RESEARCH ARTICLE

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Mapping EORTC-QLQ-C30 onto EQ-5D-5L Index in Indonesian Cancer Patients

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Abstract

Objective: This study aims to develop a mapping algorithm for EORTC QLQ-C30 to EQ-5D-5L which can produce utility values in patients with cancer. **Methods:** We used a cross sectional study design with 300 cancer patients. The research instruments used were EORTC QLQ-C30 and EQ-5D-5L. Data were collected by interviewing cancer patients who were hospitalized in the Kasuari Installation of Dr Kariadi Hospital Semarang, Indonesia. The Ordinary Least Squares (OLS) regression method was used to predict the utility value of EQ-5D-5L. This study uses two models to predict utility values, namely model 1 with all domains, and model 2 with domains that affect the EQ-5D-5L. The predictive power of regression on the model is evaluated by calculating the mean absolute error (MAE) and root mean square error (RMSE) values. **Result:** The highest score in the functional domain is the 'emotional function' domain (mean: 85.89; SD: 16.04) and the highest symptom domain is 'weakness' (mean: 36.21; SD:21.69). The predicted utility values of models 1 and 2 are 0.683. The mean absolute error (MAE) and root mean square error (RMSE) values of model 1 are 0.128 and 0.173, while in model 2 the MAE and RMSE values obtained are 0.125 and 0.168. **Conclusion:** The development of the mapping algorithm from the EORTC QLQ-C30 to EQ-5D-5L instrument shows a predictive value of utility in a sample of patients with cancer at Dr. Kariadi Hospital, Semarang, Indonesia. The utility prediction in both model is similar, however model 2 involves fewer domains and symptoms.

Keywords: Mapping- utility- EORTC-QLQ-C30- EQ-5D-5L- cancer

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Introduction

Appraisal of the effects of available alternatives regarding health, health care costs, and other effects, namely health technology assessment (HTA), are important in addition to assessing clinical efficacy. Cost-utility analysis (CUA) is one of the most prevalent methods in HTA, by evaluating health-related quality of life (HRQOL) outcomes and comparing costs and outcomes between different health care programs in terms of cost per Quality Adjusted Life Years (QALY) (Drummond et al., 2015). To obtain a QALY, utilities of a health state are differentiated over a lifetime. This utility is measured by generic multi-attribute utility instruments (MAUIs). The three most frequently mentioned MAUIs in HTA guidelines across the world are the EQ-5D, Health Utility Index (HUI), and the Short-Form 6-Dimension (SF-6D) (Kennedy-Martin et al., 2020).

Measures of HRQOL are often applied as a secondary outcome of studies in cancer patients. Researchers often prefer to use disease specific HRQOL questionnaires over generic ones in their studies. It has been argued that generic measures are not as sensitive to changes in quality of life in certain diseases as condition-specific measures (Lorgelly et al., 2017). However, these disease-specific questionnaires are not preference-based measures and unable to produce utilities of health states. Therefore, these questionnaires cannot be used directly for estimating the QALYs.

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) is one of the most widely used instrument to measure the quality of life of cancer patients (Aaronson et al., 1993). The Indonesian version of the EORTC QLQ-C30 has been validated for use in Indonesian cancer patients (Perwitasari et al., 2011). For obtaining utility from a disease-specific questionnaire such as the EORTC QLQ-C30, one solution offered is

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mapping technique. This technique usually consists of two stages: (i) calculate the relationship between the preference-based questionnaires (as the outcomes) and the non-preference-based as the independent variables, and (ii) use this relationship in the datasets containing the non-preference-based measure for prediction of EQ-5D-5L index (Ameri et al., 2020; Chen et al., 2019).

In this study, we used the EQ-5D-5L as the preference-based questionnaire, because it has been proven as valid in Indonesian cancer patients (Setiawan et al., 2018) and has a national value set to obtain utilities (Purba et al., 2017). Therefore, the aim of the present study was to map the EORTC QLQ-C30 responses to the EQ-5D-5L in cancer patients in Indonesia.

Materials and Methods

Respondents

We collected data from three patient groups: breast cancer, nasopharyngeal cancer, and colorectal cancer. The inclusion criteria were: (i) diagnosed with breast cancer, nasopharyngeal cancer, or colorectal cancer, (ii) aged 18 years and above, (iii) having an adequate command of the Indonesian language (Bahasa Indonesia), and (iv) willing to participate in this study. Exclusion criteria were the following: (i) refusing to participate, (ii) having complications such as type 2 diabetes mellitus, cardiovascular disorders, impaired kidney function disorders, liver function disorders, or communication disorders, as assessed by physician which were reported in the medical records. The researcher assisted the patients in completing the questionnaires, thus we also involved the patients who illiterate. The clinical data were collected from patients' medical records.

Procedures

The present study was approved by the Health Research Ethics Committee, Dr. Kariadi Hospital, Semarang (Number: .401/EC/KEPK-RSDK/2019). This study was conducted in RSUP Dr. Kariadi in Semarang, Indonesia from May to July 2020. The researcher approached patients in the waiting room of the hospital, introduced this study and asked for their participation. After informed consent was signed, the patients completed the socio-demographic data, EQ-5D-5L, and EORTC QLQ-C30. The researcher helped patients to complete the questionnaires when needed.

Instruments

We collected the demographic of the patients, including name, age, gender, education level, marital status, and monthly income. Their medical data were collected from the medical record: cancer type, stage, and treatment cycle.

The cancer-specific health-related quality of life (HRQOL) questionnaire being used in this study was the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30). It consists of five function domains (physical, emotional, social, role, cognitive), three symptom scales (fatigue, nausea and vomiting, pain), and six single items for various symptoms (shortness of breath, insomnia, loss of appetite, constipation, diarrhea, and financial difficulties) and one general health status scale (Aaronson et al., 1993). Patients respond on a four-point scale from "not at all" to "very much" for most items. Most items use a "past week" recall period. The scores of each scale were calculated in two stages: first, the raw score is calculated. Then, a linear transformation is used to convert the score into a range of 0 to 100. Higher functional scale and global health status/QoL scale scores indicate better functioning and HRQOL, respectively, whereas higher symptom and single items scores depict worse status (Fayers et al., 2001). The EORTC QLQ-C30 has been translated into Bahasa Indonesia and validated to assess the quality of life in cancer patients in Indonesia (Perwitasari et al., 2011).

The generic HRQOL instrument being used was the Bahasa Indonesia version of EQ-5D-5L provided by the EuroQol Group. [The EQ-5D-5L is a generic HRQOL instrument which consists of two parts: the descriptive system and the EQ-visual analogue scale (EQ-VAS). The descriptive system consists of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression), each of which can take one of five severity level responses (no problems, slight problems, moderate problems, severe problems, and unable/extreme problems). Combination of these five dimensions and five severity level resulted in 3125 (5) unique health states. Each health state is then translated into utility values using the Indonesian EQ-5D-5L value set (Purba et al., 2017). The EQ Visual Analogue Scale (EQ-VAS) records the respondent's self-rated health on a 20 cm vertical visual analogue scale with endpoints labelled "the best health you can imagine" and "the worst health you can imagine" (Herdman et al., 2011). The EQ-5D-5L has been proven to be valid (Setiawan et al., 2018) and reliable (Purba et al., 2018) to be used on the Indonesian population.

Data analysis

The demographic and medical characteristics are described as percentages within the subgroups: i.e., age, gender, education level, marital status, monthly income, cancer types, cancer stage and cycle number. We divided our final dataset into derivation (n=266) and validation (n=34) data sets. The proportion of training data set was bigger than the proportion of validation data set The validation was applied to get the description that the conceptual model approached the real situation. To obtain the mapping algorithm, ordinary least squares (OLS) regression was used. EQ-5D-5L utility value served as the dependent variable and the EORTC QLQ-C30 scale and item scores were the explanatory or independent variables. We treated all variables as continuous. The model 1 (full model) was determined using all scales and items of the EORTC QLQ-C30. The second model (model 2) was developed using backward elimination with a significance level of 0.1 from the model 1. The model 2 was run to get the optimum performance after the backward elimination of model 1.

The validation of the obtained algorithm was done by assessing the accuracy of the prediction: (i) mean absolute error (MAE) is the mean absolute difference between the

observed and predicted values, (ii) and root-mean-squared error (RMSE) is the root of the mean squared difference, also reported as a percentage of the scale size (i.e., 1.865, the range of the EQ-5D-based utility according to the Indonesian value set), referred to as the normalized RMSE (Versteegh et al., 2012). Smaller MAE and RMSE values indicate better model performance.

Statistical analyses were performed using SAS software (ver. 9.1; SAS Institute Inc., Cary, NC). P<0.05 was considered statistically significant.

Results

Our study has the aim to explore the mapping of utility value of cancer patients using EORTC-QLQ-C30 and EQ-5D-5L. We also describe the cancer patients' quality of life measured by the two instruments.

Table 1 shows the patients characteristics. Most of the patients are female (N=216; 72.0%), diagnosed with breast cancer (139; 46.33%), less than 60 yo (266; 88.67%), advanced stage of cancer (234; 78.00%), graduated from senior high school (97; 32.43%), having occupation (148; 49.33%) and married (246; 82.00%).

Table 2 shows that the mean of EQ-5D-5L utility values is 0.68 (SD: 0.32) while the mean of self-rated health is 74.34 (SD: 12.22). For EORTC QLQ-C30, the general QoL mean is 72.19 (SD: 17.42). All domains had the score between 72.19- 87.78, which is in the category of good quality of life. The highest domain score is cognitive domain (mean: 87.78; SD: 16.24) and the lowest score domain is physical domain (mean: 72.51, SD: 24.92). Among the symptoms, the worst symptom reported by the patients is weakness (mean: 36.22; SD: 21.69). The EORTC QLQ overall mean score is lower than the score on its lowest domain (i.e., 'physical domain').

Table 3 shows the results of OLS regression analysis for the mapping model from two models: i.e., Model 1 with all scales included and Model 2 with only scales with a significance level of 0.1 from the model 1. The statistically significant values are shown in the physical domain, role domain, emotional domain, pain symptom and financial difficulties score ('financial difficulties' are not a symptom). The most influential domain in both models is physical domain.

The predicted utility scores are defined from individual patients in the validation sample (Table 4). Table 4 also shows the performance of the two models in predicting EQ-5D-5L utility values. The explanatory power for model 1 and model 2 is 73.7% and 74.4%, respectively. Model 2 shows better MAE and RMSE compared to Model 1. Table 5 shows the validation result of model analysis.

Table 1. Cancer Patients' Characteristics (n=300) in Dr. Kariadi Hospital from May to July 2020

Characteristics	N	%
Age (yo)		
≤60	266	88.67
>60	34	11.33
Sex		
Male	84	28.00
Female	216	72.00
Cancer type		
Breast	139	46.33
Colorectal	41	13.67
Nasopharing	120	40.00
Cancer stage		
1-2	66	22.00
3-4	234	78.00
Last education		
No schooling	12	4.00
Elementary	76	25.33
Junior High School	43	14.33
Senior High School	97	32.33
Undergraduate	72	24.00
Work		
Yes	148	49.33
No	152	50.67
Marietal Status		
Married	246	82.00
Not married	54	18.00
Salary per month (IDR)		
< 2.500.000	108	35.00
≥ 2.500.000	192	65.00

IDR, Indonesian Rupiah

Table 2. Utility and VAS of EQ-5D-5L and Domains' Scores of EORTC QLQ-C30 in Cancer Patients of Dr. Kariadi Hospital from May to July 2020 (N=300)

EQ5D5L	Mean	SD
Utility	0.68	0.32
Visual Analog Scale	74.34	12.22
EORTC QLQ-C30		
Domains		
Physical	72.51	24.92
Role	73.17	29.64
Emotional	85.89	16.04
Cognitive	87.78	16.24
Social	79.67	25.41
Symptoms		
Weakness	36.22	21.69
Nausea-Vomiting	24.67	24.47
Pain	34.5	30.69
Dyspnea	4.78	14.53
Insomnia	33.00	35.28
Loss of appetite	32.67	30.9
Constipation	14.89	25.42
Diarrhea	7.67	18.4
Financial difficulties	30.67	33.26
General QoL	72.19	17.42

QoL, Quality of life

Table 3. Performance of Model for Predicting the Utility Value from Derivation Dataset from Cancer Patients of Dr. Kariadi Hospital from May to July 2020 (n=266)

	Model 1			Model 2		
	β	S.E	*p-value*	β	S.E	*p-value*
Intercept	-0.105	0.114	0.359	-0.033	0.760	
Physical domain	0.008	0.001	0.000	0.008	0.001	0.000
Role domain	0.001	0.001	0.032	0.001	0.001	0.029
Emotional domain	0.001	0.001	0.098	0.001	0.001	0.020
Cognitive domain	0.001	0.001	0.175			
Social domain	0.001	0.005	0.210			
Weakness	0.000	0.001	0.645			
Nausea-Vomiting	0.000	0.005	0.320			
Pain	-0.002	0.005	0.001	-0.002	0.000	0.000
Dyspnea	0.000	0.001	0.971			
Insomnia	0.000	0.000	0.449			
Loss of appetite	0.000	0.000	0.919			
Constipation	0.000	0.000	0.931			
Diarrhea	0.000	0.001	0.814			
Financial difficulties	-0.001	0.000	0.023	-0.001	0.000	0.008
General QoL	-0.001	0.001	0.365			

QoL, Quality of life

Discussion

Our study defines the algorithm of mapping the EORTC QLQ-C30 onto the EQ-5D-5L. Based on the regression analysis, model 2, consisted of the physical domain, role domain, emotional domain, pain symptom and financial difficulties symptoms as the predictors for EQ-5D-5L utility value. The parameters of predictability and consistency in both models are similar, presented by the lower MAE and RMSE and high R square.

Our study finds that the two models show a good predictive power of regression performance. The results of the predictability and consistency values are similar to the previous studies in colorectal cancer and non-small cell lung cancer (Khan et al., 2016; Marriott et al., 2017; Versteegh et al., 2012). Another previous study in breast cancer, shows lower MAE and higher RMSE (E. Kim et al., 2012).

The physical domain and role domain became the predictors of EQ-5D-5L, due to the physical condition after cancer treatment and the patients have to limit their role in some activities to keep their body fit (Zandbergen et al., 2019). Dyspnea was experienced by around 40% advanced cancer of patients. Its prevalence may be increased due to the worsening of other symptoms and can cause deterioration of quality of life (Damani et al., 2018). Furthermore, nausea-vomiting is the most frightening side effect for the cancer patients, due to the emetogenic effect of cytostatic drugs (Perwitasari et al., 2012). Our study shows that weakness is the most experienced symptom, which could be caused by the advanced stage of cancers as well. The previous study shows that the predictors of

Table 4. The Models for Predicting the Utility Value in Cancer Patients of Dr. Kariadi Hospital from May to July 2020

Model	Actual EQ-5D-5L mean utility (SD)	Predicted EQ-5D-5L mean utility (SD)	Adjusted R^2	MAE	RMSE
Model 1: full	0.682 (0.323)	0.683 (0.279)	0.737	0.128	0.173
Model 2: Backward Method	0.682 (0.323)	0.683 (0.278)	0.744	0.125	0.168

Table 5. Results of Model Analysis in Validation in Cancer Patients of Dr. Kariadi Hospital from May to July 2020 (n=34)

	Mean Actual (SD)	Mean Predicted (SD)	Mean Absolute Error	R-Square	RMSE
Validation data set					
Model 1 : EORTC	0.7109 (0.2703)	0.7076 (0.2207)	0.1095	0.6706	0.1528
Model 2 : EORTC (Backward Method)	0.7109 (0.2703)	0.7114 (0.2255)	0.1119	0.6793	0.1508
Derivation data set					
Model 1 : EORTC	0.7197 (0.2749)	0.7197 (0.2315)	0.1058	0.7089	0.1477
Model 2 : EORTC (Backward Method)	0.7197 (0.2749)	0.7197 (0.2307)	0.1075	0.7042	0.1488

EQ-5D-5L were global health, physical, role, emotional functions and pain. This model has MAE of 0,069 and RMSE of 0.095 (Kim et al., 2012).

The two models in our study, using the OLS with full model and backward elimination model, show similar performance. Other previous studies showed that the backward elimination model had a good performance (Crott and Briggs, 2010). Another study with stepwise regression model demonstrated a good performance with global, physical and emotional domains (Kontodimopoulos et al., 2009). With these results, we suggest the use of model 2 for predicting the utility value of EQ-5D-5L.

One limitation from the present study is that we only collected data for the validation and derivation data set from one hospital. This might limit the generalizability of our findings. Further study involving patients from various hospitals is warranted. Another limitation pertains to the inclusion of patients with one of three types of cancer due to the available diagnosis during the study period. According to the Globocan 2018, the most frequent cancer in Indonesia are breast cancer both in male and female, lung cancer and colorectal cancer in males (GLOBOCAN, 2018) .

Author Contribution Statement

DAP and FDP are contributed in the conceptualization of the study, study design, data validation, data analysis, writing the manuscript and reviewing the manuscript; SFC contributed in data validation, data analysis, investigation, writing the manuscript and reviewing the manuscript; MM, AP and MBUF contributed to the data collection, investigation, data analysis, writing the manuscript and reviewing the manuscript; BPS and AAK contributed in study design, data collection, data validation, writing the manuscript and review the manuscript, AAK contributed to the conceptualizations and reviewing the manuscript.

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General

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Approval

All authors have approved the manuscript content

Ethical Declaration

This research is registered and approved by Ethics Committee of Dr. Kariadi Hospital No.401/EC/KEPK-RSDK/2019

Data Availability

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request

Conflict of Interest

All authors have no conflict of interest

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