Themed Section: Evolution of EuroQoL

Cost-Utility Analysis Using EQ-5D-5L Data: Does How the Utilities Are Derived Matter?

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A B S T R A C T

Objectives: To explore how the use of EQ-5D-5L value set and crosswalk from EQ-5D-5L to EQ-5D-3L (and use of 3L value set) would affect cost-effectiveness analysis results for England and six other countries (Canada, the Netherlands, China, Japan, South Korea, and Singapore). **Methods:** Individual-level utilities derived from primary 5L data using both value set (5L) and crosswalk (c5L) approaches were applied to three Markov models assessing the cost-effectiveness of hemodialysis (HD) and peritoneal dialysis (PD) for end-stage renal disease (ESRD) patients to estimate incremental quality-adjusted life years (QALYs). The mathematic functions between incremental QALY and utility were derived. **Results:** 5L- and c5L-based incremental QALYs were similar in the model for non-diabetic patients (range: 1.910–2.149, 1.922–2.121). 5L tends to generate more incremental QALYs than c5L in the model for diabetic patients (range: 1.454–1.633, 1.365–1.568) but fewer incremental QALYs in the model for all ESRD patients (range: 0.290–0.480, 0.315–0.493).

In all models, 5L (c5L) generated more incremental QALYs when Chinese (South Korean) value sets were used. The largest and smallest differences in 5L- and c5L-based incremental QALYs were observed when Chinese and Dutch value sets were used. Incremental QALYs was a positive linear function of both utility of PD and difference in utilities of HD and PD. **Conclusions:** The value set and crosswalk approaches may not be used interchangeably in economic evaluation when EQ-5D-5L data are used to estimate utilities. Results of cost-effectiveness analysis using Markov models may be affected by both absolute utilities and their differences.

Keywords: cost-utility analysis, crosswalk, EQ-5D-3L, EQ-5D-5L, value set

Introduction

Cost-utility analysis (CUA) has been widely used to guide health care resource allocation. In such analyses, quality-adjusted life year (QALY) is used to quantify health outcomes [1]. The 3-level EQ-5D (EQ-5D-3L or, in short, 3L) [2] has been the preferred instrument of National Institute for Health and Care Excellence (NICE) in England for QALY estimation in economic evaluation [3] and it is also being recommended or accepted by health technology assessment agencies of many other countries [4–6]. 3L uses a health-state classification system for collecting quality of life data directly from patients and a value set, which reflects the general public's health preferences, for generating the quality of life weights ("utilities") required to estimate QALYs [7]. The

classification system defines health with five dimensions (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression) [2] and three descriptive levels (no problems, some problems, and extreme problems) for each dimension.

Recently, a new, 5-level EQ-5D (EQ-5D-5L or 5L) was developed by the EuroQol Group [8]. It measures health in the same five dimensions as 3L but with five descriptive levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. Many studies have demonstrated the superiority of 5L versus 3L in measurement properties such as ceiling effects, reliability, and sensitivity [9–11]. Using a standardized study protocol and data collection instrument [12], many countries have developed their own 5L value sets, for example, Canada, England, and the Netherlands [13], and more are underway. Moreover, a

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5L-to-3L crosswalk algorithm was developed by van Hout et al. as an interim solution for countries where only a 3L value set is available [14].

Although the 5L was developed with the intention to supersede the 3L, little is known about the impact of this switch on outcomes of economic evaluation. Nevertheless, a recent study by Hernandez et al. [15] found that the English 5L value set is very likely to generate fewer QALYs and higher incremental cost-effectiveness ratios (ICERs) than the UK 3L value set in cost-effectiveness analysis of health technologies, raising concerns about consistency in decision making if 3L is replaced with 5L in decisions affecting the National Health Service. As a result, NICE recently stated its position of continuing to recommend EQ-5D-3L and recommended using van Hout et al.'s [16] crosswalk algorithm, as opposed to the English 5L value set, to estimate QALYs when 5L data are available; health technology assessment agencies in other countries have not formally stated a position on use of the 5L, either because they have less formalized "reference case" requirements than NICE, or because no 5L value set studies have been undertaken in their jurisdictions yet.

NICE's position is partly based on the assumption that the 5L value set and the crosswalk approaches would lead to different conclusions in cost-effectiveness analysis [17]. This assumption, however, has not adequately been tested empirically. The study by Hernandez et al. [15] used mapping functions to generate 5L data from 3L data. It has been well documented that mapping or crosswalk generally produces biased estimates [18].

Therefore, in the present study, we aimed to examine whether the use of 5L value set and crosswalk approaches would affect cost-effectiveness analysis results by incorporating primary 5L data collected in patients with end-stage renal disease (ESRD) into three Markov models for assessing the cost-effectiveness of dialysis treatments with utilities derived from applying the two approaches to primary 5L data. We used the 3L and 5L value sets of England and six other countries in order to evaluate the transferability of the issue across countries. We also aimed to explore the reasons for the different cost-effectiveness analysis results if such variations exist.

Methods

Decision Analytic Models

Three decision analytic models used in two recently published CUA studies of hemodialysis (HD) and peritoneal dialysis (PD) for ESRD patients conducted in Singapore [19] and Norway [20] were used in the present study. In the Singaporean study, two Markov models were constructed for non-diabetic and diabetic patients separately using different parameter values. Those two models were rerun in this study as model 1 (non-diabetic patients) and model 2 (diabetic patients). In the Norwegian study, an overall Markov model was estimated. It was used as model 3 (all ESRD patients) in this study. Models 1 and 2 assume that patients start in either HD or PD state and remain in this state or move to transplantation or death state in a subsequent cycle (1 cycle = 1 year). The structure of model 3 is identical to that of models 1 and 2 except that transition between HD and PD is allowed (Fig. 1).

Transition probabilities of models 1 and 2 were estimated using a cohort of dialysis patients followed up by a tertiary hospital in Singapore [21] and the national renal registry of Singapore [22] (see Appendix Table 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.05.008 for details), and a 10-year time horizon was assumed. In model 3, the time horizon (5-year) and transition probabilities were estimated using Norwegian renal registry data and the relative risk for mortality (PD vs. HD) was based on a systematic review and meta-analysis of 10
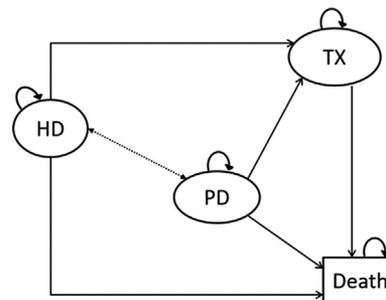

Fig. 1 – Markov diagram for the cost-effectiveness model of HD and PD for patients with end-stage renal disease. Arrows indicate allowed transitions. Dashed arrow indicates transitions between HD and PD that were only allowed in model 3.
HD-hemodialysis, PD-peritoneal dialysis, TX-transplantation.

published effectiveness and cost-effectiveness studies comparing HD and PD (see Appendix Table 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.05.008 for details).

Quality of Life Data

In a cross-sectional survey, a consecutive sample of 150 ESRD patients undergoing dialysis (HD: 75, PD: 75) for at least 3 months was interviewed by a trained interviewer using the EQ-5D-5L questionnaire and questions assessing sociodemographic characteristics [23].

Estimation of Utilities

Individual-level utilities were generated using both 5L value sets and 3L value sets from seven countries via a "crosswalk" between the 5L and 3L descriptive systems. The main characteristics of the value sets are summarized in Table 1.

First, utilities were calculated using seven recently developed country-specific 5L value sets: England [24], Canada [25], Japan [26], the Netherlands [27], South Korea [28], China [29], and Singapore (unpublished data; see Appendix Table 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.05.008). These value sets were developed using time trade-off (TTO) data alone or both TTO and discrete choice experiment (DCE) data collected from the general public using a standardized protocol and survey tool [12].

Second, utilities were calculated using van Hout et al.'s crosswalk algorithm [14] and 3L value sets available for the UK [30], Canada [31], Japan [32], the Netherlands [33], South Korea [34], China [35], and Singapore [36]. The algorithm was developed using a large dataset containing responses of individuals in varied health status to both 3L and 5L items. It maps each 5L state to one or more 3L states with corresponding probabilities [14]. The utilities were calculated as the weighted sums of the 3L values by the probabilities. The crosswalk-derived utilities are hereafter referred to as "c5L" values.

After individual-level EQ-5D utilities were calculated, multivariate OLS regression models were used to predict the mean utility values for HD- and PD-treated non-diabetic and diabetic ESRD patients and used in model 1 and 2, respectively. And then using the proportion of diabetic patients in Norway, the mean utility values for all ESRD patients were calculated and used in model 3. The analysis was done for each set of country-specific 5L and c5L values. The predicted health utilities for HD and PD were

Table 1 – Methods to generating health utilities from EQ-5D-5L

Calculation methods	Author	Value set country	Sample size	Valuation method	Value range
5L value set	Devlin et al. [24]	England	912	Composite TTO & DCE	(−0.285, 1)
	Xie et al. [25]	Canada	1073	Composite TTO	(−0.148, 0.949)
	Versteegh et al. [27]	The Netherlands	979	Composite TTO	(−0.446, 1)
	Luo et al. [29]	China	1271	Composite TTO	(−0.391, 1)
	Shiroiwa et al. [26]	Japan	1026	Composite TTO	(−0.025, 1)
	Kim et al. [28]	South Korea	1080	Composite TTO	(−0.066, 1)
	Luo et al. [36]	Singapore	1000	Composite TTO	(−0.984, 1)
3L value set	Dolan et al. [30]	UK	3395	Conventional TTO	(−0.594, 1)
	Bansback et al. [31]	Canada	1145	Conventional TTO	(−0.340, 1)
	Lamers et al. [33]	The Netherlands	309	Conventional TTO	(−0.329, 1)
	Liu et al. [35]	China	1147	Conventional TTO	(−0.149, 1)
	Ikeda et al. [32]	Japan	621	Conventional TTO	(−0.111, 1)
	Lee et al. [34]	South Korea	1264	Conventional TTO	(−0.171, 1)
	Luo et al. [36]	Singapore	456	Composite TTO	(−0.769, 1)

DCE, discrete choice experiment; TTO, time trade-off.

used in cost-utility models. The health utilities for transplantation were obtained from a published meta-analysis [37].

Analysis of Markov Models

For each set of the utilities, a hypothetical cohort of 10,000 patients was modeled to estimate the incremental QALYs gained from HD and PD for an average patient in the three models. Discounting at an annual rate of 3% was applied. Direction and magnitude of the difference in 5L and c5L based incremental QALYs estimated from the models were examined for each country. The mathematic functions based on the Markov processes for estimating incremental QALYs were used to examine the relationship between utility and incremental QALY. All the Markov models were analyzed using Microsoft Excel 2016 (Microsoft Corporation, Redmond, WA, USA).

Results

All EQ-5D utilities showed that patients on HD had better quality of life than those on PD (Table 2). For all three models, the mean absolute utilities for HD and PD and the differences between the two dialysis treatments varied with the approach used to generate the utilities. All countries considered, the 5L values were generally higher and exhibited slightly smaller differences than the c5L values (Table 2).

The estimated incremental QALYs are summarized in Table 2. In the model for non-diabetic ESRD patients, incremental QALYs based on 5L and c5L estimated using value sets of the seven countries ranged from 1.910 to 2.149 and 1.922 to 2.121, respectively. In the model for diabetic ESRD patients, incremental QALYs based on 5L (range: 1.454–1.633) were generally higher than those based on their corresponding c5L values (range: 1.365–1.568). In the model for all ESRD patients, incremental QALYs based on 5L

Table 2 – Utilities and incremental QALYs estimated using two approaches of seven countries

Value set country	Value	Utilities									Incremental QALYs		
		Model 1			Model 2			Model 3					
		HD	PD	Difference (HD − PD)	HD	PD	Difference (HD − PD)	HD	PD	Difference (HD − PD)	Model 1	Model 2	Model 3
England/UK	5L	0.882	0.803	0.079	0.739	0.677	0.062	0.833	0.760	0.073	2.011	**1.603**	0.318
	c5L	0.828	0.714	0.114	0.631	0.544	0.087	0.761	0.656	0.105	**2.094**	1.508	**0.416**
Canada	5L	0.873	0.789	0.084	0.743	0.675	0.068	0.829	0.750	0.079	**2.021**	**1.633**	0.337
	c5L	0.838	0.749	0.089	0.705	0.640	0.065	0.793	0.712	0.081	1.985	1.554	**0.341**
The Netherlands	5L	0.849	0.773	0.076	0.708	0.650	0.058	0.801	0.731	0.070	1.939	**1.533**	0.306
	c5L	0.845	0.767	0.078	0.693	0.634	0.059	0.794	0.721	0.073	**1.942**	1.510	**0.315**
China	5L	0.874	0.768	0.106	0.704	0.618	0.086	0.816	0.717	0.099	**2.134**	**1.633**	**0.401**
	c5L	0.831	0.750	0.081	0.695	0.637	0.058	0.785	0.712	0.073	1.932	1.510	0.315
Japan	5L	0.850	0.780	0.070	0.721	0.668	0.053	0.807	0.742	0.065	1.910	**1.536**	0.290
	c5L	0.819	0.736	0.083	0.669	0.611	0.058	0.768	0.693	0.075	**1.922**	1.464	**0.320**
South Korea	5L	0.858	0.782	0.076	0.725	0.670	0.055	0.813	0.744	0.069	1.954	1.551	0.304
	c5L	0.852	0.757	0.095	0.702	0.632	0.070	0.801	0.714	0.087	**2.040**	**1.568**	**0.361**
Singapore	5L	0.796	0.660	0.136	0.555	0.447	0.108	0.714	0.588	0.126	**2.149**	**1.454**	0.480
	c5L	0.765	0.624	0.141	0.498	0.387	0.111	0.674	0.543	0.131	2.121	1.365	**0.493**

Bold values indicate the higher estimated incremental QALY.
ESRD, end-stage renal disease; HD, hemodialysis; PD, peritoneal dialysis; QALY, quality-adjusted life year.
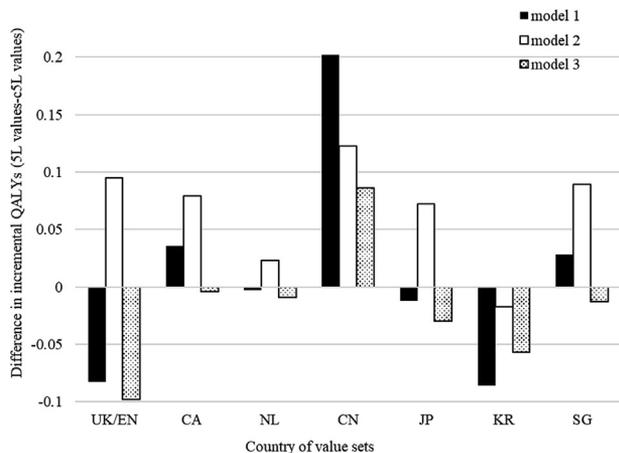
Fig. 2 – Difference in 5L and c5L based incremental QALYs by country of value sets.
CA-Canada, CN-China, EN-England, JP-Japan, KR-South Korea, NL-the Netherlands, SG-Singapore, UK-United Kingdom.

(range: 0.290–0.480) were lower than those based on their corresponding c5L values (range: 0.315–0.493).

In all three models, 5L (c5L) generated more incremental QALYs when value sets of China (South Korea) were used. Such patterns were not observed for other counties. The magnitude of the differences in 5L- and c5L-based incremental QALYs estimated in the models varied with the value sets used (Fig. 2). The largest and smallest differences were observed when value sets of China (range: 0.086–0.202) and the Netherlands (range: −0.009 to 0.023) were used, respectively. In all models, incremental QALY was a positive linear function of both utility of PD and difference in utilities of PD and HD (see Appendix Table 3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.05.008 for details).

Discussion

To the best of our knowledge, this is the second study aiming to assess the impact of switching from 3L to 5L on economic evaluation. There are two important differences between our study and the earlier work by Hernandez et al. [15]. First, we used 5L data, whereas Hernandez et al. used 3L data. Second, we examined multiple models for assessing the same health technologies, but Hernandez et al. studied multiple models each assessing a different health technology. Our finding is consistent with that of Hernandez et al.'s analysis [15] in one respect: the estimated incremental QALYs derived from the English 5L value set and the crosswalk approach differ, supporting the concern that concurrent use of 3L and 5L value sets in England could lead to inconsistent decisions. However, in contrast to Hernandez et al. [15], we observed that the English 5L value set has a fairly reasonable chance (1 in 3 models) of exhibiting higher incremental QALYs than the UK 3L value set when applied to primary EQ-5D-5L data. This is in contrast to Hernandez et al.'s finding that in eight of nine cost-effectiveness case studies, the UK 3L value set led to higher estimates of incremental QALYs compared to the English 5L value set [15]. This inconsistent finding is not surprising because both studies are based on convenient CUAs; generalizability of both studies is limited. Nevertheless, our study shows that certain cost-effective health technologies may be erroneously rejected by the National Health Service if only crosswalk-based QALY estimates

are used in CUA when 5L data are available. This suggests that it may be important to use both utility values derived from the crosswalk and the English 5L value set and to check the sensitivity of results before either approach is adopted as the reference case.

We found that the incremental QALYs derived from the Dutch 5L value set and the crosswalk approach were very similar, suggesting that the two approaches may be used interchangeably for economic evaluation in the Netherlands. This may be because that Dutch 5L and 3L value sets are similar in terms of minimum value, value range, and shape of distribution [27], whereas there are great differences between English 5L and UK 3L values sets [38]. This finding in turn suggests that switching from 3L to 5L may not cause any inconsistency in reimbursement decision making and therefore unlike England, Dutch 3L and 5L value may be used concurrently in health technology assessment because EQ-5D is the preferred utility instrument in the Netherlands. The finding that the magnitude of differences between the two approaches varied across the seven countries suggests that experience from any one country may not be transferrable to other countries, in line with previous findings that country-specific EQ-5D value sets would generate different CUA results [39,40]. This result also suggests that switching from 3L to 5L could lead to more favorable or unfavorable cost-effectiveness outcomes in Canada, China, Japan, South Korea, and Singapore. This is not an immediate issue for the health technology assessment agencies in those countries because a reference case has not been implemented. However, it would be wise to designate a utility instrument within each jurisdiction, at least for the five countries studied if both the 3L and 5L are candidates. Which version of the EQ-5D should be used is a complex question, involving both the measurement properties of the two versions in describing patient health, and the characteristics of the value sets used to preference weight them. Addressing this as an issue arguably supersedes other considerations such as continuity and consistency in decision making of health authorities.

The finding that incremental QALYs were a function of both utility of PD and difference in utilities of PD and HD suggests that the effect of heath-state utility on cost-effectiveness outcomes is not solely through the difference in utilities of the alternatives. Absolute utilities of the alternatives also matter and may have a greater effect than the difference in the utilities of the alternatives. This was clearly demonstrated by results of models 1 and 2, for example, when the English 5L value set was used to estimate utilities for model 2, more incremental QALYs were estimated even though the difference in 5L-based utilities of HD and PD was smaller than that based on c5L-based utilities. Thus, this finding invalidated the naïve notion that magnitude of the difference in utilities of alternatives alone determines incremental QALYs in CUA, an implicit assumption used by many studies of utility instruments [23,41,42].

The main limitation of the study is the use of conveniently available EQ-5D data and models for assessing dialysis treatments, which undoubtedly limits the generalizability of its findings. A systematic investigation of the issue of concern for health technologies in all main therapeutic areas with models and EQ-5D primary data from all main populations would be ideal. However, such a study would be very costly and therefore is not feasible. Tapping on the issue in the manner of case studies is a more pragmatic approach. Therefore, we call for more studies into the issue to further our knowledge about it. It would be particularly useful to make head-to-head comparison of 3L and 5L value sets using primary 3L and 5L data, respectively [17]. Both Hernandez et al. and us used only one type of EQ-5D data and generated the other type of data through crosswalk. Because the crosswalk is bound to suffer from biases, such studies cannot accurately assess the impact of switching from 3L to 5L on CUA results.

Conclusions

The value set and crosswalk approaches may not be used interchangeably in economic evaluation when EQ-5D-5L data are used to estimate utilities. Results of cost-effectiveness analysis may be affected by both absolute utilities and their differences. More research is needed to inform how the two versions of EQ-5D should be used in health technology assessment.

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Supplementary Materials

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2018.05.008.

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