). The Chinese standard EQ-5D-5L value set (18) and Crosswalk UK value set (24) were used to derive the utility values in the studies that reported the highest value and lowest value, respectively. The former focused on diabetes patients without diabetic retinopathy with a mean disease duration of 10.3 years and a mean age of 67.9 years (18), while the latter involved patients with severe comorbidities on hemodialysis, with a mean age of 60.3 years (24). Additionally, Lamu et al. (19) used eight country value sets (England, the Netherlands, Spain, Canada, Uruguay, China, Japan, and Korea) to analyze 924 diabetic patients from six countries. The results showed that the utility value calculated with the Uruguay value set was the highest at 0.880, while the lowest, 0.735, was derived with the value set from the Netherlands. The EQ-5D VAS scores were reported to range from 50.9 to 72.6 in six studies (14, 20, 22–25). Among the five dimensions of the EQ-5D-5L, pain/discomfort was the dimension with the most reported problems. The prevalence of diabetes comorbidities ranged from 55 to 100%, which was one of the most important factors negatively affecting the HRQoL of patients.

The meta-analytic utility estimate of diabetes mellitus was 0.83 (95% confidence interval (CI) = 0.77–0.90, heterogeneity $I^2 = 100\%$, $P = 0.00$) using the random-effect model, and it was 0.93
(95% CI = 0.93–0.93) using the fixed-effect model. The results are presented in Figure 2A.

Neoplasms
Seven studies reported health utility values for cancer patients ranging from 0.62 to 0.90 (26, 28–33). The highest utility value was in early-stage prostate cancer patients using the crosswalk UK value set (29), while the lowest value was in colorectal cancer patients, 49.7% of whom had stage III–IV disease, applying the China value set (28). The EQ-5D VAS scores ranged from 56.2 to 77.5 in two studies (30, 32). The decrease in health utility in cancer patients was mainly due to problems related to the pain/discomfort dimension of the EQ-5D-5L. As the cancer progressed, the health utility value decreased.

The pooled utility value of cancer patients was 0.75 (95% CI = 0.68–0.82, heterogeneity $I^2 = 96\%$, $P < 0.01$) using the random-effect model, and it was 0.80 (95% CI = 0.78–0.81) using the fixed-effect model (Figure 2B).

Multiple Sclerosis
The health utility ranged from 0.31 to 0.78 for multiple sclerosis patients in six studies (34–39). The upper and lower utility values were generated with the crosswalk France value set (35) and the crosswalk UK value set (39), respectively. The study with the highest value (39) reported a shorter disease duration (9 vs. 15 years) than the study with the lowest utility value (35). In addition, the former had a higher proportion of relapsing–remitting multiple sclerosis patients than the latter (71.5 vs. 52.8%). EQ-5D VAS scores ranged from 58.3 to 78.0 in five studies (35–39). Pain/discomfort and usual activities were the dimensions with the most reported problems among multiple sclerosis patients.
### TABLE 1 | Basic characteristics of the included studies.

| Author year | Country/region | Survey time | Sample size | Male (%) | Diseases | Age (SD) | AHQR scores |
|-------------|----------------|-------------|-------------|----------|----------|----------|-------------|
| Natasya et al. 2018 | Indonesia | October to December 2017 | 108 | 31.5 | Diabetes mellitus (type 2) | - | 5 |
| Sothornwit et al. 2018 | Thailand | January 2014 to September 2016 | 254 | 47.0 | Diabetes mellitus | 63.2 (12.1) | 6 |
| Pan et al. 2018 | China | 2015 | 722 | 43.1 | Diabetes without diabetic retinopathy | 67.9 (8.2) | 5 |
| Lamu et al. 2018 | Australia, Canada, Germany, Norway, UK and USA | 2012 | 924 | 58.7 | Diabetes | 55.9 (12.6) | 7 |
| Adibe et al. 2018 | Nigeria | - | 147 | 44.9 | Diabetes mellitus (type 2) | - | 5 |
| Arifin et al. 2019 | Indonesia | November 2015 to October 2017 | 907 | 57.0 | Diabetes mellitus (type 2) | 59.3 (9.7) | 6 |
| Schmitt et al. 2018 | Germany | September 2015 to August 2016 | 606 | 45.2 | Diabetes mellitus | 50 (15) | 7 |
| Collado et al. 2015 | Spain | July 2011 to June 2012 | 1,857 | 45.3 | Diabetes mellitus | ≥18 | 6 |
| Khatib et al. 2018 | Palestine | November 2016 to June 2017 | 141 | 52.5 | Diabetes mellitus (type 2) | 60.3 | 8 |
| Zyoud et al. 2015 | Palestine | June 2013 to October 2013 | 385 | 44.9 | Diabetes mellitus (type 2) | 59.3 (11.2) | 5 |
| Xu et al. 2017 | China | July to December 2014 | 1,721 | - | Heart disease | ≥18 | 5 |
| | | | 4,528 | - | Hypertension | ≥18 | 5 |
| | | | 2,326 | - | Diabetes | ≥18 | 5 |
| | | | 267 | - | Cancer | ≥18 | 5 |
| Pan et al. 2016 | China | March 2014 to June 2014 | 289 | 30.5 | Diabetes mellitus (type 2) | 64.9 (9.1) | 7 |
| Huang et al. 2018 | China | December 2016 to April 2017 | 300 | 65.0 | Colorectal cancer | 59 | 7 |
| Gavin et al. 2016 | Republic of Ireland | 2012 | 1,431 | 100.0 | Prostate cancer early stage | 64.9 (7.6) | 7 |
| | Northern Ireland | 2012 | 407 | 100.0 | Prostate cancer late stage | 64.9 (7.6) | 7 |
| | | | 269 | 100.0 | Prostate cancer early stage | 64.9 (7.6) | 7 |
| | | | 282 | 100.0 | Prostate cancer late stage | 64.9 (7.6) | 7 |
| Lloyd et al. 2015 | UK | - | 50 | 100.0 | Prostate cancer asymptomatic/mildly symptomatic | 71.8 (8.8) | 5 |
| | | | 50 | 100.0 | Prostate cancer currently receiving chemotherapy | 69.8 (11.9) | 5 |
| | | | 12 | 100.0 | Prostate cancer symptomatic before chemotherapy | 59.9 (15.2) | 5 |
| | | | 46 | 100.0 | Prostate cancer post chemotherapy | 68.4 (8.24) | 5 |
| Philipp-Dormston et al. 2018 | Germany | October 2015 to February 2016 | 869 | 61.3 | Actinic keratosis | 74 | 8 |
| | | | 578 | 61.3 | Basal cell carcinoma | 74 | 8 |
| | | | 204 | 61.3 | Squamous cell carcinoma | 74 | 8 |
| Noel et al. 2015 | Canada | August 2014 to October 2014 | 100 | 75.0 | Squamous cell carcinoma | 61 | 5 |
| Mastboom et al. 2018 | Netherlands | December 2016 to May 2017 | 69 | 20.3 | Localized tenosynovial giant cell tumor | 41 | 6 |
| | | | 230 | 22.2 | Diffuse tenosynovial giant cell tumor | 41 | 6 |

(Continued)
### TABLE 1 | Continued

| Author year | Country/region      | Survey time                  | Sample size | Male (%) | Diseases                              | Age (SD) | AHQR scores |
|-------------|---------------------|------------------------------|-------------|----------|---------------------------------------|----------|-------------|
| Zhang et al. 2017 (34) | Australia | 2015                    | 231         | 36.8     | Progressive-onset multiple sclerosis | 61.8 (9.6) | 7           |
| Alqahtani et al. 2017 (35) | Saudi Arabia | June 2016 to April 2017    | 1,514       | 18.4     | Relapse-onset multiple sclerosis     | 53.5 (11.0) | 7           |
| Fogarty et al. 2012 (36) | Ireland | -                           | 214         | 33.6     | Multiple sclerosis                    | 47.6 (12.8) | 6           |
| Carney et al. 2018 (37) | Ireland | Spring of 2015            | 541         | 28.7     | Multiple sclerosis                    | 47        | 7           |
| Nohara et al. 2017 (38) | Japan | 2016                      | 96          | 38.5     | Multiple sclerosis                    | 47.4 (14.2) | 7           |
| Barin et al. 2018 (39) | Switzerland | June 2016 to September 2017 | 855         | 27.3     | Multiple sclerosis                    | 48.0 (8.8) | 8           |
| Buanes et al. 2015 (40) | Norway | October 2012              | 30          | 80.0     | Cardiac arrest                        | 62        | 5           |
| Berg et al. 2017 (41) | Denmark | April 2013 to April 2014  | 7,179       | 73       | Ischemic heart disease                | 65.5 (9.5) | 9           |
|                          |                |                             | 4,322       | 65       | Arrhythmia                            | 63.6 (9)  |             |
|                          |                |                             | 987         | 73       | Heart failure                         | 65.4 (9)  |             |
|                          |                |                             | 115         | 47       | Congestive heart disease              | 43.9 (9)  |             |
|                          |                |                             | 204         | 75       | Infectious heart disease              | 59.4 (9)  |             |
|                          |                |                             | 975         | 66       | Heart valve disease                   | 71.2 (9)  |             |
|                          |                |                             | 136         | 74       | Heart transplant                      | 51.2 (9)  |             |
|                          |                |                             | 321         | 61       | Other diagnoses of heart disease      | 61.4 (9)  |             |
|                          |                |                             | 2,473       | 53       | Observation for heart disease         | 61.5 (9)  |             |
| Squire et al. 2017 (42) | UK | January to May 2015        | 191         | 73.0     | Heart failure                         | 70 (6)    | 6           |
| Meroño et al. 2017 (43) | Spain | November 2012 to October 2015 | 139        | 66.0     | Iron deficiency in acute coronary syndrome | 67 (15) | 9           |
| Tran et al. 2018 (44) | Vietnam | July to December 2016      | 105         | 83.0     | Acute coronary syndrome non-iron deficiency | 61 (12) |             |
| Wang et al. 2018 (45) | China | -                          | 600         | 41.5     | Cardiovascular disease                | 57.2 (9)  | 5           |
| De Smedt et al. 2016 (46) | 24 European countries | 2012 to 2013 | 7,449     | 76.1     | Stable coronary disease               | 64 (9)    | 5           |
| Garcia-Gordillo et al. 2017 (47) | Spain | July 2011 and June 2012 | 1,130       | 48.7     | COPD                                  | 15-102 (5) | 5           |
| Igarashi et al. 2018 (48) | Japan | -                          | 71          | 84.5     | COPD age < 65 years                   | 60.5 (5.3) | 6           |
| Lin et al. 2014 (49) | USA | 2006 to 2010              | 151         | 95.4     | COPD age ≥ 65 years                   | 75.2 (5.8) |             |
| Nolan et al. 2016 (50) | UK | April 2012 to October 2014 | 670         | 58.0     | COPD                                  | 68.5 (10.4) | 6           |
| Keaei et al. 2016 (51) | Colombia | May to June 2014          | 616         | 59.7     | COPD                                  | 70.4 (9.3) | 8           |
| Dang et al. 2018 (52) | Vietnam | January to August 2013    | 138         | 77.5     | HIV/AIDS                              | 46.4 (11.4) | 7           |
| Tran et al. 2012 (53) | Vietnam | 2012                      | 138         | 58.7     | HIV-positive                          | 35.5 (6.9) | 7           |
| Van Duin et al. 2017 (54) | Columbia | -                         | 1,016       | 63.8     | HIV                                  | 35.4 (7.0) | 6           |
| Yang et al. 2015 (55) | Singapore | June 2012 to May 2013     | 100         | 77.0     | HIV with comorbidities                | 48.0 (11.2) | 5           |
| Hiragi et al. 2019 (56) | Japan | July 2015 to March 2017   | 83          | 21.1     | HIV without comorbidities             | 42.2 (11.1) | 6           |
|                          |                |                             | 150         | 51.3     | End-stage renal disease               | 60.1 (11.6) | 6           |
|                          |                |                             | 67          | 62.7     | Chronic kidney disease (TR)           | 49.8 (13.1) | 4           |
|                          |                |                             | 65          | 53.8     | Chronic kidney disease (TRC)          | 49.4 (11.6) |             |
| Author year | Country/region | Survey time | Sample size | Male (%) | Diseases | Age (SD) | AHQR scores |
|-------------|----------------|-------------|-------------|----------|----------|----------|-------------|
| Zyoud et al. 2016 (57) | Palestine | June 2014 to January 2015 | 267 | 52.1 | End-stage renal disease | 53.3 (16.2) | 8 |
| Al-Jabi et al. 2015 (59) | Palestine | July 2012 and October 2012 | 410 | 48.0 | Hypertension | 58.4 (10.7) | 8 |
| van der Linde et al. 2017 (60) | Netherlands | January 2006 to December 2014 | 101 | 77.2 | Midshaft clavicular fractures | 44.5 (13.6) | 7 |
| Larsen et al. 2015 (61) | Denmark | Autumn 2013 to spring 2014 | 48 | 77.1 | Femoral shaft fracture | 38.0 (19.4) | 6 |
| Kim et al. 2018 (62) | Korea | August 2014 to February 2017 | 59 | 11.9 | Osteoporotic vertebral compression fracture | 73.5 (8.5) | 6 |
| Chevreul et al. 2016 (63) | France | September 2012 to May 2013 | 38 | 45.0 | Prader–Willi syndrome | 17.4 (12.2) | 4 |
| López-Bastida et al. 2016 (64) | Spain | September 2011 to April 2013 | 26 | - | Prader–Willi syndrome | 13.7 (8.5) | 5 |
| | | | | | | | |
| Vaizey et al. 2014 (65) | UK | October 2011 to March 2012 | 100 | 55.0 | Ulcerative colitis remission | 47.5 | 5 |
| Gibson et al. 2014 (66) | Australia | July to October 2011 | 94 | 47.4 | Ulcerative colitis mild | 48 |
| | | | 42 | 40.5 | Ulcerative colitis moderate/severe | 40.5 |
| | | | 29 | 47.4 | Ulcerative colitis remission | 47.8 (12.7) | 5 |
| | | | 52 | 47.4 | Ulcerative colitis moderate/severe | 47.8 (12.7) |
| Yfantopoulos et al. 2017 (67) | Greece | December 2012 to March 2013 | 396 | 60.1 | Psoriasis | 52.0 (16.5) | 5 |
| Zhao et al. 2017 (68) | China | May 2014 to February 2015 | 350 | 69.7 | Psoriasis | 39 | 7 |
| Choi et al. 2018 (69) | Korea | January to December 2017 | 105 | 76.0 | Ankylosing spondylitis | 39 | 5 |
| Chiovchanwisawaki et al. 2019 (70) | Thailand | May 2012 to March 2016 | 119 | 61.3 | Ankylosing spondylitis | 40.4 (11.6) | 5 |
| Alvarado-Bolaños et al. 2015 (71) | Mexico | - | 585 | 54.4 | Parkinson's disease | 62.9 (12.3) | 4 |
| García-Gordillo et al. 2014 (72) | Spain | May 1 to July 15, 2012 | 133 | 71.4 | Parkinson's disease | 64.3 (9.7) | 6 |
| Lee et al. 2015 (73) | South Korea | July to December 2013 | 625 | 32.5 | Overactive bladder | 63.5 (12.0) | 6 |
| Lloyd et al. 2017 (74) | UK | 2014 | 249 | 54.6 | Idiopathic overactive bladder | 57.3/58.1 | 6 |
| Nordenfelt et al. 2017 (75) | Sweden | May and October 2016 | 64 | 40.6 | Hereditary angioedema | 51 | 6 |
| Nordenfelt et al. 2014 (76) | Sweden | June 2011 | 103 | 47.6 | Hereditary angioedema | 41/44 | 4 |
| Whitehurst et al. 2016 (77) | Canada | March to June 2013 | 364 | 62.9 | Spinal cord injury | 50.4 (13.2) | 8 |
| Engel et al. 2018 (78) | Canada | March to June 2013 | 364 | 62.9 | Spinal cord injury | 50.4 (13.2) | 3 |
| Buckner et al. 2017 (79) | USA | September to November 2015 | 299 | 71.0 | Hemophilia B | 29 | 5 |
| Kempston et al. 2018 (80) | USA | October 2013 to October 2014 | 381 | 100.0 | Hemophilia | 34 | 7 |
| Arraras et al. 2018 (81) | Spain | May 2015 to June 2016 | 61 | 66.0 | Schizophrenia and schizoaffective disorder | 37.9 (10.5) | 7 |

(Continued)
| Author year, Country/region | Survey time | Sample size | Male (%) | Diseases | Age (SD) | AHQR scores |
|-----------------------------|-------------|-------------|----------|-----------|----------|-------------|
| Kitic et al. 2018 (81) Serbia | - | 153 | 54.9 | Schizophrenia | 50.8 (10.1) | 4 |
| Tennvall et al. 2015 (82) Denmark | May to June in 2012 | 312 | 51.9 | Actinic keratosis | 71 (11.0) | 7 |
| Gray et al. 2018 (83) Australia, Canada, Germany, Norway, the United Kingdom, and the United States | 2012 | 852 | 37.7 | Asthma | 43.0 (15.0) | 4 |
| Hernandez et al. 2018 (84) French | - | 222 | 38.7 | Asthma | 30.3 (6.7) | 8 |
| Wong et al. 2018 (85) UK | March 2014 to January 2017 | 990 | 19.7 | Autoimmune hepatitis | 58 | 7 |
| Cook et al. 2019 (86) Canada, Germany, UK, and USA | - | 166 | 49.4 | Non-alcoholic steatohepatitis | 52.0 (11.8) | 5 |
| van Dongen-Leunis et al. 2016 (87) Netherlands | 2012 | 111 | 52.3 | Acute leukemia | 51.0 (13.4) | 6 |
| Hendriksz et al. 2014 (88) Brazil, Colombia, Germany, Spain, Turkey, UK | June 2012 to April 2013 | 25 | - | Morquio A syndrome adults | <18 | 5 |
| Andersson et al. 2016 (89) France, Germany, Spain, USA | February to May 2013 | 1,104 | 59.1 | Nocturia | 65.1 | 8 |
| Mealy et al. 2019 (90) USA | October 6, 2014 | 21 | 90.5 | Neuromyelitis optica spectrum disorder | 42.8 (10.6) | 5 |
| Nikphorou et al. 2018 (91) Multinational | - | 3,370 | 66.0 | Spondyloarthritis | 42.9 (13.7) | 5 |
| Van Assche et al. 2016 (92) 11 European countries | - | 250 | 58.8 | Ulcerative colitis | 46.6 (16.3) | 6 |
| Mijnarends et al. 2016 (93) Dutch | May 2013 to February 2014 | 53 | 52.8 | Sarcopenia | 80.4 (7.1) | 7 |
| Tran et al. 2018 (94) Vietnam | September to November 2017 | 223 | 51.1 | Dengue fever | 31.6 (12.4) | 7 |
| Chevreul et al. 2015 (95) France | September 2012 to May 2013 | 82 | 42.7 | Cystic fibrosis | 28.6 (8.1) | 5 |
| Collado-Mateo et al. 2017 (96) Spain | October 2014 to October 2015 | 192 | 0.0 | Fibromyalgia | 53.8 (10.0) | 5 |
| Chevreul et al. 2015 (97) France | September 2012 to May 2013 | 95 | 87.4 | Fragile X syndrome | 19.4 (13.1) | 5 |
| Juul-Kristensen et al. 2017 (98) Denmark | January to June 2015 | 300 | 24.3 | Generalized joint hypermobility | 48 | 6 |
| Bewick et al. 2018 (99) UK | January 2013 to January 2014 | 52 | 51.0 | Rhinosinusitis | 55 | 6 |
| Forestier-Zhang et al. 2016 (100) UK | September 2014 to March 2016 | 43 | 23.0 | Osteogenesis imperfecta | 40.4 (14.4) | 6 |
| Katchamart et al. 2019 (101) Thailand | September 2016 to March 2018 | 464 | 31.0 | Fibrous dysplasia | 44.3 (14.5) | 5 |
| Román Ivorra et al. 2019 (102) Spain | October 2015 to March 2016 | 190 | 14.9 | X-Linked hypophosphatemia | 46.3 (16.3) | 5 |
| Aguirre et al. 2016 (103) UK | - | 272 | 39.0 | Dementia | 82.6 (8.1) | 5 |

(Continued)
The meta-analytic utility estimate of multiple sclerosis patients was 0.56 (95% CI = 0.47–0.66, heterogeneity $I^2 = 99\%$, $P < 0.01$) using the random-effect model, and it was 0.67 (95% CI = 0.66–0.68) using the fixed-effect model (Figure 2C).

### Cardiovascular Disease

For cardiovascular disease patients, the health utility values ranged from 0.56 to 0.85 in eight studies (26, 40–46). The lowest value was derived from the Chinese value set (45), while the study with the highest value did not report the value set used (40). In the study with the highest utility value (40), all patients were evaluated 4 years after cardiac arrest, and the proportion of men was 80%. In the study with the lowest value, the patients had atrial fibrillation; 43% of them were men, and 23% had diabetes mellitus (45). Berg et al. (41) compared utility values among nine subgroups of patients with different cardiovascular diseases. Among these subgroups, heart transplant patients had the highest value, which was 0.82, while arrhythmia patients had the lowest value, which was 0.70. The EQ-5D VAS scores ranged from 61.4 to 77.8 in six studies (26, 40–44). Anxiety/depression and pain/discomfort were the dimensions with the most reported problems among cardiovascular disease patients.

The pooled utility value of cardiovascular disease patients was 0.77 (95% CI = 0.75–0.79, heterogeneity $I^2 = 99\%$, $P < 0.01$) using the random-effect model, and it was 0.76 (95% CI = 0.75–0.76) using the fixed-effect model (Figure 2D).

### COPD

For patients with COPD, the health utility values ranged from 0.68 to 0.79 in four studies (47–50). The crosswalk US value set and UK standard EQ-5D-5L value set were used in the studies that reported the highest utility value (49) and the lowest value (50), respectively. The mean age of COPD patients in the study reporting the lowest utility was 70.4 years, and the mean predicted forced expiratory volume in 1 s (FEV1) was 49.8% (50). Meanwhile, the patients in the study with the highest value had a younger mean age (68.5 years old) and a better predicted FEV1 (49). The EQ-5D VAS scores ranged from 60.5 to 70.6 in four studies (47–50). Mobility was the dimension with the most problems affecting the HRQoL of COPD patients based on EQ-5D-5L. In addition, as the predicted FEV1 decreased, the health utility value in COPD patients decreased.

The synthesized utility value of COPD patients was 0.75 (95% CI = 0.71–0.80, heterogeneity $I^2 = 96\%$, $P < 0.01$) using the random-effect model, and it was 0.76 (95% CI = 0.75–0.77) using the fixed-effect model (Figure 2E).

### HIV Infection

The health utility values of patients infected with HIV ranged from 0.65 to 0.90 in four studies (51–54), and both extreme values were derived with a crosswalk value set [Thailand (53) and Spain (54)]. The study (54) with the highest utility value involved patients in relatively good condition and without any comorbidities, while the study (53), with the lowest value focused...
| Diseases | Health Utility | VAS scores | Have any problem in 5 dimensions (%) | Administration |
|----------|----------------|------------|--------------------------------------|----------------|
| Diabetes mellitus | | | | |
| Natasya et al. 2018 (14) | Diabetes mellitus (type 2) | 0.74 0.23 | Indonesia 65.5 16.0 | - |
| Sothornwit et al. 2018 (15) | Diabetes mellitus | 0.80 0.25 | Thailand 44.4 16.6 | - |
| Pan et al. 2018 (18) | Diabetes without diabetic retinopathy | 0.99 0.05 | China 7.1 1.1 | - |
| Diabetes with unilateral retinopathy | 0.97 0.08 | China | 12.5 5.4 | - |
| Diabetes with bilateral retinopathy | 0.97 0.15 | China | 7.8 3.9 | - |
| Lamu et al. 2018 (19) | Diabetes mellitus | 0.79 0.22 | England 72.6 10.5 | - |
| Diabetes mellitus | 0.74 0.26 | Dutch | 37.0 12.0 | - |
| Diabetes mellitus | 0.76 0.21 | Spain | 66.0 20.0 | - |
| Diabetes mellitus | 0.78 0.19 | Canada | 61.1 20.5 | - |
| Diabetes mellitus | 0.88 0.14 | Uruguay | 63.7 19.2 | - |
| Diabetes mellitus | 0.76 0.25 | China | 60.4 19.2 | - |
| Diabetes mellitus | 0.77 0.19 | Japan | 60.4 19.2 | - |
| Diabetes mellitus | 0.78 0.17 | Korea | 60.4 19.2 | - |
| Adibe et al. 2018 (20) | Diabetes mellitus (type 2) | 0.72 0.13 | - 72.6 10.5 | - |
| Arifn et al. 2019 (21) | Diabetes mellitus (type 2) | 0.77 - | Indonesia 37.0 12.0 | - |
| Schmitt et al. 2018 (22) | Diabetes mellitus | 0.80 0.20 | Crosswalk (Germany) 66.0 20.0 | - |
| Collado et al. 2015 (23) | Diabetes mellitus | 0.74 0.32 | Crosswalk (Spain) 61.1 20.5 | - |
| Khatib et al. 2018 (24) | Diabetes mellitus (type 2) | 0.31 - | Crosswalk (UK) 50.9 22.4 | - |
| Zyoud et al. 2015 (25) | Diabetes mellitus (type 2) | 0.70 0.20 | - 63.7 19.2 | - |
| Xu et al. 2017 (26) | Diabetes mellitus | 0.84 0.23 | Hong Kong | - |
| Pan et al. 2016 (27) | Diabetes mellitus (type 2) | 0.88 0.14 | Crosswalk (China) | - |
| Neoplasms | | | | |
| Huang et al. 2018 (28) | Colorectal cancer | 0.62 0.37 | China 46.3 49.0 | - |
| Gavin et al. 2016 (29) | Prostate cancer late stage (RoI) | 0.80 - | Crosswalk (UK) | - |
| Prostate cancer late stage (NI) | 0.70 - | Crosswalk (UK) | - |
| Prostate cancer early stage (RoI) | 0.90 - | Crosswalk (UK) | - |
| Prostate cancer early stage (NI) | 0.80 - | Crosswalk (UK) | - |
| Lloyd et al. 2015 (30) | Prostate cancer asymptomatic/mildly symptomatic | 0.83 0.13 | Crosswalk 77.5 12.6 | - |
| Diseases                                                                | Health Utility                                                                 | VAS scores          | Have any problem in 5 dimensions (%) | Administration |
|------------------------------------------------------------------------|-------------------------------------------------------------------------------|---------------------|---------------------------------------|----------------|
| Prostate cancer currently receiving chemotherapy                        | 0.69 (±0.22) Crosswalk-Delta1                                                 | 67.4 (±14.3)        | -                                     | Self-administered |
| Prostate cancer symptomatic before chemotherapy                         | 0.63 (±0.17) Crosswalk-Delta1                                                 | 56.2 (±16.7)        | -                                     | Self-administered |
| Prostate cancer post chemotherapy                                       | 0.70 (±0.18) Crosswalk-Delta1                                                 | 66.0 (±17.9)        | -                                     | Self-administered |
| Basal cell carcinoma                                                   | 0.87* (±) Dutch                                                               | -                   | -                                     | -               |
| Squamous cell carcinoma                                                | 0.84 (±) Dutch                                                                | -                   | -                                     | -               |
| Squamous cell carcinoma                                                | 0.82 (±0.18)                                                                  | 76.0 (±19.0)        | -                                     | -               |
| Diffuse tenosynovial giant cell tumor                                   | 0.72 (±) Crosswalk-US                                                        | -                   | -                                     | Self-administered |
| Localized tenosynovial giant cell tumor                                | 0.76 (±) Crosswalk-US                                                         | -                   | -                                     | Self-administered |
| Cancer                                                                 | 0.84 (±0.22) Hong Kong                                                        | -                   | -                                     | Telephone survey |
| Relapse-onset multiple sclerosis                                        | 0.73 (±0.22)                                                                  | -                   | -                                     | Self-administered |
| Progressive-onset multiple sclerosis                                   | 0.54 (±0.27)                                                                  | -                   | -                                     | Self-administered |
| Multiple sclerosis                                                     | 0.31 (±0.51) Crosswalk-Delta1                                                 | 73.9 (±23.4)        | 72.9 (±60.3)                          | Face-to-face     |
| Multiple sclerosis                                                     | 0.59 (±0.33) Crosswalk-Delta1                                                 | 65.0 (±22.4)        | 70.1 (±36.2)                          | Face-to-face     |
| Multiple sclerosis                                                     | 0.59 (±0.29) Crosswalk-Delta1                                                 | 63.3 (±21.7)        | -                                     | Self-administered |
| Multiple sclerosis                                                     | 0.68 (±0.19)                                                                  | 58.3 (±27.0)        | -                                     | Self-administered |
| Multiple sclerosis                                                     | 0.78 (±) Crosswalk-Delta1                                                     | 78.0 (±)            | -                                     | Face-to-face     |
| Cardiac arrest                                                         | 0.85 (±)                                                                      | 70.6 (±)            | -                                     | Self-completed   |
| Ischemic heart disease                                                 | 0.76 (±0.16) Crosswalk-Delta1                                                 | 68.6 (±19.7)        | -                                     | Self-administered |
| Arrhythmia                                                             | 0.70 (±0.16) Crosswalk-Delta1                                                 | 72.2 (±19.6)        | -                                     | Self-administered |
| Heart failure                                                          | 0.73 (±0.16) Crosswalk-Delta1                                                 | 61.4 (±19.5)        | -                                     | Self-administered |
| Congenital heart disease                                               | 0.77 (±0.16) Crosswalk-Delta1                                                 | 69.9 (±19.7)        | -                                     | Self-administered |
| Infectious heart disease                                               | 0.73 (±0.16) Crosswalk-Delta1                                                 | 68.4 (±19.6)        | -                                     | Self-administered |
| Heart valve disease                                                    | 0.74 (±0.16) Crosswalk-Delta1                                                 | 66.1 (±19.7)        | -                                     | Self-administered |
| Heart transplant                                                       | 0.82 (±0.16) Crosswalk-Delta1                                                 | 76.0 (±19.6)        | -                                     | Self-administered |
| Other diagnoses of heart disease                                       | 0.73 (±0.16) Crosswalk-Delta1                                                 | 65.3 (±19.5)        | -                                     | Self-administered |
| Observation for heart disease                                          | 0.76 (±0.16) Crosswalk-Delta1                                                 | 70.5 (±19.6)        | -                                     | Self-administered |

(Continued)
TABLE 2 | Continued

| Diseases                                      | Health Utility | VAS scores | Have any problem in 5 dimensions (%) | Administration |
|-----------------------------------------------|----------------|------------|--------------------------------------|----------------|
|                                               | Mean | SD | Value set  | Mean | SD | MO | SC | UA | PA | AD   |                     |
| Squire et al. 2017 (42) Heart failure         | 0.60 | 0.25 | UK         | 63.0 | 20.0 | -  | -  | -  | -  | Self-administered  |
| Merono et al. 2017 (43) Iron deficiency in acute coronary syndrome | 0.76 | 0.25 | -          | 66.0 | 16.0 | 52.0 | 20.0 | 49.0 | 50.0 | 61.0 | Self-administered  |
| Acute coronary syndrome non-iron deficiency | 0.84 | 0.16 | -          | 72.0 | 17.0 | 29.0 | 12.0 | 33.0 | 49.0 | 52.0 | Self-administered  |
| Tran et al. 2018 (44) Cardiovascular disease  | 0.82 | 0.21 | Crosswalk  | 77.8 | 13.6 | 24.8 | 19.8 | 22.7 | 38.8 | 35.2 | Face-to-face       |
| Wang et al. 2018 (45) Atrial fibrillation     | 0.56 | -   | China      | -    | -    | -    | -    | -    | -    | -    | Face-to-face       |
| Xu et al. 2017 (26) Heart disease             | 0.84 | 0.24 | Hong Kong  | -    | -    | -    | -    | -    | -    | -    | -    | Telephone survey   |
| De Smedt et al. 2016 (46) Stable coronary disease | 0.78 | 0.20 | Crosswalk  | 67.1 | 21.4 | -    | -    | -    | -    | -    | -    | -    |                     |
| COPD                                          | 0.74 | 0.31 | Crosswalk  | 60.5 | 21.9 | 45.4 | 22.2 | 37.5 | 57.1 | 34.9 | Face-to-face       |
| Garcia-Gordillo et al. 2017 (47) COPD         | 0.74 | 0.31 | Crosswalk  | 60.5 | 21.9 | 45.4 | 22.2 | 37.5 | 57.1 | 34.9 | Face-to-face       |
| Igarashi et al. 2018 (48) COPD age ≥ 65 years | 0.77 | 0.18 | Japan      | 69.2 | 18.7 | 56.3 | 26.5 | 46.7 | 37.7 | 35.1 | Self-administered |
| COPD age < 65 years                           | 0.79 | 0.22 | Japan      | 70.5 | 23.8 | 43.7 | 23.9 | 43.7 | 30.0 | 38.6 | Self-administered |
| Lin et al. 2014 (49) COPD                     | 0.79 | 0.15 | Crosswalk  | 70.6 | 19.6 | 63.6 | 19.5 | 54.8 | 61.9 | 36.3 | -                |
| Nolan et al. 2016 (50) COPD                   | 0.68 | 0.24 | UK         | 61.0 | 20.6 | -    | -    | -    | -    | -    | -                |
| HIV infection                                 |      |    |            |      |     |      |      |      |      |      |                  |
| Keaei et al. 2016 (51) HIV/AIDS               | 0.85 | 0.21 | Crosswalk  | 84.4 | 14.3 | 18.8 | 8.7  | 15.9 | 38.4 | 40.6 | Face-to-face       |
| Dang et al. 2018 (52) HIV-positive            | 0.80 | 0.20 | -          | 68.8 | 17.3 | 20.5 | 9.7  | 16.6 | 37.7 | 44.9 | Face-to-face       |
| Tran et al. 2012 (53) HIV                     | 0.65 | -   | Crosswalk  | 70.3 | -    | 45.1 | 20.2 | 35.4 | 58.2 | 72.5 | Face-to-face       |
| Van Duin et al. 2017 (54) HIV with comorbidities | 0.84 | 0.22 | Crosswalk  | 84.4 | 16.1 | -    | -    | -    | -    | -    | Face-to-face       |
| HIV without comorbidities                     | 0.90 | 0.19 | Crosswalk  | 88.6 | 10.4 | -    | -    | -    | -    | -    | Face-to-face       |
| Chronic kidney disease                        |      |    |            |      |     |      |      |      |      |      |                  |
| Yang et al. 2015 (55) End-stage renal disease | 0.68 | 0.36 | Crosswalk  | -    | -    | -    | -    | -    | -    | -    | Face-to-face       |
| Hiragi et al. 2019 (56) Chronic kidney disease (TRC) | 0.89 | 0.15 | Japan      | -    | -    | -    | -    | -    | -    | -    | Face-to-face       |
| Chronic kidney disease (TR)                   | 0.85 | 0.18 | Japan      | -    | -    | -    | -    | -    | -    | -    | Face-to-face       |
| Zyoud et al. 2016 (57) End-stage renal disease | 0.37 | 0.44 | Crosswalk  | 59.4 | 45.4 | 27.3 | 54.7 | 37.5 | 25.5 | 35.2 | Face-to-face       |
| Hypertension                                  |      |    |            |      |     |      |      |      |      |      |                  |
| Al-Jabi et al. 2015 (58) Hypertension         | 0.80 | 0.16 | Crosswalk  | 74.1 | 15.6 | -    | -    | -    | -    | -    | Face-to-face       |
| Xu et al. 2017 (26) Hypertension              | 0.85 | 0.22 | Hong Kong  | -    | -    | -    | -    | -    | -    | -    | Telephone survey   |

(Continued)
| Diseases                      | Health Utility | VAS scores | Have any problem in 5 dimensions (%) | Administration   |
|-------------------------------|----------------|------------|--------------------------------------|------------------|
|                               | Mean    | SD      | Value set<sup>3</sup> | Mean | SD | MO | SC | UA | PA | AD |
| Fractures                     |         |         |                       |      |    |    |    |    |    |    |
| Van der Linde et al. 2017     | 0.88    | 0.14    | -                      | 77.2 | 26.8 | - | - | - | - | - |
| (55) Midshaft clavicular fractures |       |         |                       |      |    |    |    |    |    |    |
| Larsen et al. 2015 (60)       | 0.80    | -       | Crosswalk (Denmark)   | 80.3 | -   | - | - | - | - | - |
| Femoral shaft fracture        |         |         |                       |      |    |    |    |    |    |    |
| Kim et al. 2018 (61)          | 0.56    | 0.24    | -                      | -    | -   | - | - | - | - | - |
| Osteoporotic vertebral compression fracture |         |         |                       |      |    |    |    |    |    |    |
| Prader–Willi syndrome         |         |         |                       |      |    |    |    |    |    |    |
| Chevreul et al. 2016 (62)     | 0.44    | 0.33    | Crosswalk<sup>5</sup> | 59.5 | 17.7 | - | - | - | - | - |
| Prader–Willi syndrome (UK)    | 0.48    | 0.22    | -                      | 56.9 | 19.7 | - | - | - | - | - |
| Prader–Willi syndrome (Sweden)| 0.63    | 0.10    | -                      | 51.3 | 10.3 | - | - | - | - | - |
| Prader–Willi syndrome (Spain) | 0.60    | 0.78    | -                      | 62.6 | 20.5 | - | - | - | - | - |
| Prader–Willi syndrome (Italy) | 0.40    | 0.29    | -                      | 56.2 | 19.7 | - | - | - | - | - |
| Prader–Willi syndrome (Germany)| 0.81   | 0.14    | -                      | 60.7 | 26.4 | - | - | - | - | - |
| Prader–Willi syndrome (France)| 0.41    | 0.34    | -                      | 56.5 | 17.7 | - | - | - | - | - |
| Ulcerative colitis            |         |         |                       |      |    |    |    |    |    |    |
| Vaizey et al. 2014 (64)       | 0.86    | 0.15    | Crosswalk<sup>5</sup> | -    | -   | - | - | - | - | - |
| Ulcerative colitis remission  |         |         |                       |      |    |    |    |    |    |    |
| Gibson et al. 2014 (65)       | 0.81    | 0.18    | -                      | -    | -   | - | - | - | - | - |
| Ulcerative colitis remission  |         |         |                       |      |    |    |    |    |    |    |
| Vaizey et al. 2014 (64)       | 0.66    | 0.24    | Crosswalk<sup>5</sup> | -    | -   | - | - | - | - | - |
| Ulcerative colitis moderate/severe |       |         |                       |      |    |    |    |    |    |    |
| Gibson et al. 2014 (65)       | 0.68    | 0.19    | -                      | -    | -   | - | - | - | - | - |
| Ulcerative colitis moderate/severe |       |         |                       |      |    |    |    |    |    |    |
| Vaizey et al. 2014 (64)       | 0.77    | 0.11    | Crosswalk<sup>5</sup> | -    | -   | - | - | - | - | - |
| Ulcerative colitis mild       |         |         |                       |      |    |    |    |    |    |    |
| Gibson et al. 2014 (65)       | 0.78    | 0.18    | -                      | -    | -   | - | - | - | - | - |
| Psoriasis                     |         |         |                       |      |    |    |    |    |    |    |
| Yiantopoulos et al. 2017 (66)| 0.74    | 0.23    | Crosswalk<sup>5</sup> | 74.7 | 18.1 | 18.4 | 9.8 | 15.7 | 33.6 | 78.0 |
| Psoriasis                     |         |         |                       |      |    |    |    |    |    |    |
| Zhao et al. 2017 (67)         | 0.90    | 0.10    | China                 | 72.7 | 15.7 | - | - | - | - | - |
| Psoriasis                     |         |         |                       |      |    |    |    |    |    |    |
| Psoriasis                     | 0.86    | 0.10    | Japan                 | 72.7 | 15.7 | - | - | - | - | - |
| Psoriasis                     | 0.90    | 0.09    | UK                    | 72.7 | 15.7 | - | - | - | - | - |
| Ankylosing spondylitis        |         |         |                       |      |    |    |    |    |    |    |
| Choi et al. 2018 (65)         | 0.69<sup>*</sup> | - | Japan                 | -    | -   | - | - | - | - | - |
| Ankylosing spondylitis        |         |         |                       |      |    |    |    |    |    |    |
| Chiowchanwisawakit et al. 2019 (69) | 0.75 | 0.20    | Thailand              | 68.8 | 18.8 | 77.3 | 37.0 | 68.9 | 93.3 | 54.6 |
| Ankylosing spondylitis        |         |         |                       |      |    |    |    |    |    |    |
| Actinic keratitis             |         |         |                       |      |    |    |    |    |    |    |
| Tennvall et al. 2015 (82)     | 0.88    | 0.14    | Crosswalk (Denmark)   | 79.3 | 18.9 | 21.0 | 7.0 | 18.0 | 39.0 | 22.0 |
| Actinic keratitis             |         |         |                       |      |    |    |    |    |    |    |
| Philipp-Dormston et al. 2018 (81) | 0.89<sup>*</sup> | - | Dutch                 | -    | -   | - | - | - | - | - |
### TABLE 2 | Continued

| Diseases                     | Health Utility                      | VAS scores                      | Have any problem in 5 dimensions (%) | Administration |
|------------------------------|-------------------------------------|----------------------------------|---------------------------------------|-----------------|
|                              | Mean  SD Value set<sup>※</sup>       | Mean  SD MO  SC  UA  PA  AD       |                                       |                 |
|                             |                                     | (US) (Spain) (UK) (US) (Spain)   |                                       |                 |
| Parkinson's disease          |                                     |                                  |                                       |                 |
| Alvarado-Bolaños et al. 2015 | Parkinson's disease 0.71 0.20       | 73.8 18.7                        |                                       | Self-administered |
| Garcia-Gordillo et al. 2014  | Parkinson's disease 0.59 0.26       | 57.6 19.7 75.9 60.2 75.9 75.9 66.2 | -                                     | Self-administered |
| Overactive bladder           | Lee et al. 2015 0.79 0.20           | - 73.8 18.7 - - - - - - - Self-administered |
|                             | Lloyd et al. 2017 0.73 0.26         | 68.2 21.6 - - - - - - - - - - - Face-to-face |
| Hereditary angioedema        | Nordenfelt et al. 2017 0.84         | - - - - - - - - - - - - - - - Self-administered |
|                             | Nordenfelt et al. 2014 0.83         | - - - - - - - - - - - - - - - Self-administered |
| Spinal cord injury           | Whitehurst et al. 2016 0.49         | - - 97.0 67.0 80.0 93.0 57.0 47.0 | - - - - - - - - - - - - - Self-administered |
|                             | Engel et al. 2018 0.49              | - - 97.0 67.0 80.0 93.0 57.0 47.0 | - - - - - - - - - - - - - Self-administered |
| Schizophrenia                | Arraras et al. 2018 0.80            | - - - - - - - - - - - - - - - Self-administered |
|                             | Kittic et al. 2018 0.86             | - - - - - - - - - - - - - - - Self-administered |
| Hemophilia                   | Buckner et al. 2017 0.67            | - - 54.4 50.0 13.8 - - - - - - - Self-administered |
|                             | Kempston et al. 2018 0.77           | - - 65.6 61.4 18.9 53.2 76.1 43.4 | - - - - - - - - - - - - - Self-administered |
| Asthma                       | Gray et al. 2018 0.84               | - - 54.4 61.4 18.9 53.2 76.1 43.4 | - - - - - - - - - - - - - Self-administered |
|                             | Hernandez et al. 2018 0.83          | - - 77.3 76.1 76.1 76.1 76.1 76.1 | - - - - - - - - - - - - - Self-administered |
| Hepatitis                    | Wong et al. 2018 0.89*              | - - 80.0 54.4 54.4 54.4 54.4 54.4 | - - - - - - - - - - - - - Self-administered |
|                             | Cook et al. 2019 0.81               | - - 67.2 18.9 18.9 18.9 18.9 18.9 | - - - - - - - - - - - - - Self-administered |
| Other diseases               | van Dongen-Leunis et al. 2016      | - - 54.4 54.4 54.4 54.4 54.4 54.4 | - - - - - - - - - - - - - Self-administered |
|                             | Acute leukemia 0.81 0.22            | - - 67.2 18.9 18.9 18.9 18.9 18.9 | - - - - - - - - - - - - - Self-administered |
|                             | Acute leukemia 0.85 0.18            | - - 67.2 18.9 18.9 18.9 18.9 18.9 | - - - - - - - - - - - - - Self-administered |
|                             | Hendriksz et al. 2014 0.66          | - - 54.4 54.4 54.4 54.4 54.4 54.4 | - - - - - - - - - - - - - Self-administered |

(Continued)
| Diseases                              | Health Utility | VAS scores | Have any problem in 5 dimensions (%) | Administration |
|--------------------------------------|----------------|------------|--------------------------------------|----------------|
|                                      | Mean  SD Value set | Mean  SD MO SC UA PA AD |                      |                |
| MAS use wheelchair when needed        | 0.58 - - | - - - - - - - - - - - | - - - - - - - - - - - | Self-administered |
| (adult)                               |               |            |                                      |                 |
| MAS don’t need wheelchair (children)  | 0.63 - - | - - - - - - - - - - - | - - - - - - - - - - - | Self-administered |
| MAS don’t need wheelchair (adult)     | 0.85 - - | - - - - - - - - - - - | - - - - - - - - - - - | Self-administered |
| MAS always use wheelchair (children)  | -1.18 - - | - - - - - - - - - - - | - - - - - - - - - - - | Self-administered |
| MAS use wheelchair (adult)            | 0.06 - - | - - - - - - - - - - - | - - - - - - - - - - - | Self-administered |
| Andersson et al. 2016 (89)            |                |            |                                      |                 |
| Nocturia                              | 0.78 - UK | - - - - - - - - - - - | - - - - - - - - - - - | Self-administered |
| Mealey et al. 2019 (90)               |                |            |                                      |                 |
| Neuromyelitis optica spectrum disorder| 0.74 0.16 Crosswalk | - - | 66.7 33.3 61.9 76.2 71.4 | Face-to-face. |
| Nikiphorou et al. 2018 (91)           |                |            |                                      |                 |
| Spondyloarthritis                     | 0.60 0.30 | - - - - - - - - - - - | - - - - - - - - - - - | - |
| van Assche et al. 2016 (92)           |                |            |                                      |                 |
| Ulcerative colitis                    | 0.77 0.19 | - - 70.5 19.1 | - - - - - - - - - - - | - |
| Mijarends et al. 2016 (93)            |                |            |                                      |                 |
| Sarcopenia                            | 0.78 0.19 Crosswalk | 72.0 16.0 | - - - - - - - - - - - | Face-to-face |
| Tran et al. 2018 (94)                 |                |            |                                      |                 |
| Dengue fever                          | 0.66 0.24 Crosswalk | - | 62.3 71.8 64.6 32.3 64.1 | Face-to-face |
| Chevreul et al. 2015 (95)             |                |            |                                      |                 |
| Cystic fibrosis                       | 0.67 0.25 Crosswalk | 66.6 20.0 | - - - - - - - - - - - | Self-administered |
| Collado-Mateo et al. 2017 (96)        |                |            |                                      |                 |
| Fibromyalgia                          | 0.49 0.26 Crosswalk | - | - - - - - - - - - - - | Face-to-face |
| Chevreul et al. 2015 (97)             |                |            |                                      |                 |
| Fragile X syndrome                    | 0.49 0.24 Crosswalk | 70.0 | - - - - - - - - - - - | Self-administered |
| Juul-Kristensen et al. 2017 (98)      |                |            |                                      |                 |
| Generalized joint hypermobility       | 0.82* - | Crosswalk | 81.0 | - - - - - - - - - - - | Self-administered |
| Bewick et al. 2018 (99)               |                |            |                                      |                 |
| Rhinosinusitis                        | 0.75 0.23 UK | 73.4 30.8 9.6 39.5 67.3 42.3 | Face-to-face |
| Forestier-Zhang et al. 2016 (100)     |                |            |                                      |                 |
| Fibrous dysplasia                     | 0.66 0.29 UK | 64.1 57.0 38.0 67.0 98.0 62.0 | Self-administered |
| X-linked hypophosphatemia             | 0.65 0.29 UK | 60.8 87.0 50.0 75.0 92.0 58.0 | Self-administered |
| Osteogenesis imperfecta               | 0.66 0.28 UK | 69.4 81.0 39.0 65.0 93.0 60.0 | Self-administered |
| Katchamart et al. 2019 (101)          |                |            |                                      |                 |
| Rheumatoid arthritis                  | 0.87 0.13 | - | 79.4 17.0 51.5 16.8 35.3 70.5 38.8 | - |
| Román Ivoral et al. 2019 (102)        |                |            |                                      |                 |
| Systemic lupus erythematosus          | 0.74 0.25 | - | 65.7 23.5 | - - - - - - - - - - - | Face-to-face |
| Aguirre et al. 2016 (103)             |                |            |                                      |                 |
| Dementia                              | 0.78 0.23 | - | 64.1 20.5 | - - - - - - - - - - - | - |
| Wong et al. 2017 (104)                |                |            |                                      |                 |
| Adolescent idiopathic scoliosis       | 0.93 0.11 Crosswalk | - | - - - - - - - - - - - | Self-administered |
| Christensen et al. 2016 (105)         |                |            |                                      |                 |
| Opioid-induced constipation           | 0.59 0.27 | - | 60.7 22.6 | - - - - - - - - - - - | Self-administered |
| Vo et al. 2018 (106)                  |                |            |                                      |                 |
| Migraine                              | 0.68 - - | - - - - - - - - - - - | - - - - - - - - - - - | Self-administered |
| Voormolen et al. 2019 (107)           |                |            |                                      |                 |
| Post-concussion syndrome              | 0.81 0.23 Dutch | 74.7 19.6 | - - - - - - - - - - - | Self-administered |
| Lim et al. 2017 (108)                 |                |            |                                      |                 |
| Stoma                                 | 0.80 0.16 Crosswalk | 76.0 8.7 | - - - - - - - - - - - | - |
| Villoro et al. 2016 (109)             |                |            |                                      |                 |
| Chronic depression                    | 0.74 0.28 Spain | - | 30.1 13.3 28.6 57.4 73.5 | Face-to-face |

(Continued)
The pooled utility value of patients infected with HIV was 0.84 (95% CI = 0.80–0.88, heterogeneity $I^2 = 83\%$, $P < 0.01$) using the random-effect model, and it was 0.81 (95% CI = 0.80–0.82) using the fixed-effect model (Figure 2F).

**Chronic Kidney Disease**

For chronic kidney disease patients, the health utility values ranged from 0.37 to 0.89 in three studies (55–57). The Japan value set and crosswalk UK value set were used to calculate the highest utility value (56) and the lowest value (57), respectively. The mean age of chronic kidney disease patients in the study reporting the highest value was 49.8 years old, and all of them had received kidney transplants (56), while those in the study reporting the lowest value were 59.4 years old, and 33.7% of them had been on dialysis for 4 years or longer (57). One study (57) reported that the EQ-5D VAS score was 59.4. Among the five dimensions, self-care was the dimension with the most reported problems among chronic kidney disease patients. The meta-analytic utility estimate of chronic kidney disease was 0.70 (95% CI = 0.48–0.92, heterogeneity $I^2 = 99\%$, $P < 0.01$) using the random-effect model, and it was 0.76 (95% CI = 0.74–0.78) using the fixed-effect model (Figure 2G).

**Fracture**

The health utility values of patients with fractures ranged from 0.56 to 0.88 in the three studies (59–61). However, neither of the studies that reported the maximum and minimum values described the value sets used (59, 61). The patients in the study reporting the highest value (59) had midshaft clavicular fractures and a much younger mean age (44.5 vs. 73.5 years old) than the osteoporotic vertebral compression fracture patients in the study reporting the lowest value (61). Two studies reported EQ-5D VAS scores of 80.3 (60) and 77.2 (59). No information was available for the dimensions that contributed the most to the HRQoL of fracture patients.

**Other Diseases**

For Prader–Willi syndrome, hypertension, ulcerative colitis, ankylosing spondylitis, psoriasis, actinic keratosis, Parkinson’s disease, overactive bladder, hereditary angioedema, spinal cord injury, schizophrenia, hemophilia, asthma, and hepatitis, only two studies reported the health utility values for patients with each disease. For the remaining 29 diseases (87–113), the HRQoL and utility values were only reported by one study each. Patients with adolescent idiopathic scoliosis had the highest utility value of 0.93 (104), while children with Morquio A syndrome, who must use wheelchairs, had the lowest value of −0.18 (88).

Furthermore, two studies compared utility values calculated with different country-specific value sets in the same sample (67, 87). For patients with psoriasis living in central South China (67), value sets for Japan, China, and the UK were used separately on patients who had symptomatic HIV infections. The EQ-5D VAS scores ranged from 68.8 to 88.6 in four studies (51–54). The decrease in utility in HIV-infected patients was mainly due to problems related to the anxiety/depression dimension of the EQ-5D-5L.
FIGURE 2 | Continued
FIGURE 2  (A) Forest plot of the health utility of patients with diabetes mellitus. (B) Forest plot of the health utility of patients with neoplasms. (C) Forest plot of the health utility of patients with multiple sclerosis. (D) Forest plot of the health utility of patients with cardiovascular diseases. (E) Forest plot of the health utility of patients with chronic obstructive pulmonary disease. (F) Forest plot of the health utility of patients with human immunodeficiency virus infection. (G) Forest plot of the health utility of patients with chronic kidney disease.
to obtain the EQ-5D-5L utility values, and the results were 0.86, 0.90, and 0.90, respectively. van Dongen-Leunis et al. (87) used two EQ-5D-5L country-specific value sets to calculate the health utility of acute leukemia patients, and the value derived from the Dutch value set (0.81) was lower than that derived from the UK value set (0.85). The rest of the studies all used a single value set. Compared with other dimensions, pain/discomfort was the dimension with the most problems reported by patients in most of the studies.

**DISCUSSION**

In this study, we reviewed the health utility values in patients with different diseases according to the EQ-5D-5L in cross-sectional surveys. We found that the EQ-5D-5L has been widely applied in populations with specific diseases, including various chronic non-communicable diseases, such as diabetes mellitus, neoplasms, multiple sclerosis, and cardiovascular disease, and infectious diseases, such as HIV and Dengue fever. The health utility values for a specific disease measured by the EQ-5D-5L differed based on patient characteristics, survey location, the use of country-specific value sets, and other factors. Meta-analyses were performed to synthesized utility data of any specific disease reported in three or more studies.

Health utility measures the preference of people for a given health state and reflects their status with regard to quality of life (1). Sex is one of the factors that affect health utilities (47). There are differences in the perception of health status between males and females, and in most of the included studies that reported sex-specific utilities, men had better HRQoL as measured by the EQ-5D-5L than women. For instance, the utility value was 0.80 for men with COPD and 0.69 for women with COPD, and the proportion of men who reported having problems on all five dimensions was lower than the proportion of women (47). In addition, health utility values decreased as the age of patients increased due to the deterioration of physical function and reduced disease tolerance. Among patients with COPD, for example, the utility value for patients under 65 years of age (0.77) was lower than that for patients who were 65 years old and older (0.79) (48).

In general, the severity of disease is reflected by the magnitude of the health utility value. The variation in values measured by EQ-5D-5L for the same disease under different conditions reflects its discriminative ability. As the disease progresses, the utility value decreases. Alvarado-Bolaños et al. (70) used Hoehn and Yahr staging to categorize Parkinson's disease patients into groups with mild, moderate, and severe disease, and the utility values were 0.77, 0.65, and 0.47, respectively. In addition, the number of comorbidities and the different types of comorbidities substantially affect the HRQoL of patients. Patients who have comorbidities usually report a lower utility value than those without comorbidities. Van Duin et al. (54) reported that the utility value was 0.90 in patients with HIV infections who did not have any comorbidities; however, it was reduced to 0.84 when patients had comorbid diseases. In Al-Jabi's study (58), for hypertension patients with one, two, and three or more comorbidities, the utility values were 0.81, 0.73, and 0.66, respectively.

Various living environments result in different lifestyles, which may influence HRQoL and health utility. Zyoud et al. (57) reported that among patients with end-stage renal disease in Palestine, those living in villages had a higher mean utility value than those living in cities (0.44 vs. 0.29). In another study (44), among patients with cardiovascular disease, the utility value was a little bit higher for those living in urban Vietnam than those in rural areas (0.82 vs. 0.81).

To calculate health utility, the target patients’ responses to the EQ-5D-5L and a country-specific value set are needed. The health preferences of patients living in different countries are affected by their social environment, living standards, and health system. Therefore, the EQ-5D-5L value sets based on residents' preferences for health states vary across countries or regions. Different results can be observed in the same sample when various country value sets are used to calculate health utility values. In the same sample of patients with acute leukemia, van Dongen-Leunis et al. (87) reported that the value obtained with the Dutch value set was higher than that obtained with the UK value set. In countries where the EQ-5D-5L utility value set has been estimated, it is more appropriate to use the local value set. Before any standard country-specific EQ-5D-5L value set was published, the crosswalk method developed by van Hout et al. (13) in 2012 was an alternative means of calculating health utility measured by EQ-5D-5L. For cost-utility analyses performed in England, the NICE recommends the use of the crosswalk method to obtain EQ-5D-5L utility values and calculate quality-adjusted life-years (QALYs) because there are some concerns about the current standard value set published by Devlin et al. (114). In this review, a crosswalk value set was used in half of the studies to calculate utility values due to the lack of a local standard EQ-5D-5L value set when the survey was conducted. Therefore, the crosswalk value set is still important for researchers to calculate health utility.

The heterogeneity of health utility derived from different studies for any specific disease is significant. Although, this may lead to some issues of the direct comparison among these studies, the trend of variation and the influence factors of health utility can be observed. In addition, to perform CUA, different sources of health utilities are needed to be identified and applied in the model (1). The summarization and review of health utility for different diseases are helpful and useful.

There are some limitations of this study. Among the 50 different diseases analyzed in this review, nearly half of them were only discussed in one study each. The included studies were limited to those published in English. In addition, some of the studies did not describe the value set used. This review focused on health utility measured by the EQ-5D-5L in cross-sectional studies, and the comparison of different utility-based instruments (i.e., SF-6D, HUI) in populations with specific diseases needs further exploration.

A deeper understanding of the HRQoL and health utility of patients with different diseases facilitates the provision of a more appropriate range of services for disease management and treatment. In addition, health utility is used for HRQoL weighting when calculating QALYs. QALY is used as the outcome measure in CUA and plays an important role in health technology assessments (12). The summarization of health utility...
reviewed the title/abstract independently. TZ and LW performed the original study review. TZ, HG, and YZ extracted and analyzed the data from included studies. TZ and MR assessed the methodological quality with AHRQ checklist. TZ and YZ contributed to the writing of the manuscript. All the authors approved the final version of this systematic review.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2021.675523/full#supplementary-material

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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