Establishing Minimal Clinically Important Differences for the Quality of Life Instrument in Patients with Esophageal Cancer QLICP-ES (V2.0) Based on Anchor-Based and Distribution-Based Methods

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Research article

Keywords: esophageal cancer, quality of life, MCID, anchor-based methods, distribution-based methods

Posted Date: August 20th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-57319/v1

Abstract

Background: The minimal clinically important difference (MCID) is an important phrase with big appeal in a field struggling to interpret quality of life (QOL) and other patient-reported outcomes (PRO), is also a bridge between statistics and clinical medicine. This paper is aimed to determine the MCID of esophageal cancer scale among Quality of Life Instruments system for Cancer Patients, QLICP-ES (V2.0).

Methods: According to the scoring rule of QLICP-ES (V2.0), the scores of each domain and the overall of the scale were calculated. The MCID values of this scale were established by anchor-based and distribution-based methods. Two criteria A (improves one level after treatments) and B (at least improves one levels after treatments) were defined treatments effects in anchor-based methods, while methods of ES, SEM and RCI were used in distribution-based methods.

Results: Using the anchor-based method, according to standard A, the MCID values of physical domain, psychological domain, social domain, common symptom and side-effects domain, the specific domain and the overall were 15.1, 4.4, 3.1, 6.7, 8.5 and 6.0 respectively. According to standard B, the MCID values of above domains and the overall were 19.3, 4.2, 4.8, 7.7, 9.5 and 7.5 respectively. Under the distribution-based methods, the MCID values above calculated by each method (ES, SEM and RCI) are in different ranges from 1.1 to 13.3.

Conclusion: All methods have its own advantages and disadvantages to develop the MCID values, so it is necessary to develop the MCID values of QLICP-ES (V2.0) comprehensively with a variety of methods considering the actual situation.

Background

Esophageal cancer (ES) is the sixth most common cancer in the world and the fourth most common cause of cancer deaths in China. Nearly half a million new ES cases are diagnosed each year [1,2]. In China, the incidence of esophageal cancer ranks the sixth among malignant tumors, and the incidence of male cancer is higher than female cancer, and the incidence of rural cancer is higher than urban cancer [3]. The clinical symptoms of early esophageal cancer are not obvious, and dysphagia is often the main symptom, which may be combined with gastrointestinal and other system-related symptoms [4], resulting in somatic or functional damage, which seriously affects the physical and mental health of patients and reduces their quality of life (QOL) and other patient-reported outcomes (PRO). With the medical model entering the bio-psycho-social medical model (modern medical model), people pay more attention to the improvement of QOL while paying more attention to the prolonging of life.

Therefore, the assessments of QOL have been applied as significant outcome indicators for patients with ES [5.6], given the time course of the disease, the difficulty in curing and the burden of treatments. Consequently, several specific instruments for patients with ES have been developed and are used in cancer clinical researches, including European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Group questionnaire, the QLQ-OES23 [7.8], the Functional Assessment of Cancer Therapy-Esophageal cancer questionnaire (FACT-E) [9]. In China, the QOL team led by professor Chonghua Wan

developed a scale system called QLICPs (Quality of Life Instruments for Cancer Patients), in which the QLICP-ES (the first version and the second version) is an instrument for quality of life measurement of esophageal cancer[10,11]. The QLICPs is a Chinese QOL instruments system developed by module approach with a general module (QLICP-GM) being used with all types of cancer, and some specific modules for different cancers [12,13].

The QLICP-ES (V2.0) includes a generic module QLICP-GM (V2.0) and an esophageal cancer specific module, with the QLICP-GM (V2.0) including physical function (8 items), psychological (9 items), social functions (8 items), common symptoms and side effects (7 items), a total of 10 side and 32 items in 4 domains. The esophageal cancer specific module includes four domains and 16 items. The whole scale consists of 14 facets and 48 items in 5 domains (dimensions), which can be used for patients with various types of esophageal cancer, and can be used for the measurement of patients' quality of life in the period of onset, treatment and rehabilitation.

For reasonable explanation of the actual clinical significance of questionnaire survey and the scale score, the minimal clinically important differences (MCID) as an important change assessment tools or scale responsiveness of appropriate benchmarks have been proposed for the first time in 1987. Canadian scholar Jaeschke and others defined MCID as the minimum variation of questionnaire dimension score acceptable to patients without considering side effects and costs [14,15].

The MCID is an important phrase with big appeal in a field struggling to interpret QOL and other patient-reported outcomes (PRO), is also a bridge between statistics and clinical medicine. How to develop reasonable and reliable MCID values has become a hot topic for scholars. There are mainly two traditional methods, including anchor-based method and distribution-based method. At present, although QLICP-ES (V2.0) has been developed, MCID has not been developed. For this reason, in this paper, the MCID of QLICP-ES (V2.0) was developed by using the commonly used anchor-based method and distribution-based method, and the advantages and disadvantages of the two methods were compared to lay a foundation for clinical application.

Methods

Data sources

In this study, 232 inpatients with esophageal cancer diagnosed by pathological examination and diagnosed by thoracic surgery in a provincial cancer hospital were selected as the research objects. The inclusion and exclusion criteria are as follows:

Inclusion criteria: (1)Patients diagnosed with esophageal cancer by X-ray and fiberoptic esophagoscopy or gastroscopy biopsy; (2) Inpatients receiving treatments for esophageal cancer; (3) Understanding of the questionnaire due to the fact that the patient himself have a primary school education or above; (4)Patients who voluntarily participated in the test on this quality of life scale[16].

Exclusion criteria: (1) Patients who are illiterate or lack the ability to read and write;(2) Patients who are unable to express their true feelings clearly due to vague consciousness during hospitalization;(3) Patients who are unable to participate the test due to suffering from other serious diseases.

The QLICP-ES (V2.0) scale and EORTC QLQ-C30 were given to 232 patients with esophageal cancer before and after treatments, and was filled in once before and after treatments.

Anchor-based methods

The anchor-based method is to clarify the meaning of the scale score change by examining the relationship between the scale and another independent measurement tool score or other indicators. There are cross-sectional anchors and longitudinal anchors. In this study, longitudinal anchors were selected to compare the curative effect before and after treatments. First, the Raw Score (RS) of domains were computed according to the number of questions and the answers of patients in each domain. Then, linear transformation is carried out with range method to convert the original score into a standardized score within 0-100.The score calculation method of each domain is as follows[17]:

$$SS = (RS - Min) \times 100 / R \qquad R = Max - Min$$

Second, the Q29 item in the EORTC QLQ-C30 scale, "how would you evaluate your overall health in the past week", was selected as an anchor after considering the correlation coefficient between Q29 and QLICP-ES (V2.0) . Then, patients with a difference of one grade (standard A) and at least one grade (standard B) in Q29 before and after treatments were selected, and the score differences in various domains before and after treatments were calculated respectively, and the mean value of the difference was denoted as MCID.

Distribution-based methods

The distribution method is to determine the MCID from a statistical point of view by using the distribution(variation) of the sample data of the evaluation tool. The commonly used indexes to calculate variation include Effect-Size (ES), Standard Error of the Measurement (SEM), and Reliable Change Index (RCI).

Effect-Size (ES) is obtained by dividing the difference in mean scores from baseline $_0$ to post-intervention $_1$ by the standard-deviation of the baseline score ($SD_{baseline}$) [18], the calculation formula and the corresponding MCID are as follows:

$$ES = \frac{\bar{x}_1 - \bar{x}_0}{\sqrt{\sum (x_0 - \bar{x}_0)^2 / n - 1}} \qquad MCID = ES \times SD_{baseline}$$

ES is often used to compare two or more groups to measure the size of the difference between groups. In health-related quality of life assessments, ES is currently the most recognized parameter in determining the

importance of group or individual changes. Cohen [19] empirically defined an effect size of 0.2 as small,0.5 as moderate, and 0.8 as large.

Standard Error of the Measurement (SEM), defined as the baseline SD multiplied by the square root of one minus sample test-retest reliability coefficient, were also calculated for comparison purpose [20]. The reliability is usually estimated using a test-retest reliability estimate, but some authors also use an internal consistency estimate, for example Cronbach's alpha [21]. The calculation formula and the corresponding MCID are as follows:

$$SEM = \sqrt{1-r} \times \sqrt{\sum (x_0 - \bar{x}_0)^2 / n-1} \qquad MCID = X \times SD_{\text{baseline}} \times \sqrt{1-r}$$

SEM is assumed to be fairly sample-independent [22], which is its best advantage: a growing standard deviation is balanced by a higher reliability. Some authors like Wyrwich et al. consider one SEM as an approximation of the MCID [23,24]. X can be assigned to 1(small effect), 1.96 (medium effect), 2.77(large effect).

Reliable Change Index (RCI) is the change value of the questionnaire score divided by the square root of SEM. If RCI is greater than 1.96, then the change value has a 95% chance of being a meaningful change [25]. The calculation formula and the corresponding MCID are as follows:

$$RCI = \frac{\bar{x}_1 - \bar{x}_0}{\sqrt{2(SEM)^2}} \qquad MCID = X \times SD_{baseline} \times \sqrt{2(1-\mathrm{r})}$$

Results

The demographic characteristics of the sample

Table 1 showed the general demographic characteristics of the sample. A total of 232 patients with esophageal cancer were investigated in this study. There were 204 males and 28 females. The age distribution was 35-82 years old, with the mean of 59.3(SD8.9). Male elderly patients are more common. The occupations were mostly workers and farmers, with 20 workers (20.0%) and 35 farmers (35.0%) respectively. The educational level varies, among which Middle school or High school has the highest proportion(55.6%).

Table 1
Socio-demographic and clinical characteristics of the Sample (n=232)

Characteristics	N	%	Characteristics	N	%
Gender			**Marital status**		
Male	204	87.9	Married	226	97.4
Female	28	12.1	Others	6	2.6
Age			**Ethnicity**		
30-39	3	1.3	Han	203	87.5
40-49	32	13.8	Others	29	12.5
50-59	67	28.9	**Education**		
≥60	130	56.0	Primary school	81	34.9
Average*	59.3 (8.9)		Middle school or High school	129	55.6
			College/University	22	9.5
Perceived Income			**Medical insurance**		
Poor	52	22.4	Self-paid/Private insurance	4	1.7
Fair	139	59.9	Medical insurance	228	98.3
High	41	17.7			
Occupation			**Treatments**		
Worker	62	26.7	Surgery	134	57.8
Farmer	74	31.9	chemotherapy	51	22.0
Others	96	41.4	Others	31	13.4
* Data was expressed as mean (standard deviation)					

The MCID values using Anchor-based methods

Table 2 showed different MCID values obtained with anchor-based methods. With the Q29 item in the EORTC QLQ-C30 scale as anchor, "how would you evaluate your overall health in the past week", the correlation coefficient between Q29 and the score of QLICP-ES (V2.0), was calculated r=0.75. The correlation coefficients between Q29 and other domains (physical domain, psychological domain, social domain, common symptom and side-effects domain and the specific domain) were 0.69, 0.17, 0.32, 0.57 and 0.68 respectively. Then according to standard A, 102 patients with exactly one grade difference in Q29 before and after treatments were selected, and the difference of scores in all domains and total scale of QLICP-ES (V2.0) before and after treatments was calculated. In the same method, 165 patients with at least one grade

difference in Q29 before and after treatments were selected according to standard B, and the difference of scores in all domains and total scale of QLICP-ES (V2.0) before and after treatments was calculated. The mean standard deviations of the difference scores in each domain and the total scale under the two standards were calculated, and the mean values of the difference scores were recorded as MCID.

Table 2
The MCID value of QLICP-ES (V2.0) determined by anchor-based method (n_A=102, n_B=165)

Domain	Items	Standard A	Standard B	Standard A MCID	Standard B MCID
Physical domain (PHD)	8	15.1±14.8	19.3±16.1	15.1	19.3
Psychological domain (PSD)	9	-4.4±11.8	-4.2±12.4	4.4	4.2
Social domain (SOD)	8	3.1±10.2	4.8±11.2	3.1	4.8
Common symptoms and side effect domain (SSD)	7	6.7±10.7	7.7±11.3	6.7	7.7
Core/general module (CGM)	32	4.8±6.5	6.5±7.3	4.8	6.5
Specific domain (SPD)	16	8.5±8.3	9.5±9.2	8.5	9.5
Total (TOT)	48	6.0±6.0	7.5±6.8	6.0	7.5

The MCID values using Distribution-based methods

The distribution method estimates MCID values based on the observed distribution of score changes, and the distribution variation can be measured using several statistical effects. Three variation indexes, Effect-Size (ES), Standard Error of the Measurement (SEM) and Reliable Change Index (RCI), were used to calculate the MCID values of esophageal cancer in this study.

Table 3 showed the MCID values calculated using ES method under different effects (X of 0.2, 0.5 and 0.8 were used to define small, medium and large effects) in detail.

Table 3
The MCID value of QLICP-ES (V2.0) was determined by ES（n=232）

Domain	$SD_{baseline}$	0.2ES	0.5ES	0.8ES
Physical domain (PHD)	15.9	3.2	8.0	12.7
Psychological domain (PSD)	13.7	2.7	6.8	10.9
Social domain (SOD)	11.8	2.4	5.9	9.5
Common symptoms and side effect domain (SSD)	14.3	2.9	7.1	11.4
Core/general module (CGM)	9.2	1.8	4.6	7.4
Specific domain (SPD)	14.3	2.9	7.1	11.4
Total (TOT)	9.7	2.0	4.9	7.8

Some scholars believe that the Standard Error of the Measurement (SEM) is not completely dependent on the sample information and maintains a certain stability between different studies, which is better than the Effect-Size (ES). Wyrwich[24] et al. considered that 1SEM could be regarded as the minimum change value of clinical significance, and some scholars conservatively used 1.96SEM as the minimum change value of clinical significance [26,27]. Table 4 and Table 5 showed the MCID values calculated using SEM and RCI methods in detail.

Table 4
The MCID value of QLICP-ES (V2.0) determined by SEM (n=232)

Domain	r	$SD_{baseline}$	SEM	1.96SEM
Physical domain (PHD)	0.98	15.9	2.1	4.2
Psychological domain (PSD)	0.96	13.7	2.9	5.7
Social domain (SOD)	0.92	11.8	3.4	6.7
Common symptoms and side effect domain (SSD)	0.99	14.3	1.6	3.1
Core/general module (CGM)	0.99	9.2	1.1	2.2
Specific domain (SPD)	0.96	14.3	2.8	5.5
Total (TOT)	0.99	9.7	1.1	2.2

Table 5
The MCID value of QLICP-ES (V2.0) determined by RCI (n=232)

Domain	r	$SD_{baseline}$	RCI	1.96RCI	2.77RCI
Physical domain (PHD)	0.98	15.9	3.0	5.9	8.4
Psychological domain (PSD)	0.96	13.7	4.1	8.0	11.4
Social domain (SOD)	0.92	11.8	4.8	9.4	13.3
Common symptoms and side effect domain (SSD)	0.99	14.3	2.2	4.3	6.1
Core/general module (CGM)	0.99	9.2	1.6	3.1	4.4
Specific domain (SPD)	0.96	14.3	3.9	7.7	10.9
Total (TOT)	0.99	9.7	1.6	3.1	4.4

Discussion

The main function of MCID is to assist researchers and clinical staff to explain the significance of changes or differences in the score of evaluation tools. MCID values can be used to determine whether changes in the score of the scale brought by clinical interventions have "clinical significance"[28]. For clinicians and researchers, the key for using measurement instruments is the effectiveness and stability of the MCID score. Lower MCID values may lead to overestimation of the positive effects of treatment, while higher MCID values may incorrectly classify patients as ineffective when the treatment is actually beneficial. There are various methods to calculate MCID for esophageal cancer. Using the anchor-based method, according to standard A, the MCID values of physical domain, psychological domain, social domain, common symptom and side-effects domain, the specific domain and the overall were 15.1, 4.4, 3.1, 6.7, 8.5 and 6.0 respectively. According to standard B, the MCID values of above domains and the overall were 19.3, 4.2, 4.8, 7.7, 9.5 and 7.5 respectively in this study.

The correlation coefficient r between the selected anchor Q29 and the score of the total scale was 0.72, but the correlation coefficient between the anchor Q29 and some domains, such as psychological domain and social domain, was 0.17 and 0.32, which were not too high. Therefore, the distribution-based methods were further adopted and the MCID values under ES, SEM and RCI were calculated respectively. Studies have shown that when calculating MCID values by ES method, 0.5 medium effect was the most appropriate, while 0.2 and 0.8 were easy to be too large or too small in calculation [29]. And the results are closer to the MCID values calculated by the anchor-based method. SEM is not completely dependent on the sample information and is slightly affected by the sample size. Therefore, scholars recommend 1SEM or 1.96 SEM as MCID values.

Anchor-based methods and distribution-based method have their own advantages and disadvantages, so this study used a variety of methods to calculate the MCID values. The advantage of the anchor-based methods is that the change in the outcome measure score is associated with a meaningful external anchor

that reflects the patient's point of view and provides a professional explanation for the minimum change in clinical significance determined. However, the disadvantage is that the measurement error is not taken into account, different criteria will produce different changes in the minimum clinical significance, and it is often difficult to find a suitable anchor. Moreover, in this paper, the sample size is not too large and only subjective anchors are used, subsequent studies will expand the sample size and use objective anchors for further studies. The distribution-based methods take measurement error into account to determine the MCID values, which is relatively easy to implement, but the results obtained from different samples may be different, so the professional explanation cannot be given for the determined minimum measurable change value, and there is a lack of recognized judgment criteria for the obtained minimum measurable change values. In developing MCID, the anchor-based method is generally preferred. When there are no good criteria or a small sample size, the distribution-based methods will be considered comprehensively.

MCID is not a fixed value, and different determination methods can produce different MCID values. Not all methods produce similar MCID values, and not all MCID values are generic. The interpretation and application of MCID values should be carefully considered in combination with the actual clinical situation. In this paper, a lot of different MCID values were presented so that it can be easy and convenient to select by users.

Although MCID as a minimum threshold plays an important role in determining the scale score changes, its stability and variability may be affected by many factors, such as defects in the measurement method, demographic characteristics, patient comprehension and study cycles and so on [30].

Conclusion

In conclusion, appropriate methods should be adopted to evaluate the MCID of each scale. When MCID is applied to evaluate the clinical efficacy of esophageal cancer, it is necessary to carefully review and fully understand the concepts and influencing factors of each method, so as to evaluate the efficacy of esophageal cancer patients with scales more objectively. In this paper, a lot of different MCID values were presented so that it can be easy and convenient to select by users.

Abbreviations

MCID: Minimal clinically important difference; QOL: Quality of life; PRO: Patient-reported outcomes; QLICPs: Quality of Life Instruments for Cancer Patients; ES: Esophageal cancer; QLICP-ES(V2.0): Quality of Life Instruments for Cancer Patients-Esophageal cancer(the second version); QLICP-GM(V2.0): Quality of Life Instruments for Cancer Patients-General Module(the second version); EORTC: European Organization for Research and Treatment of Cancer; QLQ-OES23: Quality of Life Questionnaire - Oesophageal 18; QLQ-C30: Quality of Life Questionnaire - Core 30; FACT-E: Functional Assessment of Cancer Therapy- Esophageal cancer questionnaire; ES: Effect-Size; SEM: Standard Error of the Measurement; RCI: Reliable Change Index; RS: Raw Score; SD: Standard-deviation; SDbaseline: Standard-deviation of the baseline score.

Declarations

Acknowledgements

In carrying out this research project, we have received substantial assistance from Prof. Gary Lyman from Hutchinson Institute for Cancer Outcomes Research, and Prof. David Cella, Benjamin J. Arnold and Hiramatsu Toshiko at the Center on Outcomes, Research, and Education (CORE), and many stalfs at the third affiliated hospital of Kunming Medical University (Yunnan Tumor Hospital), and Sun Yat-sen University Cancer Center. We sincerely acknowledge all the support.

Funding

This study is supported by the National Natural Science Foundation of China (71974040, 81273185), the Features Innovative Projects of Key Platform and Major Scientific Research Project of Universities in Guangdong Province (2016KTSCX046, 2017KZDXM040). The funding bodies provided funds to support project development. The grant recipient (Chonghua Wan) designed the study, performed the data collection and data analyses, and extensively revised the manuscript.

Availability of data and materials

Not applicable.

Authors' contributions

CHW, GFL designed the study. TW, DDR, YBQ, JDZ and JYF performed the data collection. TW, DDR performed data analyses and drafted the manuscript. CHW revised the manuscript deeply. All authors contributed to interpreting the data, and have read and approved the final manuscript.

Ethics approval and consent to participate

The study protocol and the informed consent form were approved by the IRB (institutional review board) of the affiliated hospital of Guangdong Medical University (PJ2012052, YJYS2019010). The respondents were voluntary and provided written consent for participation.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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