Health Variations Among Breast-Cancer Patients from Different Disease States: Evidence from China

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Abstract

**Background** To obtain health utility data for different disease status of breast cancer in China in order to obtain important parameters in health economics modeling. To explore the feasibility of establishing a breast cancer health utility mapping model in China.

**Methods** Multivariate regression models, including linear regression model, ordinal logistic regression model and Tobit model, were employed to analyze. Subgroup analyses were performed to analyze variations in sub-dimensional health attributes derived from FACT-B and EQ-5D-5L. A mapping function was used to estimate health utility from quality of life.

**Results** 446 breast cancer patients with different disease states were analyzed. The utility of breast cancer patients with P state (without cancer recurrence and metastasis), R state (with cancer recurrence within a year), S state (with primary and recurrent breast cancer for the second year and above) and M state (metastasis cancer) were 0.81 (SD ±0.23), 0.90 (SD ±0.12), 0.78 (SD ±0.31), and 0.74 (SD ±0.27), respectively. All scores, including the FACT-B domain, showed a positive correlation (p <0.001). Multivariate analysis suggested that patients in R and M state had lower scores in overall quality of life (R, β = -9.45, p < 0.01; M, β = -6.72, P <0.05). Patients in M state had a lower probability of achieving higher health utility compared with patients in P state (β = -0.11, p < 0.05).

Estimated health utilities derived from quality of life, using mapping function, were significantly correlated with directly measured health utilities ( p <0.001).

**Conclusions** We obtained the health utility and HRQoL scores of Chinese breast cancer patients with different disease states. Mapping health utilities from quality of life in four disease states could be a plausible approach in health economic analysis, while the mapping function may need further revise.

**Background**

As a leading women-health killer, breast cancer has caused around 23% of global cancer deaths \(^1\). In China, the number of breast cancer patients escalated in both urban and rural areas during past decades, leading to an dramatic increase in health expenditures and disease burden for both society and patients’ family\(^2, 3\).

Recognized as an effective tool to evaluate disease burden, health economic evaluation has gained
increasing attention in cancer research. As one of the important method in health economic evaluation, cost-utility analysis aims to compare participants’ health attributes such as quality-adjusted life years (QALYs), which incorporates the duration and health utility weights under specific health status\[^4\]. EQ-5D series, one of the most popular scales in measuring health utility, were developed by European Quality of Life Organization, and were recommended as a generalized scale by National Institute for Health and Care Excellence (NICE) in UK\[^5\]. The evaluation research on health utility among breast cancer patients, however, is rare in developing countries, such as China, which limits the potential to conduct CUA in these regions\[^6\].

For cost-utility analysis, it is important to assess the health utility of stratification by disease status of breast cancer in order to apply utility to the state transition model. The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and the Society of Medical Decision Making (MDM) have published reports on best practices for state transition models (Markov and micro-simulation models)\[^7\]. The Markov model is the most commonly used model for evaluating health economics of breast cancer using utility values. Currently, the commonly used Markov model considers four different states of breast cancer\[^8,9\], which are based on the trajectory and economic modeling of breast cancer. The four mutually exclusive disease states for breast-cancer patients, namely P, S, R, and M\[^10\]. Patients in P state are diagnosed with breast cancer within a year and do not suffer from cancer recurrence and metastasis. Patients in S state are with primary and recurrent breast cancer for the second year and above. Patients in R state are with recurrent breast cancer for the first year. Last, patients in M state suffer from cancer metastasis. Patients in P, R and M state generally receive various clinical treatment such as surgery, chemotherapy and radiotherapy, while patients with cancer recurrence (R state) and metastasis (M state) may suffer more than patients in P state since they may receive more treatments to cure the disease. Additionally, although cancer recurrence exists in patients in S state, they may generally report better health compared with patients in R states, since they may complete the treatment and go back to normal life.

Despite that extensive observations have focused on breast-cancer patients’ health variations,
especially as a function of various treatment approaches \cite{11, 12}, TNM stage \cite{13}, and social determinants such as race\cite{14}, marital status\cite{13, 15}, income\cite{16}, medical insurance \cite{17}, and education\cite{13, 16}, a limited number of investigations have directed attention on variations among patients from different disease states\cite{10}. To the best of our knowledge, Lidgren et al (2007) is the only examination that investigated health variations among breast-cancer patients from four different states. The descriptive study, however, provided little information about health variations after controlling for socioeconomics, demographic and clinical attributes, which may be significantly impact patients’ health regardless of disease states. Furthermore, in order to measure health utility, the study employed preference-based EQ-5D inquiring five-dimension heath with three-level severity. While, as discussed later, our study employed the refined version of EQ-5D, namely, EQ-5D-5L with five-level severity to more accurately measure health utility.

At present, the health utility value of breast cancer in China is lacking \cite{6}. Instead of health utility derived from preference scales, quality of life derived from a fair number of generalized or specific non-preference scales, such as FACT-B and QLICP-BR, were commonly measured in prior literatures \cite{12, 15, 18}. However, in order to transforming quality of life to health utility, a mapping function is necessary \cite{18}. While current literature on mapping function based on China’s population is limited. Whether the mapping functions based on other Asian nations such as Singapore, could be applicable to China’s population is, however, unknown.

To offer guidance for data analysis and result interpretation, we offered a hypothesis here. We hypothesized that health variations may exist among breast-cancer patients in different disease states even when socioeconomic, demographic, and clinical attributes were introduced (H1a). Specifically, patients with metastatic cancer (M state) and those with cancer recurrence (R state) may achieve worse health particularly mental health and feel more painful as they may have heavier psychological load and greater adverse effects \cite{19}. Additionally, we hypothesized that the variations would not appear in every dimension of health, since breast-cancer patients generally would not
suffer greatly in dimensions such as functional status, mobility, self-care and usual activities (H1b). To validate the hypothesis, this study would analyze health variations among patients in four disease states as a function of clinical, demographic, and socioeconomic attributes. In addition, we would estimate health utilities for patients in four disease states by using mapping algorithm developed by prior investigators\(^{[20]}\), and compare estimated health utilities with measured ones to evaluate the feasibility of four disease states in health economic analysis by using existed mapping function. For a comprehensive assessment, this study measured the preference-based generic HRQoL, the health utility, using the EuroQol-5 Dimension-5 Level (EQ-5D-5L). At the same time, the EQ visual analogue scale (EQ-VAS) of the EQ-5D-5L questionnaire and the non-preferred disease-specific scale FACT-B were also measured in Chinese breast cancer patients.

**Methods**

**Data source**

We recruited both breast cancer outpatients and inpatients in Sichuan Oncology Hospital from November 2017 to May 2018. Ethical permission was granted by the Ethics Committee, West China School of Medicine/West China Hospital, Sichuan University(approval number 2017 – 255). We were authorized the right to use FACT-B (Simplified Chinese version) and EQ-5D-5L (Simplified Chinese version).

**Study Participants**

Inclusion criteria were as follows. First, participants were clinically and/or pathologically diagnosed with breast cancer. Second, patients were aged 18 and above. Third, patients should not have any mental problems and have the ability to express. In addition, patients should agree to participate this study. Informal consent were obtained from all participants. We excluded patients that had comorbidities such as cardiovascular disease and mental health problems. We interviewed 451 breast cancer patients with 5 respondents who did not complete the interview. Overall, 446 participants were included in data analysis.

**Measures**

We measured participants’ quality of life by FACT-B, which measures quality of life from five dimensions including physiological conditions(PWB), social and family support (SWB), emotional
conditions (EWB), functional status (FWB), and additional symptoms with breast cancer (BCS). The FACT-B scale consists of 37 questions. Since the scale of scores of these five dimensions differed, we standardized them into a scale of 100. The validity and reliability of FACT-B at Chinese version was examined by prior investigators [21].

In parallel, patients’ health utility was measured by EQ-5D-5L (Simplified Chinese version), which measures five health dimensions including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression with five-level severity from no problems, slight problems, moderate problems, severe problems to extreme problems/unable. The severity of each dimension was coded from 0 to 4 with as the reference group. For example, 0 in mobility represents that individuals have no problems with walking, and 4 represents that they could not walk. In addition, participants were required to report self-rated health status ranging from 0 to 100 with 100 represents the best health status one can imagine (EQ-VAS). In contrast, 0 represents the worst health status. The validity and reliability of 5Q-5D-5L (Simplified Chinese version) were examined by prior Chinese investigators as well [22]. We calculate health utility by employing the value set based on Chinese data [23].

The main independent variable of interest is disease states, i.e., P, R, S, and M. In addition, we introduced covariates including TNM stage (0, I, II, III, and IV), surgical approaches (breast conserving surgery, modified radical surgery vs. no surgery), menopaus state (yes vs. no), radiotherapy (yes vs. no), chemotherapy (yes vs. no), targeted therapy (yes vs. no), endocrine therapy (yes vs. no), and inpatients (vs. outpatients) to control for clinical confounders which may affect patients’ health via adverse effects, which are not mediated by disease states [12, 19].

Furthermore, we included patients’ demographic attributes (age and marital status) and socioeconomic characteristics including education attainment, household income, location of Hukou (urban vs rural), occupation, and medical insurance type as covariates to controlling for the effect of social deprivation on health [15, 17].

Data analysis
To gauge the difference of variables in four kinds of disease states, descriptive analyses including Chi-
square test, Fisher exact probability test, and ANOVA test were performed according to variables’ characteristics. We calculated health utilities by a value set developed based on China’s population in prior investigation\(^ {23}\). To clarify the degree of overlap between instruments, Spearman's rank correlation coefficient is calculated not only between each instrument, but also between the FACT-B domains.

Univariate regression analysis was conducted to figure out potential predictors of participants’ health, which was reflected as overall scores of FACT-B, scores of each dimensions in FACT-B, self-rated health, health utility from EQ-5D-5L, and the degree of five dimensions in EQ-5D-5L, respectively (results available from authors). In this regard, we performed multiple regression models according to dependents’ characteristics. Linear regression model was performed for overall scores of FACT-B since it was normally distributed. Ordinal logistic regression models were respectively performed for BCS, FWB, EWB, SWB, and PWB, self-rated health, and the degree of mobility, self-care, usual activities, pain, and depression, as the distribution of BCS, FWB, EWB, SWB, PWB, and self-rated health were highly skewed, and the degree of mobility, self-care, usual activities, pain, and depression are ordinal data. For BCS, FWB, EWB, SWB, and PWB, we divided each variable into four balanced groups coded as 0 to 3 with 0 representing the lowest group and the reference group in the model, each group consisting of similar number of participants. Similar treatment was used for self-rated health status with five balanced groups coded as 0 to 4 with 0 representing the group of the worst health. Tobit model was performed for health utilities, as they were right-censored.

Independent variables of statistical significance (\(p < 0.05\)) in univariate analysis were then introduced to multivariate analysis. Variance inflation factors were performed to examine multicollinearity among independent variables in multivariate models.

Furthermore, we analyzed correlation between quality of life and health utilities from EQ-5D-5L by employing rank correlation test. Lastly, we estimated health utilities from quality of life from FACT-B by employing a mapping function derived from Singaporean population\(^ {20}\), and conducted rank correlation test between estimated health utilities and those directly measured from participants with
The mapping function based on Singaporean patients was below\(^{(20)}\):

\[
\text{Estimated health utility} = 0.2846 + 0.0121 \times \text{PWB} + 0.0044 \times \text{FWB} + 0.0034 \times \text{BCS}
\]

Data analyses were performed with SPSS 23.0 and SAS University Edition. \(p\) value less than 0.05 was considered statistically significant.

Results
Descriptive analysis

Table 1 showed the socio-demographic and clinical characteristics of patients stratified by breast cancer disease status. The average age of patients with R state is the smallest (49.9 ± 7.08). Table 2 listed the quality of life of different disease status of breast cancer, included HRQoL and EQ-5D-5L, EQ-VAS mean (SD) scores, which can be used for cost-benefit analysis. The utility of breast cancer patients with P, R, S and M state were 0.81 (0.23), 0.90 (0.12), 0.78 (0.31), and 0.74 (0.27), respectively. The distributions of these scores were represented by histograms (Figs. 1–3). A strong ceiling effect was observed in the EQ-D-5L score. According to descriptive analysis, patients in S state appeared to have better health in all dimensions (Table 2). Patients in M state had the worst health in terms of PWB, EWB, BCS, and health utility, while patients in R state reported to have the lowest score in overall quality of life, SWB, FWB, and self-rated health.
| Variable                          | All (N = 446) | P (N = 125) | S (N = 258) | R (N = 20) | M (N = 43) | ρ    |
|----------------------------------|---------------|-------------|-------------|------------|------------|------|
| **age±**                         | 52.03±8.97    | 51.37±8.62  | 52.65±8.75  | 49.9±7.08  | 51.23±11.6 |      |
| marital status                   |               |             |             |            |            |      |
| married                          | 92.15         | 6.40        | 6.59        | 10.00      | 18.60      |      |
| others                           | 7.85          | 6.40        | 6.59        | 10.00      | 18.60      |      |
| education attainment             |               |             |             |            |            |      |
| illiteracy and primary school    | 32.29         | 39.20       | 31.40       | 35.00      | 16.28      |      |
| junior high school               | 33.63         | 26.40       | 35.66       | 35.00      | 41.86      |      |
| senior high school               | 19.73         | 19.20       | 19.38       | 20.00      | 23.26      |      |
| college or above                 | 14.35         | 15.20       | 13.57       | 10.00      | 18.60      |      |
| Hukou system                     |               |             |             |            |            |      |
| rural                            | 49.33         | 56.00       | 47.67       | 50.00      | 39.53      |      |
| urban                            | 50.67         | 44.00       | 52.33       | 50.00      | 60.47      |      |
| medical insurance                |               |             |             |            |            |      |
| others                           | 44.62         | 56.00       | 39.53       | 55.00      | 37.21      | *    |
| UEMI                             | 43.27         | 36.80       | 44.96       | 40.00      | 53.49      |      |
| URMI                             | 12.11         | 7.20        | 15.50       | 5.00       | 9.30       |      |
| occupation                       |               |             |             |            |            |      |
| unemployed                       | 33.18         | 30.40       | 35.66       | 50.00      | 18.60      |      |
| retired                          | 21.52         | 16.00       | 23.64       | 10.00      | 30.23      |      |
| blue-collar                      | 27.58         | 33.60       | 24.03       | 35.00      | 27.91      |      |
| white-collar                     | 17.71         | 20.00       | 16.67       | 5.00       | 23.26      |      |
| household income                 |               |             |             |            |            |      |
| < 30,000 RMB                     | 52.47         | 53.60       | 50.39       | 90.00      | 44.19      | **   |
| 30,000 | 80,000 RMB                  | 33.18         | 26.40       | 37.21       | 10.00      | 39.53      |      |
| > 80,000 RMB                     | 14.35         | 20.00       | 12.40       | 0.00       | 16.28      |      |
| TNM stage                        |               |             |             |            |            |      |
| 0 and I                         | 19.95         | 25.60       | 20.54       | 0.00       | 9.30       | ***  |
| II                              | 50.22         | 44.80       | 58.14       | 50.00      | 18.60      |      |
| III                             | 22.20         | 25.60       | 20.93       | 20.00      | 20.93      |      |
| IV                              | 7.62          | 4.00        | 0.39        | 30.00      | 51.16      |      |
| inpatients (vs. outpatients)     |               |             |             |            |            |      |
| outpatients                      | 84.30         | 52.80       | 100.00      | 90.00      | 79.07      | ***  |
| inpatients                      | 15.70         | 47.20       | 0.00        | 10.00      | 20.93      |      |
| surgery                         |               |             |             |            |            |      |
| no surgery                       | 3.14          | 8.80        | 0.78        | 0.00       | 2.33       | *    |
| breast conserving surgery        | 22.65         | 24.80       | 22.48       | 20.00      | 18.60      |      |
| modified radical surgery         | 74.22         | 66.40       | 76.74       | 80.00      | 79.07      |      |
| radiotherapy (yes vs. no)        | 60.76         | 44.00       | 63.95       | 95.00      | 74.42      | ***  |
| chemotherapy (yes vs. no)        | 91.70         | 88.80       | 92.25       | 100.00     | 93.02      |      |
| targeted therapy (yes vs. no)    | 9.64          | 12.00       | 8.14        | 0.00       | 16.28      |      |
| endocrine therapy (yes vs. no)   | 68.83         | 38.40       | 81.01       | 100.00     | 69.77      | ***  |
| menopaus( yes vs. no)            | 85.87         | 77.60       | 90.31       | 90.00      | 81.40      | *    |
| Note: *** p < .001; ** p < .01; * p < .05.  |
| +represents mean (standard deviation) |     |             |             |            |            |      |
Table 2
Health utility and HRQoL scores according to disease status, mean ± SD

| Variable | All (N = 446) | P (N = 125) | S (N = 258) | R (N = 20) | M (N = 43) | p   |
|----------|--------------|-------------|-------------|------------|------------|-----|
| FACT-B   | 70.29 (± 13.33) | 68.09 (± 13.85) | 73.03 (± 11.68) | 61.66 (± 16.86) | 64.27 (± 14.84) | *** |
| PWB      | 81.53 (± 16.41) | 76.17 (± 19.60) | 85.65 (± 11.68) | 74.35 (± 20.93) | 74.75 (± 20.86) | *** |
| SWB      | 68.27 (± 19.59) | 69.23 (± 18.90) | 69.42 (± 19.51) | 55.36 (± 22.48) | 64.62 (± 18.73) | *  |
| EWB      | 74.69 (± 19.65) | 73.50 (± 20.19) | 78.39 (± 16.63) | 62.29 (± 24.69) | 60.56 (± 23.38) | ***|
| FWB      | 58.33 (± 20.67) | 55.06 (± 21.11) | 61.78 (± 19.95) | 45.18 (± 20.44) | 53.24 (± 19.29) | ***|
| BCS      | 69.57 (± 13.19) | 67.50 (± 15.15) | 71.28 (± 12.44) | 65.88 (± 15.45) | 66.63 (± 15.30) | *  |
| EQ-5D-5L | 69.57 (± 13.19) | 67.50 (± 15.15) | 71.28 (± 12.44) | 65.88 (± 15.45) | 66.63 (± 15.30) | *  |
| EQ-VAS   | 78.77 (± 15.48) | 76.64 (± 16.72) | 82.08 (± 13.23) | 68.75 (± 15.80) | 69.77 (± 17.83) | ***|

Note: ***p < 0.001; **p < 0.01; *p < 0.05

In addition, there existed variations in patients’ baseline characteristics. First, patients diagnosed with 0 and I TNM stage appeared to have a lower proportion in M and R state and a larger proportion in P and S state (p < 0.001). In contrast, patients originally diagnosed with IV stage appeared to have a greater proportion in M and R state rather than in P and S state (p < 0.001). Second, 84.3% participants in this study were outpatients. Specifically, 100% patients of S, 90% of R, 79.07% of M, and 52.8% of P were outpatients (p < 0.001).

Additionally, a significant number of patients received modified radical surgery (74.22%) compared with breast conserving surgery (22.65%) and no surgery (3.14%). Specially, the proportions of patients in R (80.00%) and M (79.07%) that received modified radical surgery were greater than those of patients in P (66.40%) and N (76.74%). While, patients in P state (24.8%) had a higher proportion that received breast conserving surgery than those in S (22.48%), R (20.00%), and M (18.60%).

Furthermore, a greater proportion of patients in M and R received radiotherapy and endocrine therapy compared with those in P and N (p < 0.0001). Meanwhile, menopaus status appeared to differ in patients from four states. Lastly, patient’s socioeconomic attributes such as household income and medical insurance type differed among patients in four states as well.

Variations in Quality Of Life

Table 3 showed the rank correlation coefficient of Spearman between the scores. All scores, including the FACT-B domain, showed a positive correlation. The correlation coefficient between FACT-B and EQ-5D-5L score was higher than that of EQ-VAS.

Consistent with descriptive analysis, results from multivariate analysis suggested that patients in R and M state had lower scores in overall quality of life (R, β = -9.45, p < 0.01; M, β = -6.72, p < 0.05), after adjusting for other covariates in the model (Table 4). Additionally, patients in R state had a lower
probability for better FWB ($\beta = -0.98, p < 0.05$) and SWB ($\beta = -1.41, p < 0.01$). Patients in M state appeared to have lower odds for higher scores in EWB ($\beta = -1.07, p < 0.05$) and SWB ($\beta = -0.82, p < 0.05$).

Table 3
Spearman’s rank correlation coefficients between the scores (coefficients)

| FACT-B       | EQ-5D-5L | PWB      | SWB      | EWB      | FWB      | BCS       | EQ-VAS |
|--------------|----------|----------|----------|----------|----------|-----------|--------|
| Total        | 0.642*** | 0.601*** | 0.389*** | 0.558*** | 0.471*** | 0.545***  | 0.442***|
| EQ-5D-5L     |          | 0.657*** | 0.741*** | 0.799*** | 0.752*** | 0.744***  | 0.469***|
| FACT-B       |          |          | 0.298*** | 0.575*** | 0.330*** | 0.543***  | 0.375***|
| PWB          |          |          |          | 0.458*** | 0.574*** | 0.389***  | 0.231***|
| SWB          |          |          |          |          | 0.481*** | 0.605***  | 0.445***|
| EWB          |          |          |          |          |          | 0.379***  | 0.467***|
| FWB          |          |          |          |          |          |           | 0.283***|
| BCS          |          |          |          |          |          |           |        |

Note: *** $p < .001$; ** $p < .01$; * $p < .05$
Multivariate analysis of variations in quality of life derived from FACT-B (coefficients)

| Independent variable | Quality of life | BCS | FWB | EWB | SWB | PWB |
|----------------------|-----------------|-----|-----|-----|-----|-----|
| age                  |                 | -0.01 |     |     |     |     |
| married (vs. others) |                 | 0.74* |     |     |     |     |
| education attainment|                 |     |     |     |     |     |
| Illiteracy and primary school | reference |     |     |     |     |     |
| Junior high school   | 3.09* | 0.48* | 0.25 | 0.79** | 0.22 |     |
| Senior high school   | 4.24* | 0.56* | 0.33 | 0.65* | 0.25 |     |
| College or above     | 2.80 | -0.23 | 0.45 | 0.84* | 0.18 |     |
| Urban (vs. rural)    |                 | -0.03 |     |     |     |     |
| Medical insurance    |                 |     |     |     |     |     |
| Others               |                 |     |     |     |     |     |
| UEMI                 | 1.58 | -0.01 | 0.09 | 0.33 | 0.51* |     |
| URMI                 | 4.58* | 0.51 | 0.23 | 0.61* | 0.98** |     |
| Occupation           |                 |     |     |     |     |     |
| Unemployed           |                 |     |     |     |     |     |
| Retired              |                 | -0.12 |     |     |     |     |
| Blue-collar          |                 | -0.54 |     |     |     |     |
| White-collar         |                 | -0.23 |     |     |     |     |
| Household income     |                 |     |     |     |     |     |
| < 30,000 RMB         |                 |     |     |     |     |     |
| 30,000 - <80,000 RMB |                 | 0.03 | -0.36 |     |     |     |
| > 80,000 RMB         |                 |     | 0.87** | 0.22 |     |     |
| Inpatients (vs. outpatients) | -9.25*** | -0.48 | -0.46 | -0.94** | -0.74* | -1.50*** |
| TNM stage            |                 |     |     |     |     |     |
| 0 and I              |                 |     |     |     |     |     |
| II                   | -2.59 | -0.29 | 0.05 | -0.28 |     |     |
| III                  | -3.26 | -0.29 | 0.01 | -0.27 |     |     |
| IV                   | -3.63 | 0.29 | -0.45 | 0.12 |     |     |
| Surgery              |                 |     |     |     |     |     |
| No surgery           |                 |     |     |     |     |     |
| Breast conserving surgery |           | 0.66 |     |     |     |     |
| Modified radical surgery |           | 0.27 |     |     |     |     |
| Radiotherapy (yes vs. no) | -9.25*** |     |     |     |     |     |
| Targeted therapy (yes vs. no) | 0.46 |     |     |     |     |     |
| Endocrine therapy (yes vs. no) | -0.52 |     |     |     |     |     |
| State                |                 |     |     |     |     |     |
| P                    |                 |     |     |     |     |     |
| R                    | -9.45** | -0.07 | -0.98* | -0.91 | -1.41** | -0.67 |
| M                    | -6.72* | -0.05 | -0.59 | -1.07* | -0.82* | -0.46 |

Multivariate analysis results in terms of variations in BCS and PWB as function of four kinds of states, however, differed from those in descriptive analysis (Table 1 & Table 2). There appeared no variations in BCS and PWB among patients in all states after controlling for other covariates.
Variations in Health Utility

Variations existed in health utility, depression, and pain as a function of four disease states (Table 5).

Specifically, patients in M state had a lower probability of achieving higher health utility compared with patients in P state ($\beta = -0.11, p < 0.05$). Additionally, they had higher odds for feeling painful ($\beta = 1.17, p < 0.01$) and being depressive ($\beta = 1.21, p < 0.01$). In contrast, there appeared no difference in other dimensions of health utility including mobility, self-care, and usual activities between patients in M state and those in P state.

**Table 5**

| Independent variable | EQ-5D-5L | EQ-VAS |
|----------------------|----------|--------|
| Mobility             | 0.03     |        |
| Self-care            | -0.89    | -0.87  |
| Usual activities     | -0.73    | 0.06   |
| Pain                 |          |        |
| Depression           |          |        |
| Age                  |          |        |
| Married (vs. others) |          |        |
| Education attainment |          |        |
| Illiteracy and primary school | 0.07 | -0.06 | -0.45 |
| Junior high school   |          |        |
| Senior high school   | -0.32    | 0.02   |
| College or above     | 0.40     | -0.46  |
| Urban (vs. rural)    | -0.53    | -1.58  |
| Medical insurance    |          | 0.67   |
| Occupation           |          |        |
| Unemployed           |          |        |
| Retired              | 0.59     | 0.23   |
| Blue-collar          | 0.47     | 0.37   |
| White-collar         | -0.11    | -0.42  |
| Household income     |          |        |
| < 30,000 RMB         |          |        |
| 30,000-80,000 RMB    |          |        |
| > 80,000 RMB         |          |        |
| Inpatients (vs. outpatients) | 2.05 | 1.41 | 1.53 | 1.30 | 0.95 | -0.22 | -0.47 |
| TNM stage            |          |        |
| 0 and I              |          |        |
| II                   | 0.63     | 0.23   |
| III                  | 0.45     | 0.72   |
| IV                   | 1.37     | 0.60   |
| Surgery              |          |        |
| No surgery           |          |        |
| Breast conserving surgery | 0.45 |       | 0.67 |
| Modified radical     | 0.86     |        |

Note: *p < 0.05, **p < 0.01, ***p < 0.001.
### Variations In Self-rated Health

Similar with results from descriptive analysis (Table 2), multivariate analysis results suggested that there existed variations in self-rated health between patients in R state and those in P, S, and M. (Table 5). Compared with patients in P state, patients in R state had lower self-rated health even after controlling for all other covariates in the model ($\beta = -1.12, p < 0.05$). While there existed no significant difference in self-rated health for patients in other three states (Table 5).

Results above supported our hypothesis that patient in four diseases states may have different health status, but variations did not in existed in every aspect of health when social-demographic and clinical attributes were introduced.

The feasibility of four disease states in health economic analysis

Results from rank correlation analysis suggested that overall scores of quality of life were significantly correlated with health utilities derived from EQ-5D-5L (Table 6). In the meantime, the correlation existed among patients from all disease states, while the correlation coefficient for patients in R state ($r = 0.919, p < 0.001$) was higher than others.

| Variables | Coefficients | Reference State |
|-----------|--------------|----------------|
| Surgery   |              |                |
| Radiotherapy (yes vs. no) | 0.00 | 0.01 |
| Targeted therapy (yes vs. no) | 1.04** |
| Endocrine therapy (yes vs. no) | -0.03 | 0.44 |
| Chemotherapy (yes vs. no) | -0.77* |
| Menopause (yes vs. no) | -0.21 |

Note: *** $p < .001$; ** $p < .01$; * $p < .05$.

Variables without coefficients did not make a statistically significant difference in univariate analysis (results not presents here), therefore they were not introduced into multivariate analysis.
### Table 6
Correlation between health utility and estimated health utility

| Status | FACT-B     | EQ-5D-5L   | r<sup>a</sup> | Estimated health utility | r<sup>b</sup> |
|--------|------------|------------|---------------|--------------------------|---------------|
| P      | 68.09 ± 13.85 | 0.81 ± 0.23 | 0.680***      | 0.70 ± 0.09              | 0.719***      |
| S      | 73.03 ± 11.68 | 0.90 ± 0.12 | 0.568***      | 0.75 ± 0.06              | 0.602***      |
| R      | 61.66 ± 16.86 | 0.78 ± 0.31 | 0.919***      | 0.69 ± 0.10              | 0.961***      |
| M      | 64.27 ± 14.84 | 0.74 ± 0.27 | 0.726***      | 0.69 ± 0.09              | 0.715***      |
| All    | 70.29 ± 13.33 | 0.86 ± 0.19 | 0.642***      | 0.73 ± 0.08              | 0.681***      |

Note: ***p < .001; **p < .01; *p < .05

<sup>a</sup>represents the correlation between patient-reported quality of life and health utility.

<sup>b</sup>represents the correlation between patient-reported health utility and estimated health utility.

In addition, estimated health utilities derived from quality of life were significantly correlated with health utilities directly measured from patients (Table 6). Results suggested that mapping function generated more accurate health utilities for patients in P, S, and R state except for those in M state (r = 0.720 vs. r = 0.715).

### Discussion

Extensive observations have focused on breast-cancer patients’ health, while overlooking health variations among patients in different disease states. Even less investigators have directed attention on health of multi-dimensions. The utility parameters used in only a few studies in China come from foreign data<sup>[24, 25]</sup>, so it is urgent to conduct a quality of life study based on the Chinese population and obtain health utility values. Furthermore, this study extended the research on the validation and application of mapping function and health utility value set to China’s breast cancer patients, which has been rare<sup>[20, 23]</sup>.

This study has three major implications. First, health variations existed in patients from different states, which may result from psychological burden and adverse effects from treatment in M and R states (H1a). Consistent with prior observation<sup>[26]</sup>, this study revealed that patients in S states have higher health utilities (Table 2). Meanwhile, our study further revealed that after controlling for other covariates, there exited no difference between patients in S state and those in P and R state, while patients in M state had lower health utilities relative to patients in other three states (Table 5).

Results from subgroup analysis demonstrated that patients in M state may have higher odds for feeling painful and depressive (Table 5), and they may have poor quality of life especially in family and social support as well as emotional conditions (Table 4). The results emphasized extra care for patients in M state as metastatic cancers often lead to greater adverse effects and pain of higher
degree, which may decrease patients’ quality of life and health utility\textsuperscript{[19, 27, 28]}. 

In addition, our results suggested that patients in R state had the worst quality of life and self-rated health, which differed from variations in health utility (Table 4 & Table 5). Although local recurrence requires a similar treatment to the first treatment, the quality of life of state R is significantly lower than that of state P, mainly related to the patient’s response, and the patient’s fear of treatment, pain and discomfort may lead to a decrease in quality of life\textsuperscript{[26, 29]}. The results of the study indicate that the results of different quality of life measurement tools are slightly different. However, the two scales and the EQ-5D-5L values obtained by FACT-B conversion using the mapping model are different in different states, indicating that the three methods have good discrimination in measuring the quality of life of breast cancer, which can be used for evaluation quality of life for breast cancer patients. Our results further demonstrated that patients in R state had more severe problems in functional status as well as social and family support relative to patients in M, P and S states (Table 4). Results suggested that patients experiencing cancer recurrence may have heavier psychological burden.

The second implication is that there did not appeared to be variations in all sub-dimensions including BCS, PWB, mobility, self-care and usual activities among patients from different states (H1b). Results suggested that patients in four states achieved similar performance in these health attributes after controlling for social-demographic and clinical attributes, even though there appeared to be statistically significant difference in univariate analysis (Table 4 & Table 5).

Third, our study confirmed that the application of four disease states in health economic analysis hold great promise, since patients in four disease states reported significantly different health utilities (Table 2 & Table 5), while results also revealed that the current mapping function derived from China’s population needs further refinement in order to accurately estimate health utilities from quality of life, since the correlation coefficient declined in M state (Table 6). FACT-B is the most widely used specific quality of life scale in China, but as far as we know, only a Singapore study by Yin et al. \textsuperscript{[20, 30]} explored the health of mapping FACT-B to EQ-5D-5L. This study was the first to explore the feasibility of the FACT-B to EQ-5D-5L mapping in China. Using this mapping model to calculate the
mapped utility value\cite{20}, it was found that the EQ-5D-5L utility value score had a correlation with the FACT-B mapping utility value score ($p < 0.05$), the utility of different states. The correlation coefficient between the value scores were between 0.602 and 0.961. The utility value of each disease state after mapping was lower than the true value measured by the EQ-5D-5L scale, and the difference between the FACT-B scores of the state R and the state M becomes equal after the conversion to the health utility value. It may be related to the research in Singapore, the research object is different from this research, and the EQ-5D-5L scale is related to the UK and Japan's integral utility system, suggesting that the foreign mapping algorithms need to be localized to adapt to the Chinese population.

This study presents two aspects of improvement over prior study. First, current study included breast-cancer patients from four disease states, which were more inclusive compared with prior investigations that generally focused on one or two states\cite{11, 12, 28}. In particular, the health utility scores obtained in this study are useful for cost-utility analysis using QALYs as a metric. Second, this study included multiple dimensions of health, using three measurement tools, while the majority of existed examinations usually measured one health outcome\cite{15}. Third, this study explored the feasibility of the mapping of the quality of life scale FACT-B to EQ-5D-5L for the first time in China. Despite the strength, this study has several limitations. First, this study collected data in a single health center, which mitigated the representativeness of China's breast-cancer patients. Second, the cross-sectional study design provided wake evidence for robustness of the results and limited information for QALYs which incorporated the duration of each state. Last, participants in this study were aged from 43 to 61 years old, the middle-aged sample restricted the external validity of our results to elder and younger patients.

Conclusions
We obtained the health utility, HRQoL and VAS scores of P, S, R and M states measured by Chinese breast-cancer patients using EQ-5D-5L, EQ-VAS and FACT-B. To the best of our knowledge, this is the first study to evaluate the quality of life of multiple disease states in breast cancer using a variety of measurement tools. In our study, each score obtained was well correlated. We also used the published mapping model to explore the feasibility of establishing a mapping model for FACT-B to EQ-
5D-5L scales in China. Our work will help to develop cost-utility analysis in the Chinese environment as breast cancer treatments continue to increase.

**Abbreviations**

BCS: additional concerns for breast cancer; EQ-5 D-5 L: EuroQol-5 Dimension-5 Level; EWB: emotional wellbeing; FACT-B: Functional Assessment of Cancer Therapy – Breast; FWB: functional wellbeing; NICE: National Institute for Health and Care Excellence; PWB: physical wellbeing; QALYs: Quality-adjusted life years; SWB: social/family wellbeing

**Declarations**

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Not applicable.

**Authors' contributions**

All authors have contributed to design of the study, the acquisition of data, and the interpretation of the results. QY and XXY analyzed the data and involved in drafting the manuscript; WZ was involved in revising the manuscript critically for important intellectual content. All authors have read and approved the final manuscript.

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**Availability of data and material**

The dataset are available from the corresponding author on reasonable request.

All procedures performed in this study involving human participants were in accordance with the ethical standards of the Ethics Committee of West China Hospital, Sichuan University (approval number 2017-255), and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Competing interests**

The authors declare that they have no competing interests.

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Figures
Figure 1

Distributions of scores obtained by FACT-B
Figure 2

Distributions of scores obtained by EQ-5D-5L
Figure 3

Distributions of scores obtained by EQ-VAS