

Original article

Health state utilities for metastatic breast cancer in Taiwan

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ABSTRACT

Background: New developments in medications for metastatic breast cancer (MBC) can be of great benefit to patients, but unfortunately these medicines also increase expenditures. Cost-utility analyses (CUAs) are needed to allocate health resources properly, and health utility values are required to calculate quality-adjusted life years in those CUAs.

Objective: The aims of this study were to measure health utility values for several MBC-related health states and certain breast cancer treatment-related grade 3/4 adverse drug reactions (ADRs). In addition, we examined whether different methods and respondents' characteristics would influence the utility values elicited.

Methods: A cross-sectional survey was conducted. The visual analogue scale (VAS) and time trade-off (TTO) methods were used to measure health utilities. Four MBC and nine ADR health states were selected for evaluation based on literature review and expert opinion. Information about respondents' demographic and clinical characteristics were collected to examine the relationship between utilities and participant characteristics.

Results: A total of 102 patients participated in this study. The TTO-elicited values were higher than the VAS-derived scores except for two MBC-related health states. Among the MBC health states assessed, the TTO preference score ranged from 0.04 (palliative MBC) to 0.62 (responding MBC). For grade 3/4 ADRs, the mean TTO-derived utility values ranged from 0.35 (nausea/vomiting) to 0.79 (fatigue). The ranking of the preference scores derived from the VAS was similar to that of the TTO-elicited scores.

Conclusion: This study obtained health state utility values for MBC and grade 3/4 ADRs using both the TTO and the VAS, which provides useful data for future CUAs.

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1. Introduction

Among all the cancer types, female breast cancer has the highest incidence, with an estimated twelve thousand new cases annually in Taiwan [1]. According to the National Health Insurance (NHI) annual statistics in 2017, more than NTD thirteen billion were spent on breast cancer, and the expenditures for breast cancer increased by 7.8% from 2013 to 2017 [2]. Although the economic burden of breast cancer is huge and still growing, less than one-quarter of the

patients diagnosed with stage-four breast cancer, or so-called metastatic breast cancer (MBC), survived over five years.

New medications for MBC have been increasingly developed in the past few years [3]. Given the limited budgets of the healthcare system, policymakers require economic evaluations to decide which treatments should be reimbursed [4]. Both the Taiwanese health technology assessment agency and most of the European health-economic guidelines recommend cost-utility analysis (CUA) [5,6]. To perform a CUA, it is crucial to collect health state utilities for use in calculating quality-adjusted life years (QALYs). Health state utility is a cardinal value that reflects individuals' preference for a specific condition [7]. Three common techniques for the direct valuation of health utilities are the visual analogue scale (VAS), the standard gamble (SG), and the time trade-off (TTO).

Several studies have measured health utilities for MBC in

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various countries. Lloyd et al. measured three MBC health states with or without chemotherapy-related ADRs among 100 subjects from the general population in the UK using the SG and the VAS [8]. Frederix et al. collected utilities for stable and progressive states as well as seven grade 3/4 adverse events of HER2+ advanced breast cancer in 100 individuals sampled from the general public using the TTO and the VAS [9]. As factors such as measurement methods, respondents' sociodemographics, and country variation may have influenced the utility values elicited [10], making use of these health utilities in Taiwan might not be appropriate. Therefore, the primary objective of the present research was to measure health state utilities for several MBC-related health states and certain breast cancer treatment-related grade 3/4 adverse drug reactions (ADRs) in patients with breast cancer in Taiwan. The secondary objective was to examine whether different methods and respondents' characteristics would influence the utility values elicited.

2. Methods

A cross-sectional survey that aimed to measure health utility values in Taiwanese patients with breast cancer was conducted between January and March 2019. The study protocol was approved by the Institutional Review Board of the Koo-Foundation Sun Yat-Sen Cancer Center (No. 20181119A).

2.1. Health state selection and description development

The health states selected for examination were four chronic states relating to advanced or metastatic breast cancer along with nine grade 3/4 ADRs that have either high treatment costs [9,10] or a great impact on patients' health-related quality of life [11]. These health states included progression-free MBC, responding MBC, progressive MBC, palliative MBC, anemia, arthralgia, diarrhea, fatigue, febrile neutropenia, nausea/vomiting, hand-foot syndrome, stomatitis, and thrombocytopenia. After the health states were chosen, descriptions for each health state were developed and written in vernacular [12]. The drafted descriptions were reviewed by an expert panel that consisted of a medical oncologist and two clinical pharmacists. Before the descriptions were finalized, several non-medical people were asked to make the descriptions easier for the general public to comprehend. The finalized health state descriptions are provided in Appendix.

2.2. Patient recruitment

In this study, convenience sampling was used to recruit patients at a three-hundred-bed regional hospital in Northern Taiwan, which treats nearly ten percent of all newly diagnosed breast cancer patients in Taiwan [1]. Adult breast cancer patients (≥ 20 years old) who were followed up at the study cancer center were recruited. Patients who were pregnant, could not communicate in Mandarin or Taiwanese Hokkien, or had cognitive dysfunction were excluded. Oral consent was obtained from all participants. As participants were asked to imagine they were in each of the assessed health states, they were not required to have experienced any of the health states assessed.

2.3. Interview process

The interview was conducted by two well-trained interviewers following a standardized interview workflow and script. The respondents were first asked to answer a questionnaire containing questions about patients' socioeconomic and clinical characteristics, including age, level of education, employment status, income,

marital status, DNR status, treatment received, and breast cancer stage. Subsequently, respondents' preferences for the four MBC-related health states and nine ADRs were assessed by the VAS and TTO as detailed below.

First, the respondents were asked to imagine they were in each of the assessed health states in turn and to score each state on the VAS scale from zero (worst imaginable health state) to one hundred (best imaginable health state) according to their preferences. Fourteen cards, each card containing a description of one of the hypothetical states under assessment (i.e., dead state, four MBC-related health states, and nine ADRs), were given to the participants in a random order for placement on the VAS scale until all the cards were scored. At that point, patients' scores were confirmed and recorded.

Next, respondents were guided through the TTO exercise. Although no method was recommended for assessing temporary health states [13], a review [14] revealed that the chained TTO is a feasible, consistent, and responsive method for obtaining utility of temporary health states. As a result, the conventional TTO and the chained TTO were used for eliciting chronic and temporary health states, respectively [15]. A TTO board, designed in PowerPoint and displayed on an iPad screen, was used as a visual aid to help respondents comprehend the TTO, to standardize the interview process, and to increase inter-rater reliability. The time horizon of palliative MBC and the three other MBC-related health states was set at ten months and ten years, respectively. The time frame was adjusted to ten weeks when the utility values of ADRs were elicited [16].

For MBC-related health states, participants were asked to choose between "being in the elicited state for ten years/months and then die" and "being immediately dead." Whenever the former was chosen, this particular state was considered to be better than dead (BTD). In contrast, if immediate death was selected, the health state was deemed worse than dead (WTD). Afterwards, the "ping-pong" method, an iterative process used to measure the indifferent point of the health state, was used to acquire respondents' preferences as follows [17].

If an MBC-related health state (i) was considered to be BTD, respondents were asked to choose from three options: "living in health state i for time T followed by death," "living in perfect health for a shorter time X followed by death," and "the two options are equally preferable," where T is the time horizon of the health state i and X varies until the indifferent point is reached. For a health state considered to be WTD, however, respondents were asked to choose from among "die immediately," "living for time X in the health state i and returning to perfect health for time T - X and then die," and "the two options are equally preferable."

Finally, nine ADRs were assessed by the two-step chained TTO. First, the utility for the ADR perceived as the worst by a participant in the VAS exercise was used as an anchor state (state j), and its utility value was elicited by the conventional TTO. Subsequently, participants were asked to choose between suffering that particular ADR and one of the remaining eight ADRs for ten weeks and then returning to perfect health. Participants were also asked to choose between "living with an ADR (state i) for time T and returning to perfect health" and "living with the worst ADR (state j) for time X and returning to perfect health". The length of time X was varied until the respondent was indifferent to the two choices. The interviewers recorded the participant's response for each ADR.

2.4. Statistical analysis

Sociodemographic characteristics were summarized by mean \pm standard deviation (S.D.) or percentages where appropriate. The raw VAS scores were transformed into utilities by the

following formula: $U_{VAS\ i} = \frac{\text{Raw score of health state } i - \text{Raw score of dead}}{\text{Raw score of perfect health} - \text{Raw score of dead}}$ (i = the health state being assessed). Three formulas were used to calculate the utility values derived from the TTO. If the state was measured by the conventional TTO and considered to be BT, the utility value could be calculated through $U_{TTO\ i} = \frac{X}{T}$ (X = the respondent's final answer, T = time frame). For states considered to be WTD, the utility value was computed through $U_{TTO\ i} = \frac{-X}{T-X}$. The utility values of ADRs measured by the chained TTO were calculated by $U_{TTO\ i} = 1 - \frac{X \times (1 - U(j))}{T}$, where $U(j)$ is the utility value of the anchor state. If the respondent favored the anchor state in the chained TTO, the formula was adjusted to $U_{TTO\ i} = 1 - \frac{T \times (1 - U(j))}{X}$. Moreover, negative utility values were adjusted by a linear transformation $U' = \frac{\text{original negative utility value}}{\text{the lowest possible utility value}}$, which helped transform the highly skewed negative values into scores between -1 and 0 [18]. Utility values for each health state assessed were presented by mean, S.D., median, and interquartile range (IQR).

The Wilcoxon signed-rank test and the McNemar test were performed to examine the relationship between the VAS-derived and the TTO-derived utility values. Spearman's correlation was performed to investigate the correlation between utilities and participants' age. In addition, the Mann-Whitney U test and the Kruskal-Wallis test were used, where appropriate, to examine the association between patient characteristics and utility values. The Dunn's post hoc test with Bonferroni adjustment was performed for pairwise comparisons.

All the analyses were performed using IBM SPSS Statistics version 19. A p -value of <0.05 was considered to be statistically significant.

3. Results

3.1. Characteristics of study sample

A total of 104 patients participated in this study. Two respondents did not complete the interview; as a result, the responses of 102 respondents were included in the analyses. The demographic and clinical characteristics of the study sample are shown in Table 1. The mean age was 54.9 years (range: 2 to 73, S.D. = 8.9). All of the participants were female, 71.6% were married, and around half had the equivalent of college degree or above. Half of the study population were employed, and most of their households (58.8%) had an income between NTD 30,001 to 100,000 per month. At the time of the survey, the respondents' average time since diagnosis of breast cancer was 8.5 years (range: 2 to 22, S.D. = 5.0). More than a half (52.9%) of participants had experienced ADRs during previous breast cancer treatments, and 15 (14.7%) had signed consent for DNR.

3.2. Utility values

The adjusted utility values of four chronic health states and nine ADRs derived from the VAS and the TTO are presented in Table 2. The very few negative values observed indicated that respondents considered certain circumstances to be worse than being dead. The rankings of chronic states and ADRs with the TTO were similar to those elicited with the VAS. The most preferred state was "responding MBC" (mean TTO value = 0.62, S.D. = 0.33), followed by "progression-free MBC" (mean TTO value = 0.43, S.D. = 0.45). When the TTO-derived negative utility values were excluded, the mean \pm S.D. utility scores of responding, progression-free, progressive, and palliative MBC were 0.64 ± 0.29 , 0.55 ± 0.28 , 0.51 ± 0.27 , and 0.48 ± 0.28 , respectively. The most acceptable ADR was fatigue (mean TTO value = 0.79, S.D. = 0.31) whereas the ADR

Table 1
Demographic and clinical characteristics of the study sample.

Characteristics	Mean	S.D.
Age (years)	54.9	8.9
Breast cancer duration (years)	8.5	5.0
	n	%
Highest level of education		
Junior high school or below	7	6.9
Senior high or vocational school	42	41.2
College or university or above	53	52.0
Marital status		
Married	73	71.6
Unmarried	29	28.4
Employment		
Employed	51	50.0
Unemployed	51	50.0
Monthly household income NTD		
$\leq 30,000$	19	18.6
30,001 to 100,000	60	58.8
$>100,000$	23	22.5
Stage of breast cancer at diagnosis		
Zero	17	16.7
I	31	30.4
II	38	37.3
III	10	9.8
IV	1	1.0
Uncertain	5	4.9
Treatment received		
Surgery	99	97.1
Chemotherapy	68	66.7
Radiation	65	63.7
Hormone	63	61.8
Targeted therapy	8	7.8
DNR Status		
Yes	15	14.7
No	87	85.3
Any ADRs experience		
Yes	54	52.9
No	48	47.1

ADR, adverse drug reaction; DNR, do not resuscitate; NTD, New Taiwan Dollar; S.D., standard deviation.

with the lowest utility value was nausea/vomiting (mean TTO value = 0.35, S.D. = 0.39).

3.3. Comparison of the VAS and TTO

In all health states assessed, the TTO-derived utility values were higher than the VAS-derived values except for the values of "progressive MBC" ($p = 0.36$) and "palliative MBC" ($p = 0.01$). The McNemar's test found that, compared to the TTO, the proportion of respondents perceiving health states to be WTD was higher with the VAS for both "progression-free MBC" ($p = 0.008$) and "responding MBC" ($p = 0.001$), lower for "palliative MBC" ($p = 0.001$), and equal for "progressive MBC" ($p = 0.49$).

Fig. 1 depicts the proportion of respondents who perceived each ADR as either the worst or the most acceptable. In both the VAS and TTO assessments, the least preferred ADR was nausea/vomiting, followed by thrombocytopenia and hand-foot syndrome. These three ADRs also had the fewest respondents who perceived them as the most acceptable. On the other hand, the most acceptable ADR, or the ADR with the highest utility value, was fatigue.

3.4. Associations between adjusted TTO-derived utilities and patient characteristics

The comparison of utility values for the four MBC health states among various demographic subgroups is presented in Table 3. The

Table 2
Adjusted utility values measured by the VAS and the TTO.

Health state	VAS		TTO	
	Mean (S.D.)	Median (IQR)	Mean (S.D.)	Median (IQR)
Progression-free MBC	0.32 (0.29)	0.30 (0.00–0.51)	0.43 (0.45)	0.55 (0.13–0.75)
Responding MBC	0.51 (0.30)	0.52 (0.30–0.75)	0.62 (0.33)	0.68 (0.48–0.88)
Progressive MBC	0.16 (0.24)	0.10 (–0.001–0.30)	0.22 (0.43)	0.05 (–0.03–0.50)
Palliative MBC	0.15 (0.25)	0.10 (–0.002–0.31)	0.04 (0.47)	–0.02 (–0.09–0.28)
Fatigue	0.45 (0.31)	0.51 (0.23–0.70)	0.79 (0.31)	0.89 (0.78–0.98)
Stomatitis	0.40 (0.30)	0.45 (0.17–0.61)	0.67 (0.37)	0.76 (0.49–0.95)
Febrile neutropenia	0.40 (0.29)	0.43 (0.14–0.62)	0.65 (0.39)	0.83 (0.36–0.96)
Arthralgia	0.35 (0.28)	0.40 (0.07–0.50)	0.65 (0.37)	0.78 (0.39–0.96)
Anemia	0.35 (0.29)	0.38 (0.13–0.59)	0.65 (0.39)	0.77 (0.54–0.91)
Diarrhea	0.34 (0.30)	0.35 (0.00–0.60)	0.58 (0.37)	0.70 (0.20–0.88)
Hand-foot syndrome	0.31 (0.28)	0.33 (0.04–0.51)	0.54 (0.40)	0.69 (0.16–0.90)
Thrombocytopenia	0.28 (0.27)	0.27 (0.05–0.50)	0.60 (0.41)	0.75 (0.39–0.90)
Nausea/vomiting	0.22 (0.28)	0.20 (–0.001–0.44)	0.35 (0.39)	0.18 (0.03–0.71)

IQR, interquartile range; MBC, metastatic breast cancer; S.D., standard deviation; TTO, time trade-off; VAS, visual analogue scale.

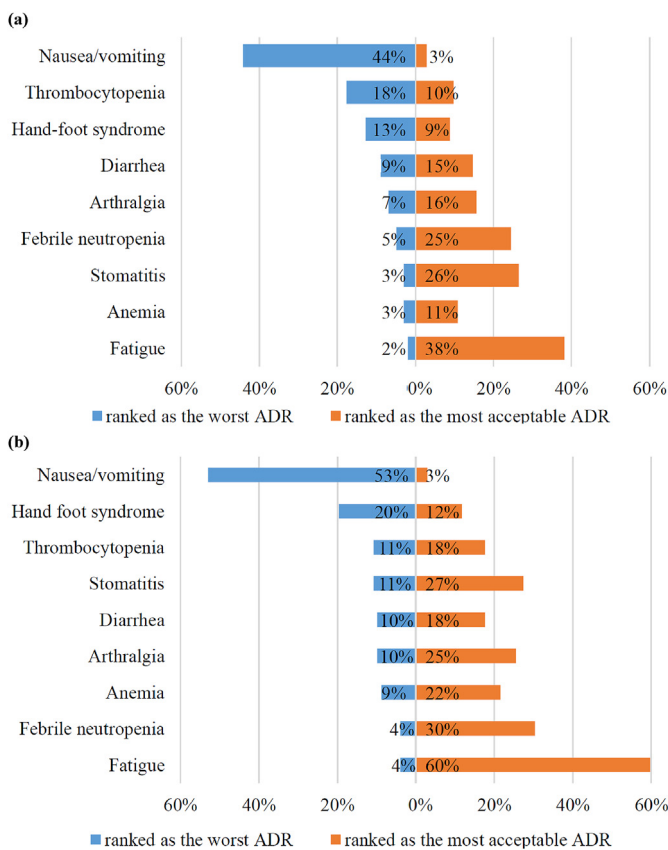


Fig. 1. ADRs ranked as the worst and the best. (a) by the VAS and (b) by the TTO.

participants' age was negatively correlated with utility values in "progression-free MBC" ($r = -0.213$, $p = 0.031$) but not in the other states. In addition, utilities were higher in respondents who had a higher level of education, but only "progression-free MBC" and "palliative MBC" reached statistical significance. In general, among all respondents, the utility values were lowest in those whose household income was \leq NTD 30,000 per month. Moreover, respondents who were married were observed to have higher utility values in all MBC states than those who were not. Patients who signed the DNR had lower utility values in all MBC health states, but a significant difference was observed only for the "progressive MBC" state.

4. Discussion

In this cross-sectional study, we assessed the utility values for health states of four MBC states and nine ADRs related to breast cancer treatment by both the TTO and VAS. To the best of our knowledge, this is the first study in Taiwan and one of the few in Asia that measured preference scores relating to breast cancer. The elicited utility values ranges from 0.04 (palliative MBC) to 0.79 (grade 3/4 fatigue).

It is difficult to directly compare the utility scores elicited here to those reported in previous studies because of the differences in measurement methods and surveyed populations. However, the mean utility values obtained in this study were generally lower than those in previous studies [8,9]. One explanation might be that all the negative utility values were retained in our analysis, whereas Frederix et al. did not measure any WTD states and Lloyd et al. converted all the negative values to 0.02. Indeed, if the negative scores had been excluded from our study, the results would have been similar. However, it is unreasonable to remove those negative values, since only one-third of the respondents did not perceive any MBC-related health states to be WTD. This high proportion of WTD observed may have reflected a cultural difference in Taiwan. Similarly, in the Taiwanese EQ-5D-5L value set development study, 38.5% of the preference scores measured by the composite TTO were negative, which proportion was the highest among Asian countries [19]. The authors believed that it was because Taiwanese people are covered by the comprehensive NHI system and adapt to milder diseases. Therefore, they were prone to trade off their lives to avoid experiencing poorer health states. These findings highlight the existence of cultural differences and the importance of developing country-specific utilities.

When examining whether the different methods influenced the utility values, we found that the rankings of utility values for the four MBC-related health states derived from the TTO were equal to those derived from the VAS, which is consistent with the findings in Frederix et al. [9]. In addition, while most of our TTO-derived utility scores were higher than those of VAS scores, as has been observed in previous studies, the utilities of "progressive MBC" and "palliative MBC" were lower when using the TTO than the VAS [20]. This inconsistency is likely due to the higher proportions of WTD in the TTO assessment, which lowered the mean utility scores. Similar results were found in a study conducted by Milne and his colleagues, where they examined the utility for hypercalcemia in patients with MBC and bone metastasis among women in New Zealand [21]. They found that the VAS-derived score was positive and the TTO-derived score was negative since more interviewees

Table 3

Associations between adjusted TTO-derived utilities and patient characteristics.

Health state Demographic		Progression-free MBC	Responding MBC	Progressive MBC	Palliative MBC
Age (Spearman's correlation) r_s		–0.213*	–0.121	–0.119	–0.180
		Mean \pm S.D. [Median (IQR)]	Mean \pm S.D. [Median (IQR)]	Mean \pm S.D. [Median (IQR)]	Mean \pm S.D. [Median (IQR)]
Educational level ^a	\leq Junior high	–0.07 \pm 0.70 [0.05 (–1.00–0.50)] *	0.45 \pm 0.41 [0.55 (0.03–0.78)]	0.004 \pm .628 [–0.07 (–0.32–0.55)]	–0.52 \pm 0.63 [–1.00 (–1.00––0.09)]**
	Senior high	0.37 \pm 0.50 [0.53 (0.03–0.75)]	0.61 \pm 0.38 [0.68 (0.51–0.88)]	0.17 \pm 0.44 [–0.01 (–0.06–0.49)]	–0.03 \pm 0.51 [–0.02 (–0.09–0.01)]
	\geq College	0.55 \pm 0.29 [0.58 (0.46–0.78)]*	0.64 \pm 0.28 [0.73 (0.48–0.88)]	0.29 \pm 0.37 [0.40 (–0.02–0.50)]	0.17 \pm 0.35 [0.03 (–0.03–0.38)]**
Marital status ^b	Married	0.50 \pm 0.41 [0.60 (0.43–0.78)]**	0.69 \pm 0.27 [0.75 (0.59–0.88)]***	0.30 \pm 0.42 [0.40 (–0.02–0.59)]***	0.10 \pm 0.46 [–0.002 (–0.07–0.33)]*
	Unmarried	0.26 \pm 0.48 [0.28 (–0.02–0.60)]**	0.43 \pm 0.42 [0.48 (0.10–0.78)]***	0.01 \pm 0.38 [–0.02 (–0.08–0.03)]***	–0.10 \pm 0.47 [–0.03 (–0.12–0.01)]*
Income ^a	\leq 30,000	0.08 \pm 0.66 [0.05 (–0.09–0.58)]*	0.42 \pm 0.50 [0.55 (0.03–0.88)]	–0.08 \pm 0.57 [–0.02 (–0.18–0.38)]*	–0.27 \pm 0.55 [–0.09 (–1.00––0.001)]*
	30,001–100,000	0.51 \pm 0.36 [0.59 (0.29–0.78)]*	0.68 \pm 0.25 [0.71 (0.56–0.88)]	0.31 \pm 0.37 [0.33 (–0.02–0.64)]*	0.10 \pm 0.40 [–0.02 (–0.05–0.28)]
	\geq 100,001	0.52 \pm 0.25 [0.58 (0.38–0.70)]	0.61 \pm 0.30 [0.73 (0.43–0.88)]	0.24 \pm 0.32 [0.08 (–0.03–0.48)]	0.14 \pm 0.49 [0.03 (–0.06–0.48)]*
DNR status ^b	Yes	0.27 \pm 0.48 [0.28 (0.03–0.68)]	0.48 \pm 0.35 [0.48 (0.03–0.78)]	–0.05 \pm 0.46 [–0.02 (–0.12–0.08)]*	–0.02 \pm 0.40 [–0.03 (–0.09––0.001)]
	No	0.46 \pm 0.44 [0.58 (0.28–0.78)]	0.64 \pm 0.33 [0.73 (0.55–0.88)]	0.27 \pm 0.40 [0.28 (–0.02–0.55)]*	0.05 \pm 0.49 [–0.01 (–0.08–0.28)]

IQR, interquartile range; MBC, metastatic breast cancer; r_s , spearman rank correlation coefficient; S.D., standard deviation.^a Kruskal-Wallis test.^b Mann-Whitney U test; significance levels are indicated by asterisks. (* $P < 0.05$, ** $P < 0.01$, *** $P \leq 0.001$)

perceived the health state to be WTD when elicited by the TTO. Moreover, Badia et al. also found that the median utility values of more severe health states derived from the TTO were significantly lower than those from the VAS, and they suggested that it was related to the context effect of the VAS that reduces the discrimination between health states [22].

In our study, the rankings of the utility values for nine ADRs were similar between the two measurement methods. Consistent with our findings, Kuchuk et al. also reported that nausea/vomiting was the least preferred among various chemotherapy side effects [23]. Given that nausea/vomiting is such undesirable for patients, healthcare providers should always be prepared to do as much as possible to alleviate and prevent this ADR. Not only the use of antiemetics but also lifestyle changes can be recommended for patients under breast cancer treatment, particularly those with a high emetic risk, such as taking anthracycline combined with cyclophosphamide [24]. Moreover, any medications that may cause nausea/vomiting should be prescribed cautiously.

Previous publications have examined the relationships between utility scores and demographic characteristics, and their results indicate that only marital status was consistently associated with health utilities [8,25–27]. As explained in Krol et al. when the length and quality of life are traded in the TTO exercise, “longevity altruism” and “quality-of-life altruism” may have an impact on the respondents’ choices [28]. People who are married are more likely to prolong their lives to live with their partners, which could result in higher utility values. Such thinking was also mentioned by some of the married participants in our study. In contrast, quality-of-life altruism may make people want to avoid being a burden to their loved ones and may make them more willing to trade off their life years, resulting in lower utility scores. Quality-of-life altruism was observed in our study, as the mean utilities of the respondents who had signed the DNR were lower than those who had not.

It should be noted that this study has several limitations. First, selection bias may have occurred since convenience sampling was used in our survey. Although we did not collect the information of patients who refused to participate, the characteristics of our

sample were similar to those of patients with breast cancer in the study center [29]. Second, the descriptions of health states were drafted without patient input, and may have therefore failed to represent patients’ views about what certain conditions entail. Nevertheless, the vignettes were drafted based on patient education handouts and confirmed by experts who had worked closely with patients. Lastly, multiple methods and time horizons were utilized in our study, which may have made comprehension challenging for patients and could have perhaps influenced responses. However, the utility scores elicited by the TTO and the VAS were generally consistent, which suggests that using the two methods is feasible in the Taiwanese population.

5. Conclusions

In conclusion, this study obtained health state utility values for MBC and grade 3/4 ADRs using both the TTO and the VAS in patients with breast cancer in Taiwan. The utility values elicited provide important and useful information for future CUAs. Among all the health states assessed, “palliative MBC,” “progressive MBC,” and “grade 3/4 nausea/vomiting” had the lowest utility scores, which indicates their considerable and negative impact on patients’ quality of life.

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Ethical approval

The study was approved by the Institutional Review Board of the Koo-Foundation Sun Yat-Sen Cancer Center (No. 20181119A).

Declaration of competing interest

All author declare that they have no conflict of interest.

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Appendix. Health States Descriptions

State A: Progression-free MBC.

- You have a life-threatening disease that **requires consistent treatment**. As a result, you routinely go to the outpatient clinic to receive treatment. You become **mentally exhausted** because of the continuing therapy.
- Your **appetite is reduced**. You sometimes experience **significant pain**, but it can be relieved with painkillers.
- You are able to go visit your family and friends, but often have to **go home early because you feel tired**.
- You are able to wash and dress yourself and work near your home. However, shopping and daily activities **take more effort than usual**.
- You feel **less physically attractive than usual** and your sexual drive is reduced.
- You feel **a bit anxious and depressed**, and you worry that your disease may **worsen in the future**.

State B: Responding MBC.

- You have a life-threatening disease. You routinely go to the outpatient clinic to receive treatment, which is **effective**.
- Your **appetite is returning**, but you still **sometimes experience pain** that can be relieved with painkillers.
- You sometimes feel tired but **are still able to go visit your family and friends** to maintain relationships.
- You are able to wash and dress yourself and work near your home. However, you **sometimes feel tired** when shopping and doing daily activities.
- You **sometimes feel less physically attractive** and your sexual drive is reduced.
- You worry about your condition but **are hopeful for the future**.

State C: Progressive MBC.

- You have a life-threatening disease and your condition is **getting worse**.
- You have experienced **severe fatigue, lost your appetite, and lost a significant amount of weight**.
- You feel **too tired to go visit your family and friends**. As a result, your relationships with some of them have become strained or gradually weakened.
- You are able to wash and dress yourself **only with assistance**. You are often unable to work near your home or do daily activities, which makes you **reliant on others much of the time**.
- You feel your **physical appearance is unappealing** and you have little or no sexual drive. You feel **depressed and feel dependent on your family and friends**. You also worry about burdening your family as a result of your disease. As such, you **have little hope for the future**.

Stage D: Palliative MBC.

- You have a life-threatening disease and your condition is **getting worse**.

- You have experienced **severe pain, fatigue, and loss of appetite**. You can use relieve these symptoms by treatment but **your disease is incurable**.
- You feel **too tired to go visit your family and friends**. However, they can understand your condition and keep your company.
- You are almost **confined to a bed or chair, and you need assistance to use the toilet and wash or dress yourself**.
- You feel your **physical appearance have become sallow** and you no longer feel attractive.
- You sometimes **feel frustrated and afraid**, but you can gradually accept that life is limited.

State E: Grade 3/4 Diarrhea.

- You have an illness currently under treatment and have the following symptoms.
- You feel **severe abdomen pain** and have a loose bowel movement at least seven times a day. As a result, you need **intravenous fluids in the hospital**. Your symptoms (abdominal pain and diarrhea) are relieved after treatment, but you are at risk for recurrence.
- You are able to do jobs and daily activities by yourself. However, you are unable to or need to make more of an effort to do these things when you have diarrhea.

State F: Grade 3/4 Hand-foot syndrome.

- You have an illness currently under treatment and have the following symptoms.
- You have **very painful blisters and peeling skin on your hands and feet**. You **have difficulty using your hands** and walking due to the blisters. You are unable to recover from this condition quickly.
- You are able to do jobs and daily activities by yourself. However, you are unable or need to take more efforts to do these things when you have blisters on your hands or feet.

State G: Grade 3/4 Nausea/vomiting.

- You have an illness currently under treatment and have the following symptoms.
- You feel **considerable stomach discomfort** and are unable to eat normally due to nausea and vomiting. As a result, you can only **have tube feeding or intravenous injections and may have to be hospitalized**. Your symptoms get better after medical treatment, but you are at risk of recurrence.
- You are able to do jobs and daily activities by yourself. However, you are unable or need to take more efforts to do these things when you experience nausea or vomiting.

State H: Grade 3/4 Fatigue.

- You have an illness currently under treatment and have the following symptoms.
- You feel **extremely tired and weak**. Your tiredness cannot be relieved by short rest. Most of the time **you are frustrated because you are too tired to do the things you used to do easily**.
- You are able to do jobs and daily activities by yourself. However, you are unable or need to take more efforts to do these things when you feel tired.

State I: Grade 3/4 Thrombocytopenia.

- You have an illness currently under treatment and have the following symptoms.
- You are suffering from **nose bleeds, blood in your urine, and bruises on your body**. As a result, you have to **spend half of the day in the hospital getting a blood transfusion**. Your symptoms get better temporarily after a blood transfusion, but you have to receive transfusions again when the bleeding comes back.
- You are able to do jobs and daily activities by yourself. However, you are unable or need to take more efforts to do these things when you have to have a blood transfusion in the hospital.

State J: Grade 3/4 Febrile neutropenia.

- You have an illness currently under treatment and have the following symptoms.
- You need to be hospitalized due to **a blood disorder, a fever lasting more than an hour, and severe flu-like symptoms** (chills, cough, and runny nose). Your symptoms get better after **receiving intravenous antibiotics**, but you are at risk of recurrence.
- You are able to do jobs and daily activities by yourself. However, you are unable or need to take more efforts to do these things when you have a fever and flu-like symptoms.

State K: Grade 3/4 Stomatitis.

- You have an illness currently under treatment and have the following symptoms.
- You have **very painful sores inside your mouth** which make you **unable to eat or drink as usual and also disturb your sleep**. Your symptoms get better after **taking painkillers and using mouthwash**, but you are unable to recover from this condition immediately and are at risk for recurrence.
- You are able to do jobs and daily activities by yourself. However, you are unable or need to take more efforts to do these things when you have pain resulting from the sores in your mouth.

State L: Grade 3/4 Anemia.

- You have an illness currently under treatment and have the following symptoms.
- You feel **very tired and weak**. Sometimes you are **unable to concentrate** and even experience **shortness of breath**. Due to these symptoms, you need to **get blood transfusions in the hospital**, but you can go home on the same day when this happens. Your symptoms get better after a blood transfusion, but you are at risk of recurrence.
- You are able to do jobs and daily activities by yourself. However, you are unable or need more efforts to do these things when you feel tired and have to have a blood transfusion.

State M: Grade 3/4 Arthralgia.

- You have an illness currently under treatment and have the following symptoms.
- You feel **severe pain when you bend your wrists, fingers, or knees**. Sometimes your palms also feel pain and

numbness so that you are unable to move your hands and feet normally, which makes it difficult for you to fall asleep. Your symptoms get better after taking painkillers, but you are at risk of recurrence.

- You are able to do jobs and daily activities by yourself. However, you are unable or need to take more efforts to do these things when you have severe pain in your hands or feet.

References

- [1] 2016 cancer registry annual report. 2018. <https://www.hpa.gov.tw/Pages/Detail.aspx?nodeid=269&pid=10227>. [Accessed 27 December 2018].
- [2] 2017 statistics of top ten cancer's medical care cost. 2018. https://www.nhi.gov.tw/Content_List.aspx?n=AE8F3C1B6EC35217&topn=CDA985A80CODE710. [Accessed 5 May 2019].
- [3] Waks AG, Winer EP. Breast cancer treatment: a review. *J Am Med Assoc* 2019;321:288–300.
- [4] Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes. fourth ed. New York: Oxford University Press; 2015.
- [5] Bracco A, Krol M. Economic evaluations in European reimbursement submission guidelines: current status and comparisons. *Expert Rev Pharmacoecon Outcomes Res* 2013;13:579–95.
- [6] Center for Drug Evaluation. Guidelines of methodological standards for pharmaco-economic evaluations in Taiwan. 2014. https://tools.ispor.org/PEguidelines/source/HTA_guidelines_Taiwan.pdf. [Accessed 26 May 2019].
- [7] Torrance GW. Measurement of health state utilities for economic appraisal. *J Health Econ* 1986;5:1–30.
- [8] Lloyd A, Nafees B, Narewska J, Dewilde S, Watkins J. Health state utilities for metastatic breast cancer. *Br J Canc* 2006;95:683–90.
- [9] Frederix GW, Quadri N, Hovels AM, et al. Utility and work productivity data for economic evaluation of breast cancer therapies in The Netherlands and Sweden. *Clin Therapeut* 2013;35: e1–7.
- [10] Hao Y, Wolfram V, Cook J. A structured review of health utility measures and elicitation in advanced/metastatic breast cancer. *Clinicoecon Outcomes Res* 2016;8:293–303.
- [11] Beusterien K, Grinspan J, Tencer T, Brufsky A, Visovsky C. Patient preferences for chemotherapies used in breast cancer. *Int J Womens Health* 2012;4: 279–87.
- [12] Furlong W, Feeny D, Torrance GW, Barr R, Horsman J. Guide to design and development health-state utility instrumentation. Hamilton: McMaster University; 1992.
- [13] Boye KS, Matza LS, Feeny DH, Johnston JA, Bowman L, Jordan JB. Challenges to time trade-off utility assessment methods: when should you consider alternative approaches? *Expert Rev Pharmacoecon Outcomes Res* 2014;14: 437–50.
- [14] Stoniute J, Mott DJ, Shen J. Challenges in valuing temporary health states for economic evaluation: a review of empirical applications of the chained time trade-off method. *Value Health* 2018;21:605–11.
- [15] Torrance GW, Thomas WH, Sackett DL. A utility maximization model for evaluation of health care programs. *Health Serv Res* 1972;7:118–33.
- [16] Breast cancer (Version 1.2018), https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. [Accessed 13 August 2018].
- [17] Brazier J, Ratcliffe J, Salomon JA, Tsuchiya A, Valuing health. Measuring and valuing health benefits for economic evaluation. second ed. New York: Oxford University Press; 2016.
- [18] Shaw JW, Johnson JA, Coons SJ. US valuation of the EQ-5D health states: development and testing of the D1 valuation model. *Med Care* 2005;43: 203–20.
- [19] Lin HW, Li Ci, Lin FJ, et al. Valuation of the EQ-5D-5L in Taiwan. *PLoS One* 2018;13:e0209344.
- [20] Morimoto T, Fukui T. Utilities measured by rating scale, time trade-off, and standard gamble: review and reference for health care professionals. *J Epidemiol* 2002;12:160–78.
- [21] Milne RJ, Heaton-Brown KH, Hansen P, Thomas D, Harvey V, Cubitt A. Quality-of-life valuations of advanced breast cancer by New Zealand women. *Pharmacoeconomics* 2006;24:281–92.
- [22] Badia X, Monserrat S, Roset M, Herdman M. Feasibility, validity and test-retest reliability of scaling methods for health states: the visual analogue scale and the time trade-off. *Qual Life Res* 1999;8:303–10.
- [23] Kuchuk I, Bouganim N, Beusterien K, et al. Preference weights for chemotherapy side effects from the perspective of women with breast cancer. *Breast Canc Res Treat* 2013;142:101–7.
- [24] Antiemesis. Version 3.2018, https://www.nccn.org/professionals/physician_gls/pdf/antiemesis.pdf. [Accessed 13 August 2018].
- [25] Schleinitz MD, DePalo D, Blume J, Stein M. Can differences in breast cancer

- utilities explain disparities in breast cancer care? *J Gen Intern Med* 2006;21:1253–60.
- [26] Färkkilä N, Torvinen S, Roine RP, et al. Health-related quality of life among breast, prostate, and colorectal cancer patients with end-stage disease. *Qual Life Res* 2014;23:1387–94.
- [27] Kim SH, Jo MW, Ock M, Lee HJ, Lee JW. Estimation of health state utilities in breast cancer. *Patient Prefer Adherence* 2017;11:531–6.
- [28] Krol M, Attema AE, van Exel J, Brouwer W. Altruistic preferences in time tradeoff: consideration of effects on others in health state valuations. *Med Decis Making* 2016;36:187–98.
- [29] Wang YA, Feng AC, Ganz PA. Health services utilisation in breast cancer survivors in Taiwan. *Sci Rep* 2014;4:7466.