Health-Related Quality of Life as Measured by EQ-5D and TFLIC-2 in Liver Cancer Patients

Thanawat Wongphan, M.D., M.P.A.*,**, Kanitta Bundhamcharoen, D.D.S., Ph.D.*

*International Health Policy Program (IHPP), Ministry of Public Health, Nonthaburi 11000, **Banmoh Hospital, Ministry of Public Health, Saraburi 18000, Thailand.*

ABSTRACT

Objective: To assess the relation and estimation function between utility weight (UW) from EQ-5D and T-FLIC 2 score (TFS). To compare quality of life (QOL) between global burden of disease (GBD) and TNM staging.

Methods: All liver cancer patients which presented in selected hospitals in 2009, were asked their QOL by EQ-5D and T-FLIC 2 questionnaires. The relation between UW and TFS was analyzed by using Pearson's correlation and the linear regression. The means of UW and TFS in specific conditions were compared with independent t-test and ANOVA.

Results: There were 53 cases. The majority (73.6 %) were men, mean age was 57.2 years, lived in suburban area (67.9%), worked in agriculture (47.2%) and graduated secondary level or lower (83.0%). These 73.6% of all samples had household monthly income not greater than 5,000 THB and used universal coverage scheme (64.2%). Seventeen cases had not been identified TNM staging because of the condition of patients. However, those cases fulfilled to be diagnosed terminal stage. The multiple comparisons between means of UW and TFS showed no statistical significance e.g. pre-terminal and terminal (0.5 vs 0.4, p=0.3 and 38.8 vs 34.0, p=0.2 respectively), TNM-stage 4 vs TNM-stage 1-3 (0.3 vs 0.5, p=0.3 and 38.9, 30.5, p=0.1), and supportive only vs. other treatment (0.5 vs 0.5, p=0.9, and 32.8 vs 36.2, p=0.5). The correlation between UW and TFS was significantly related (p<0.001) with linear pattern (p<0.001). The equation for estimating UW from TFS and specific Q1-Q22 questions was formulated.

Conclusion: This study revealed the significant correlation between UW and TFS with linear pattern. A major advantage of using regression analysis was predicting UW from TFS for economic evaluation in Thai liver cancer patients. The treatment might not alter QOL significantly. Given cancer stage and treatment choice and their QOL in this study, our findings should not be over-interpreted.

Keywords: Liver cancer; quality of life; EQ-5D; T-FLIC 2 (Siriraj Med J 2018;70: 406-412)

INTRODUCTION

Liver cancer is an abnormal and malignant growth of liver cells. The most common type of liver cancer is called hepatocellular carcinoma (HCC).[1] Liver cancer is a tumor with high lethality. The 5-year relative survival rates were about 6.5% to 8.3%.[2]

From global overall years of life lost (YLL) by cancer, liver cancer ranked the third in year 1990 and stepped up to the second rank in 2013.[3]

In Thailand, liver cancer contributed to the burden of diseases by number 5 in men and number 8 in women.[4] Moreover, liver cancer ranked the second top cancer incidence in Thailand.[5] The incidence of liver cancer in males and females ranged between 6.4 to 87.5 in males and 1.4 to 37.2 per 100,000 in females.[6]

To estimate and validate disability-adjusted life years lost from cancer, the disease model categorized liver cancer patients into two stages; terminal and

pre-terminal stages.[7] World Health Organization-Global Burden of Disease (GBD) was used in this two phases model in calculation. Terminal stage was defined by the patient-survival time less than 1 month.[8] The terminal and Pre-terminal stage definition were totally different from TNM staging[9] which has been widely used by clinicians. This difference has led to a renewed interest in comparison for quality of life (QOL) in TNM staging and GBD definition. Additionally, the QOL measurement tools could be one of these disease specific or generic tools. The generic tools e.g. EQ-5D, SF-36 etcetera were most likely to report score and then converted to utility weight (UW) by its algorithm. The EQ-5D, the tool which has been used for measuring patient preference-based quality of life, consists of 5 questions about mobility, self-care, main activity, social relationships, pain, and mood.[10] The EQ-5D for adults has 2 versions; 5L and 3L. Both versions are valid and it is now generally accepted that the generic health status questionnaires were easy to use and able to compare other diseases in case of economic evaluation, and were also valid. Whilst, quality of life in cancer patients can be measured by various tools, none of that can be converted to UW directly. The Functional Living Index Cancer (FLIC) was one of the famous questionnaires which was was first reported for using in clinical trials in 1984[11], The FLIC is a 22-item questionnaire which measures QOL in multidimensions of global, role, social, emotional, pain, and nausea scales. The latest FLIC version 2 was translated and validated into Thai language in 2005.[12] The TFLIC 2 was a reliable and valid measurement of the quality of life in clinical trials, studies of outcome and research in oncology.[12]

In spite of recent studies[13] which have explored the similarities between disease specific questionnaires and generic health status questionnaire, relatively little is known about the relationship between T-FLIC 2 and generic health status questionnaire. To avoid redundant measurement and bridging the clinical trial QOL and UW for cost-effectiveness analysis, we needed a tool to convert TFLIC-2 to UW.

MATERIALS AND METHODS

A multicenter, cross-sectional observational survey was conducted in three provinces of Thailand during 2009-2010. This study was ethical approved by The Ethical Review Committee for Research in Human Subjects. Ministry of Public Health, Thailand (Document No 98/2009).

Patients

All liver cancer patients who presented at the hospitals

in the selected period [June 2009 to December 2009] and fulfilled the inclusion criteria below were enrolled to this study.
1. Samples must have been diagnosed liver cancer as a primary source.
2. Samples must be able to read and write, co-operative and willing to complete questionnaire or interviewing.
3. Samples must agree to participate in our study.

Exclusion:
1. Samples have other underlying diseases not related to liver cancer.
2. Samples who have other congenital anomaly or co-morbidity.
3. Samples who have acute condition of sickness or injury.
4. Samples who were negative to participate in our study.

Sample size was calculated based on correlation coefficient between UW and TFS with $\alpha=0.05$, $\beta=0.2$, expected correlation coefficient (r)=0.5. The equation[14] was shown below.

$N = [(Z_\alpha + Z_\beta)/C]^2 + 3$ where $C = 0.5 * \ln[(1+r)/(1-r)]$

Thus the calculated sample size was 29. Then, we ensured the sample number by multiplying it by 2, so the expected number was around 60 cases. The recruitment proportion was shown in Fig 1.
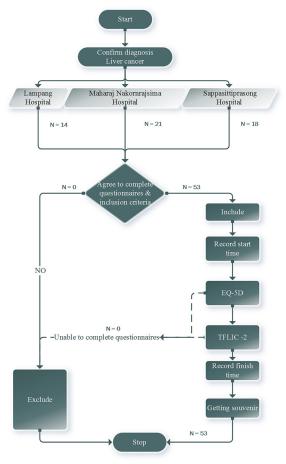

Fig 1. Sample recruitment process..

Definition

The Global Burden of Disease (GBD) group divided the liver cancer patients into two groups: pre-terminal and terminal which had definition[7] as shown below.

Pre-terminal stage of patient who lives with liver cancer not described as terminal stage.

Terminal stage means the final last month period of living of the patients.

Tools

The tools for measuring QOL were EQ-5D and T-FLIC 2 score (TFS). The EQ-5D was created by EURO-QOL® to measure QOL in all cases in term of utility weight (UW). The UW reflected the QOL by continuous score which ranged from 0 to 1. The meaning of UW 1.0 was perfect health and 0 was the worst imaginary health which roughly equaled to dead. Sometimes the UW was less than 0 which means dead would be better than that condition. The EQ-5D score was transformed to UW with specific Thai Algorithm.[15]

In addition, this study focused on the relationship of the quality of life which was measured by T-FLIC 2 and EQ-5D. T-FLIC -2 was a disease specific QOL measurement tool which was validated to use in Thai cancer patients.[12] The interpretation for both UW and TFS were likely to be the same, so higher is better.

The data collection protocol was established and standardized with resulted in a standard of practice (SOP) manual. All data collection staffs in all sites were trained for data collecting and interviewing process. Data verification and validation process were done, following the SOP manual.

Statistical analysis

Sample demographics were reported as number and percent. The relation between UW and T-FLIC 2 Score (TFS) was analyzed by using Pearson's correlation and the linear regression was performed to derive the UW from TFS and TFLIC-2 specific questions. The mean difference between UW and TFS in each groups of patients were compared with independent sample t test and ANOVA with LSD. All calculations were done by SPSS version 24.0.

RESULTS

Table 1 presented the general characteristics of 53 samples. The percentage of male was 73.6. The age was varied between 17 and 89 and the average age was 57.2 years old. The cases were collected mainly from Northeastern region based on their epidemiologic pattern. The 67.9 percent of samples lived in suburban area,

TABLE 1. Characteristic of subjects.

Demographic characteristics	n (%)
Gender	
Male	39(73.6%)
Female	14(26.4%)
Age	
Mean±SD	57.2±15.8
Range	17-89
Data collection sites	
Lampang Hospital	14(26.4%)
Sappasittiprasong Hospital	21(39.6%)
Maharaj Nakornrajsima Hospital	18(34.0%)
Health insurance scheme	
Universal coverage scheme	34(64.2%)
Social security scheme	4(7.5%)
Civil servant medical benefit scheme	15(28.3%)
Address	
Urban	17(32.1%)
Sub-urban	36(67.9%)
Education level	
Uneducated	3(5.7%)
Secondary level or lower	44(83.0%)
Upper than secondary level	6(11.3%)
Occupation	
Unemployed	7(13.2%)
Agriculture	25(47.2%)
Non-agriculture	21(39.6%)
Monthly income	
0-5,000 THB	39(73.6%)
5,001-15,000 THB	8(15.1%)
15,001+ THB	6(11.3%)

and mainly worked in agriculture (47.2 percent). The main education level was secondary level or lower. The percentages of health insurance scheme sorted from maximum to minimum were universal coverage, civil servant, and social security scheme respectively. The 73.6% of all samples had household monthly income not greater than 5,000 THB. Specifically, the characteristics of our samples mainly pointed to low socioeconomic status based on income and education level.

As shown in Table 2, seventeen cases from a total of 53 cases had not been identified TNM staging because

of the condition of patients. In addition, those seventeen cases were also diagnosed in terminal stage. Table 2 presented, that the terminal stage didn't exactly equal to stage 4 of TNM staging because there was one case of stage 1-3 which was classified to terminal stage. However, all liver cancer cases of TNM stage 4 were categorized to terminal stage.

Table 3 showed the lower values of QOL which were measured by EQ-5D and T-FLIC 2 in case of terminal stage, but there was no statistical significant. The UW and TFS in pre-terminal and terminal were 0.54, 38.78 and 0.41, 34.03 respectively.

A positive correlation between UW and TFS was obtained with correlation 0.67 and p<0.001.

To estimate UW from TFS and specific Q1-Q22 T-FLIC questions, we performed linear regression. Table 4 presented the significant (p<0.001) result of linear regression analysis between UW and TFS with R^2 0.428 and the equation for estimating UW was shown in Equation 1.

As shown in Fig 2, even the R^2 was not high, but there was no skewness of expected probability and observed probability in Probability-Probability Plot (P-P Plot). In order to improve the accuracy of UW prediction from

---

TABLE 2. Cross table of cases who have been diagnosed in TNM staging and GBD definition.

Disease stage		Unidentified	Stage 1-3	Stage 4	Total N (Col %)
Pre-terminal vs. terminal stage	Pre-terminal N (row %)	0	19(100%)	0	19(35.8%)
	Terminal N (row %)	17(50.0%)	1(1.9%)	16(48.1%)	34(64.2%)
Total N (row %)		17(32.1%)	20(37.7%)	16(30.2%)	53(100%)

Abbreviations: TNM = , GBD = burden of disease

TABLE 3. UW and TFS in pre-terminal vs. terminal stage of liver cancer patient.

The QOL score	Pre-terminal stage (Mean±SD)	Terminal stage (Mean±SD)	p-value
UW	0.54±0.40	0.41±0.40	0.293
TFS	38.78±12.22	34.03±12.56	0.203

Abbreviations: UW = utility weight , TFS = T-FLIC 2 score

TABLE 4. Linear regression analysis between UW and TFS.

	B	Std. Error	Beta	t	Sig.
(Constant)	-0.3	0.136		-2.211	0.032
			0.655		
TFS	0.021	0.004		5.935	0

Abbreviation: TFS = T-FLIC 2 score

Normal P–P Plot of Regression Standardized Residual
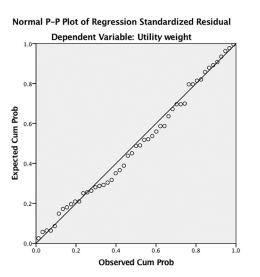**Dependent Variable: Utility weight**

Fig 2. P-P Plot of observed UW and expected UW from TFS to UW conversion equation.

T-FLIC 2, we developed the linear equation based on each of the 22 items as seen on Table 5 with R² 0.715.

Table 6 presented that the treatment receiving group had higher UW, but was not statistically significant. TFS seemed to have similar effect on only chemotherapy receiving group which had higher TFS than not receiving, although the difference showed no significance.

The samples who were diagnosed in terminal stage in the Table 7, had lower QOL in terms of UW and TFS, but this was not statistically significant. Similarly, the TNM stage 4 patients had the lowest QOL when compared to Stage 1-3 and unidentified group. Incidentally, the unidentified group in TNM staging were similarly equal UW and TFS to TNM stage1-3.

TABLE 5. Linear regression analysis between UW and individual Q1-Q22 TFLIC questions.

	B	Std. Error	Beta	t	Sig.
(Constant)	-0.08	0.25		-0.33	0.75
Q1: 1. Feel depressed?	0.04	0.11	0.076	0.37	0.71
Q2: 2. Cope well with stress?	0.00	0.12	-0.003	-0.01	0.99
Q3: 3. Think about illness?	0.18	0.16	0.241	1.16	0.26
Q4: 4. Maintain leisure activities?	0.11	0.08	0.273	1.41	0.17
Q5: 5. Nausea affecting daily functioning?	0.10	0.08	0.253	1.34	0.19
Q6: 6. Feel well?	-0.06	0.12	-0.127	-0.52	0.60
Q7: 7. Well enough for meals or repairs?	0.00	0.09	0.004	0.02	0.99
Q8: 8. Hardship on the closest?	-0.05	0.11	-0.114	-0.45	0.65
Q9: 9. Discouraged about life?	-0.08	0.11	-0.134	-0.71	0.49
Q10: 10. Satisfied with work?	-0.02	0.11	-0.042	-0.16	0.87
Q11: 11. Feel uncomfortable?	0.04	0.09	0.088	0.39	0.70
Q12: 12. Disruptive to the closest?	-0.03	0.13	-0.073	-0.25	0.81
Q13: 13. Pain/discomfort interfering activities?	-0.02	0.08	-0.052	-0.25	0.80
Q14: 14. Hardship on yourself?	0.20	0.11	0.505	1.79	0.09
Q15: 15. Able to complete housework?	0.08	0.06	0.211	1.21	0.24
Q16: 16. Willing to spend time with family?	-0.03	0.11	-0.056	-0.26	0.80
Q17: 17. How much nausea?	-0.10	0.08	-0.166	-1.21	0.24
Q18: 18. Frightened of future?	0.16	0.10	0.300	1.72	0.10
Q19: 19. Willing to spend time with friends?	-0.01	0.09	-0.031	-0.15	0.88
Q20: 20. Pain/discomfort related to cancer?	0.04	0.11	0.084	0.37	0.72
Q21: 21. Confident of treatment?	-0.08	0.07	-0.176	-1.14	0.27
Q22: 22. Appear well?	-0.09	0.13	-0.169	-0.66	0.52

TABLE 6. The QOL in Liver cancer patient categorized by their treatment choice.

Choices of treatment	n	UW				TFS			
		Yes	No	p-value		Yes	No	p-value	
		Mean±SD	Mean±SD	(2-tails)		Mean±SD	Mean±SD	(2-tails)	
Surgery	34	0.55±0.46	0.45±0.38	0.43		34.17±10.47	36.71±13.65	0.47	
Chemotherapy	15	0.61±0.38	0.43±0.41	0.16		37.43±10.62	35.11±13.29	0.53	
Surgery and chemotherapy	8	0.35±0.44	0.47±0.38	0.33		33.83±11.52	36.63±14.2	0.49	
Supportive treatment only	27	0.50±0.48	0.48±0.40	0.93		32.83±9.07	36.19±12.96	0.45	

TABLE 7. The mean UW and TFS in liver cancer patients defined stage by GBD definition and TNM staging.

	GBD Staging			TNM-Staging			
	Pre-terminal	Terminal	p-value[†]	Stage 1-3	Stage 4	Unidentified	p-value[‡]
	Mean± SD	Mean±SD		Mean±SD	Mean±SD	Mean±SD	
UW	0.54±0.41	0.41±0.41	0.29	0.53±0.40	0.32±0.40	0.51±0.42	0.29
TFS	38.78±12.51	34.03±12.56	0.20	38.89±11.88	30.53±12.54	37.07±12.42	0.14

NOTE: [†] p-value in 2-tailed test in case of equal variances not assumed in significant level .05
[‡]p-value in ANOVA test between groups in significant level .05

DISCUSSION

To interpret quality of life, the socioeconomic status (SES)[16], should also be considered with other aspects of patients. The lower SES in these samples might lead to the lower set of UW and TFS. As in previous studies[17], the results of this analysis confirmed that liver cancer was more predomint in males more than females, with the ratio about 3:1 and this ratio was in the same range from previous study (between 6.4 to 1.4 and 87.5 to 37.2 per 100,000 in females).[6] Thus, the sex difference of epidemic data urged researchers to investigate the role of sex hormone in liver tumors.[18] For instance, there was a study which suggested increasing prolactin level in men might help to reduce incidence of HCC.[19] Therefore, the level of prolactin level comparison between north-eastern, Thailand and other regions might be studied further.

There were many tools which could be used for measuring QOL in cancer patient apart from EQ-5D and T-FLIC 2 e.g. The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30), Functional Assessment of Cancer Therapy-General (FACT-G), Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep), Functional Hepatobiliary Symptom Index-8 (FHSI-8) Questionnaire, Short Form-36 (SF-36) survey, WHOQOL-100 and WHOQOL-BREF, Spitzer QoL Index (SQLI), and SF-12.[20] etcetera. However, there were no tools to estimate UW from their specific disease questionnaires. By our synthesized equation, a researcher can estimate the UW from T-FLIC 2 score, although the value should not exceed -0.59 to 1.00.[21]

In contrast, the treatment showed no significant difference to alter QOL, which it might seem counter intuitive that QOL after operation gradually increased[22], so the effect of treatment and QOL varied from time to time. The other study which compared between EQ-5D and T-FLIC also mentioned EQ-5D changed significantly over time.[23]

Our UW findings were consistent with previous results showing the range of mean index-based scores

from 0.33 (SD 0.4) to 0.93 (SD 0.12).[24] However, there was restriction to compare our TFS with other study due to no prior data, but we found our TFS results were lower than stage IV lung cancer patients (46-55).[25] The liver cancer patients might present the lower TFS from the nature of this disease.

Accordingly, future studies will have to continue to explore for a new version of EQ-5D-5L.[26] To clarify the relationship between liver cancer stage and quality of life, more samples should be considered. Moreover, this study stated the low SES has been diagnosed in liver cancer and most likely to be in terminal stage, so the recommendation of liver cancer prevention and early detection in this group of people should be supported by government.

To conclude, this study synthesized the equation to converse TFS to UW and confirmed the linear relation between these scores. The TNM stage 4 was likely to be diagnosed terminal stage in GBD definition. Given cancer stage and treatment choice and their QOL in this study, our findings should not be over-interpreted.

ACKNOWLEDGMENTS

REFERENCES

1. Mokdad AA, Singal AG, Yopp AC. JAMA PATIENT PAGE. Liver Cancer. JAMA. 2015;314(24):2701.
2. Bosch FX, Ribes J, Díaz M, Cléries R. Primary liver cancer: Worldwide incidence and trends. Gastroenterology. 2004;127(5 Suppl 1):S5-S16.
3. Global Burden of Disease Cancer C, Fitzmaurice C, Dicker D, Pain A, Hamavid H, Moradi-Lakeh M, et al. The Global Burden of Cancer 2013. JAMA Oncol. 2015;1(4):505-27.
4. Bundhamcharoen K, Odton P, Phulkerd S, Tangcharoensathien V. Burden of disease in Thailand: changes in health gap between 1999 and 2004. BMC Public Health. 2011;11:53.
5. Virani S, Bilheem S, Chansaard W, Chitapanarux I, Daoprasert K, Khuanchana S, et al. National and Subnational Population-Based Incidence of Cancer in Thailand: Assessing Cancers with the Highest Burdens. Cancers (Basel). 2017;9(8). pii: E108.
6. Deerasamee S MN, Sontipong S, Sriamporn S, Sriplung H, Srivatanakul P, Vatanasapt C, Parkin DM, Ferlay J. Cancer in Thailand Volume II, 1992-19941999.
7. Soerjomataram I, Lortet-Tieulent J, Ferlay J, Forman D, Mathers C, Parkin DM, et al. Estimating and validating disability-adjusted life years at the global level: a methodological framework for cancer. BMC Med Res Methodol. 2012;12:125.
8. Mathers C B-PC. Global burden of cancer in the year 2000: version 1 estimates. World Health Organization; 2006.
9. Stephen Edge, David R. Byrd, Carolyn C. Compton, April G. Fritz, Frederick Greene, Andrew Trotti. AJCC Cancer Staging Handbook. 7th ed: Springer-Verlag New York; 2010.
10. EuroQol G. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy. 1990;16(3):199-208.
11. Schipper H, Clinch J, McMurray A, Levitt M. Measuring the quality of life of cancer patients: the Functional Living Index-Cancer: development and validation. J Clin Oncol. 1984;2(5):472-83.
12. Thongprasert S, Intarapak S, Saengsawang P, Thaikla K. Reliability of the Thai-modified Function Living Index Cancer questionnaire version 2 (T-FLIC 2) for the evaluation of quality of life in non-small cell lung cancer patients. J Med Assoc Thai. 2005;88(12):1809-15.
13. Wilke S, Janssen DJ, Wouters EF, Schols JM, Franssen FM, Spruit MA. Correlations between disease-specific and generic health status questionnaires in patients with advanced COPD: a one-year observational study. Health Qual Life Outcomes. 2012 Aug 21;10:98.
14. Hulley SB CS, Browner WS, Grady D, Newman TB. Designing clinical research : an epidemiologic approach. 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2013.
15. Tongsiri S, Cairns J. Estimating population-based values for EQ-5D health states in Thailand. Value Health. 2011;14(8):1142-5.
16. Shebl FM, Capo-Ramos DE, Graubard BI, McGlynn KA, Altekruse SF. Socioeconomic status and hepatocellular carcinoma in the United States. Cancer Epidemiol Biomarkers Prev. 2012;21(8):1330-5.
17. Yun EH, Lim MK, Oh JK, Park JH, Shin A, Sung J, et al. Combined effect of socioeconomic status, viral hepatitis, and lifestyles on hepatocelluar carcinoma risk in Korea. Br J Cancer. 2010;103(5):741-6.
18. Giannitrapani L, Soresi M, La Spada E, Cervello M, D'Alessandro N, Montalto G. Sex hormones and risk of liver tumor. Ann N Y Acad Sci. 2006;1089:228-36.
19. Seton-Rogers S. Hepatocellular carcinoma: Gender differences. Nat Rev Cancer. 2014;14(9):578-9.
20. Gandhi S, Khubchandani S, Iyer R. Quality of life and hepatocellular carcinoma. J Gastrointest Oncol. 2014;5(4):296-317.
21. Hawthorne G, Richardson J, Day NA. A comparison of the Assessment of Quality of Life (AQoL) with four other generic utility instruments. Ann Med. 2001;33(5):358-70.
22. Chen L, Liu Y, Li GG, Tao SF, Xu Y, Tian H. Quality of life in patients with liver cancer after operation: a 2-year follow-up study. Hepatobiliary Pancreat Dis Int. 2004;3(4):530-3.
23. Conner-Spady B, Cumming C, Nabholtz JM, Jacobs P, Stewart D. Responsiveness of the EuroQol in breast cancer patients undergoing high dose chemotherapy. Qual Life Res. 2001;10(6):479-86.
24. Pickard A. WC, Lin H, Lloyd A. Health utilities using the EQ-5D in studies of cancer. Pharmacoeconomics. 2007;25(5):365-84.
25. Chantor P, Rattanabanjerdkul H, Itharat A. Case studies of Benjakul recipes in treating stage 4 non – small cell lung cancer. Thammasat Medical Journal. 2017;17(2):172-81.
26. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011;20(10):1727-36.