

The Formulation of Minimal Clinically Important Differences in the Quality of Life Instrument for Patients with Chronic Renal Failure (QLICD-CRF) Based on Combinations of Anchor-Based and Distribution-Based Methods

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1 **The formulation of minimal clinically important differences in the Quality**
2 **of Life Instrument for Patients with Chronic Renal Failure (QLICD-CRF)**
3 **based on combinations of anchor-based and distribution-based methods**

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24 **Abstract:**

25 **Background** Chronic renal failure is global problem and represents a major cause of morbidity and mortality. Studies of
26 quality of life in patients with chronic renal failure can be helpful to improve patient survival rates. The minimal clinical
27 important difference (MCID) is a score that reflects the effect of patient treatment or nursing care. Doctors or researchers use
28 this factor to assess the validity of results, and this information reflects the combined importance of the patient's opinion and
29 the doctor's explanation.

30 **Methods** Patients diagnosed with chronic renal failure and able to read and understand the questionnaires at the First
31 Affiliated Hospital of Kunming Medical University were included in this study and completed the questionnaires
32 independently. Using the anchor-based method and the distribution-based method, the MCIDs of the QLICD-CRF were
33 calculated based on the data from 164 valid questionnaires at the time of admission and 111 valid questionnaires at discharge.
34 The medians of patients' quality of life scores calculated using the anchor-based method were referred to as MCIDs based on
35 the anchor-based method, whereas the results calculated based on effect size (ES), standard error of measurement (SEM) and
36 reliable change index (RCI) were referred to as MCIDs based on the distribution-based method. Then, the final results were
37 calculated according to the weight of the calculation obtained using several methods.

38 **Results** MCIDs of the physical domain (PHD), psychological domain (PSD), social domain (SOD), core/general domain
39 (CGD), specific domain (SPD) and the total score (TOT) of the QLICD-CRF were 10, 9, 8, 7, 8 and 7, respectively.

40 **Conclusion** Calculations of MCIDs of QLICD-CRF scores could compensate for insufficient *P*-values; thus, the
41 interpretation of the outcomes in quality of life studies could be more objective and specific.

42 **Keywords:** Chronic renal failure; Quality of life; Minimal clinically important difference (MCID)

43

44 **Background**

45 Chronic renal failure is global problem and represents major cause of morbidity and mortality. Mortality

46 caused by chronic renal failure increased significantly from the 27th position in 1990 to 18th position in
47 2010^[1]. Currently, more than 2 million people worldwide receive treatment in form of dialysis or a kidney
48 transplant to stay alive, representing only 10% of people who actually need treatment to live^[2]. Study of
49 the quality of life of patients with chronic renal failure can be helpful to improve survival rates. Thus,
50 numerous scales were developed, such as the Kidney Disease Quality of Life instrument (KDQOL), the
51 Kidney Transplant Questionnaire, and the choice health experience questionnaire. However, these scales do
52 not completely reflect the background of Chinese culture.

53 To adapt these scales to Chinese culture, we developed the quality of life measurement scale (QLICD-CRF
54 V2.0) for patients with chronic renal failure through repeated expert discussions and combinations of
55 various statistical methods^[3-7]. The QLICD-CRF V2.0 consists of two parts: the generic module^[3-4] and the
56 specific module^[5]. The generic module includes physical, psychological, and social domains mainly aimed
57 at the general effects of chronic diseases, and the specific module was developed to assess the specific
58 effects of chronic renal failure. Assessment of reliability and validity of the scale were reported in another
59 article^[6-7].

60 Quality of life scores are used to evaluate subjective feelings of patients. What is the guiding significance
61 of these scores in the clinic? We should determine the effective threshold of the fraction change and other
62 traditional factors, such as reliability, validity, and reaction. Statistically, the *P*-value will be less than the
63 test level if sample size is sufficiently large. However, to what extent do changes in quality of life score
64 changes indicate clinical significance? This value can be measured using the minimal important difference
65 (MID), minimal clinically important difference (MCID), minimal clinically important changes (MCIC),
66 clinically meaningful changes (CMC), or clinically significant changes (CSC). In this article, we refer to
67 this parameter as minimal clinically important difference (MCID), which is a score change that reflects the

68 effect of the patient's treatment or nursing support^[8]. Doctors and researchers use this information to judge
69 the validity of their results, and this information importantly combines the patient's opinion with the
70 doctor's explanation.

71 Current research on MCID is mainly reported from studies abroad^[9-18]. Studies on MCID in China are
72 limited^[19-20], and most of these studies involve traditional Chinese medicine. Various methods, such as the
73 anchor-based approach, distributed-based approach, expert opinion and literature analysis, are used to
74 calculate the MCID, but there is no "gold standard". Each method has disadvantages. Most current studies
75 typically use one of these methods. The purpose of our study was to determine MCID of QLICD-CRF
76 using a combination of methods. In our study, MCID was determined according to the results of
77 QLICD-CRF scores of patients with chronic renal failure.

78 **1 Methods**

79 **1.1 Participants**

80 The subjects were patients with chronic renal failure who can read and write. These patients were treated at
81 the First Affiliated Hospital of Kunming Medical University. We relied on clinicians to recruit participants
82 who participated in the study after providing informed consent. The Institutional Review Board of the
83 investigators' institutions approved the study protocol and informed consent form.

84 Inclusion criteria: (1) clinically diagnosed with chronic renal failure, (2) at least primary and secondary
85 school-level education, (3) volunteer to participate in the evaluation, and (4) able to read and write.

86 Exclusion criteria: (1) illiterate, (2) patients who were mentally inarticulate or unable to express his inner
87 feelings clearly, and (3) critically ill patients.

88 **1.2 Investigation instruments**

89 We used the QLICD-CRF and SF-36 to investigate patients with chronic renal failure^[7]. The anchor was
90 selected from items from SF-36.

91 Our QOL team developed the QLICD-CRF. A module approach was used for the development of the
92 chronic renal failure scale of the system of quality of life instruments for chronic diseases (QLICD-CRF
93 V2.0), including the general module (QLICD-GM) for all types of chronic diseases and a disease-specific
94 module for patients with chronic renal failure. The final 28-item scale (QLICD-GM V2.0) can be classified
95 into 3 domains and 9 facets. The physical domain (PHD) includes 9 items coded from GPH1 to GPH9,
96 which are divided into 3 facets of Basic Physiological Functions (BPF), Energy and Discomfort (EAD),
97 and Independence (IND). The psychological domain (PSD) contains 11 items coded from GPS1 to GPS11,
98 which are divided into 3 facets of Cognition (COG), Will and Personality (WIP), and Emotion (EMO). The
99 social domain (SOD) comprises 8 items coded from GSO1 to GSO8, which are divided into 3 facets of
100 Interpersonal Communication (INC), Social Support and Security (SSS), and Social Role (SOR). The
101 disease-specific module for patients with chronic renal failure includes 10 items, which are divided into 3
102 facets: Respiratory and Circulation System Symptom (RCS), Musculoskeletal and Derma Symptom (MDS),
103 Abnormal Stool and Urination (ASU).

104 The Chinese version of SF-36^[21], which comprises eight domains, including Physical Function (PF),
105 Role-Physical (RP), Bodily Pain (BP), General Health (GH), Vitality (VT), Social Function (SF),
106 Role-Emotional (RE) and Mental Health (MH), was also used to obtain data to assess the criterion-related
107 validity of the QLICD-CRF as well as convergent and discriminant validity.

108

109 **1.3 Methods**

110 The participating investigators (medical postgraduates) explained the purpose and the scales to qualified

111 patients and obtained informed consent from patients who agreed to participate in the study. The patients
112 were required to complete the scales (the QLICD-CRF and SF-36) independently on the day of hospital
113 admission and once again at the day of discharge.

114 We calculated some indexes using the anchor-based method and the distribution based-method. Then, the
115 final MCID values were calculated according to the weights of the calculation of several methods.

116 **The anchor-based method:** The anchor was one of the items in SF-36 (item 10d) expressed as “My health
117 is excellent”. Possible answers include the following: 1, Definitely True; 2, Mostly True; 3, Do not Know;
118 4, Mostly False; 5, Definitely False. The data were compared before and after treatment using the following
119 steps:

120 (1) Patients completed the two questionnaires twice at the time of admission and discharge.

121 (2) Patients who report a difference of one level in responses are removed from analysis. For example,
122 patient A selects the option “Definitely True” first. After treatment, he/she chose “Mostly True”. Thus,
123 patient A was included in the analyses using the anchor-based method. Similarly, patient B chose the option
124 “Definitely False” on the first questionnaire. After treatment, he/she selected “Mostly False”. Thus, patient
125 B was also included in the analyses using the anchor-based method. Thus, when the absolute value of the
126 difference in the option number selected before and after treatments was "1", the patient’s response was
127 included.

128 (3) The absolute value of the difference of quality of life was employed to calculate the score of each
129 patient who was selected. If the absolute value of the difference exhibited a normal distribution, the mean
130 value was used as MCID. If a skewed distribution was observed, the median was reported as the MCID. In
131 our study, responses from 39 patients were analysed using the anchor-based method. The absolute values of
132 the differences exhibited a skewed distribution, so the median was reported.

133 **The distribution based-method:** The distribution based-method requires the collection of data both before
 134 and after treatment. There are three indexes, including effect size (ES), standard error of measurement
 135 (SEM) and reliable change index (RCI), which employ the following questions $MCID=ES \times SD_{before}$,
 136 $MCID=1 \times SEM^{[22]}$, and $MCID=1 \times RCI$, respectively. Computational formulas are provided in Table 1.

137 Table 1 Computational formulas of indexes for MCID

Index	Formula	Explanation
ES	$ES = \frac{\text{mean}_{before} - \text{mean}_{after}}{SD_{before}}$	ES: effect size; mean_{before} : standardized mean before treatment; mean_{after} : standardized mean after treatment; SD_{before} : standard deviation before treatment
SEM	$SEM = \sigma_x \sqrt{1 - r_{tt}}$	SEM: standard error of measurement; σ_x : standard deviation of the quality of life measurement; r_{tt} : reliability of scale
RCI	$RCI = \frac{\text{mean}_{before} - \text{mean}_{after}}{\sqrt{2} SEM}$	RCI: reliable change index

138 **Weighting method:** The MCID is comprehensively considered on the basis of the weight of results of
 139 different methods. By comparing every result from different methods with the “Mean of the four results”, a
 140 weight was given based on the deviation from the mean. We gave a higher weight value to the results of
 141 MCID (M) and ES because these methods had higher degrees of acceptance.

142 2 Results

143 2.1 Characteristics of the patient sample

144 In total, 164 patients were investigated in our study. All of the patients completed the two scales on
 145 admission, but only 111 completed the two scales at the time of discharge. The socio-demographic
 146 characteristics of the sample are presented in Table 2. The average patient age was (45.57 ± 14.94) years.
 147 There were more males than females. Most of the patients were of Han nationality, and most of had
 148 graduated from high school or technical secondary school or even less. The proportion of farmers in the
 149 vocational structure was relatively large. Regarding medical insurance, urban and rural workers comprised
 150 the largest demographic with medical insurance.

151 Table 2 The characteristics of 164 patients with chronic renal failure

Item	Group	Number	Percent (%)	Item	Group	Number	Percent (%)
Gender	Male	97	59.10	Nationality	Han	128	78.00
	Female	67	40.90		Others	36	22.00
Occupation	Worker	29	17.70	Education	Primary school	48	29.30
	Farmer	62	37.80		Junior middle school	41	25.00
	Teacher	17	10.40		High school or technical secondary school	36	22.00
	Cadre	18	11.00		Junior College	17	10.40
	Self-employed person	5	3.00		Bachelor's degree or greater	22	13.40
	Other	33	20.10				
Marital status	Unmarried	23	14.00	Medical Insurance	Self-paid	21	12.80
	Marriage	138	84.10		Social or urban health	79	48.20

		e		care	
	Divorce	2	1.20	Commercial insurance	1 0.60
	Widowed	1	0.60	Rural cooperative	57 34.80
medical service					
Family economy	Poor	84	51.20		
	Moderate	75	45.70		
	Prosperous	5	3.00		

152

153 **2.2 Calculation of MCID based on the anchor method**

154 In our study, the anchor was the item in SF-36 (10d) that was described as “My health is excellent”. In total,
 155 39 patients were included in analyses using the anchor method, and the results are provided in Table 3 in
 156 detail.

157 Table 3 Calculation of MCID based on the anchor method

Domains	Numbers	MCID (M)
Physical domain (PHD)	38	12.50
Psychological domain (PSD)	38	9.09
Social domain (SOD)	38	9.38
Core/General domain (CGD)	37	6.90
Specific domain (SPD)	37	4.00
Total (TOT)	35	6.85

158 **2.3 Calculation of MCID based on the distribution method**

159 The distribution based-method used ES, SEM, and RCI to calculate MCID. The results are presented in Tables 3

160 and 4 in detail.

161 Table 3 Calculation of MCID based on SEM and RCI

Domains	Number	σ_x	r_{tt}	SEM	RCI
Physical domain (PHD)	111	17.68	0.70	9.68	13.69
Psychological domain (PSD)	111	19.99	0.75	10.00	14.14
Social domain (SOD)	111	16.42	0.70	8.99	12.71
Core/General domain (CGD)	111	15.81	0.76	7.75	10.96
Specific domain (SPD)	111	18.27	0.67	10.50	14.85
Total (TOT)	111	15.77	0.77	7.56	10.69

162

163 Table 4 Calculation of MCID based on ES

Domain	SD_{before}	ES (0.2)	ES (0.5)	ES (0.8)
Physical domain (PHD)	17.37	3.47	8.69	13.90
Psychological domain (PSD)	20.32	4.06	10.16	16.26
Social domain (SOD)	16.56	3.31	8.28	13.25
Core/General domain (CGD)	15.87	3.17	7.94	12.70
Specific domain (SPD)	19.32	3.86	9.66	15.46
Total (TOT)	16.19	3.24	8.10	12.95

164

165 2.4 MCID comparisons of four methods

166 Table 5 MCID comparisons of four methods

Domains	MCID (M)	SEM	ES (0.5)	RCI	Mean of the four methods
Physical domain (PHD)	12.50	9.68	8.69	13.69	11.14
Psychological domain (PSD)	9.09	10.00	10.16	14.14	10.85
Social domain (SOD)	9.38	8.99	8.28	12.71	9.84
Core/General domain (CGD)	6.90	7.75	7.94	10.96	8.39
Specific domain (SPD)	4.00	10.50	9.66	14.85	9.75
Total (TOT)	6.85	7.56	8.10	10.69	8.30

167

168 2.5 Weight method

169 Every result obtained from different methods was compared with the “Mean of the four
170 methods”, and a weight was given based on the deviation from the mean. We gave a higher
171 weight value to the results of MCID (M) and ES because these methods have higher degree of
172 acceptance.

173

174 Table 6 Weights of the four methods and MCID calculated using the weight method

Domains	MCID (M)	SEM	ES (0.5)	RCI	MCID (Weighted)	Take an integer
Physical domain (PHD)	0.40	0.35	0.15	0.10	10.15	10
Psychological domain (PSD)	0.15	0.35	0.45	0.05	9.36	9
Social domain (SOD)	0.45	0.40	0.10	0.05	8.38	8
Core/General domain (CGD)	0.10	0.40	0.45	0.05	7.24	7

Specific domain (SPD)	0.05	0.45	0.50	0	8.27	8
Total (TOT)	0.15	0.35	0.45	0.05	7.22	7

175

176 According to Table 6, the mean of these domains was the weight of the corresponding method

177 result. Thus, the weight of MCID (M), SEM, ES, and RCI were 21.67%, 38.33%, 35%, and

178 5%, respectively.

179 The results of the different methods in Table 5 were multiplied by the respective weights, so

180 we obtained the MCID of every domain. For example, the MCID of PHD is calculated as

181 follows: $12.50 \times 21.67\% + 9.68 \times 38.33\% + 8.69 \times 35\% + 13.69 \times 5\% = 10.15$.

182

183 3 Discussion

184 The minimal clinically important difference score (MCID) was developed^{23]} in 1989 in an attempt to deal

185 with the problem that analysis of a PROM instrument measuring change after intervention in some cases

186 may show statistical significance without any clinical relevance. Doctors and researchers use this

187 information to judge the validity of their results, and this information importantly includes the patient's

188 opinion and the doctor's explanation. The quality of life measurement scale (QLICD-CRF V2.0) for

189 patients with chronic renal failure exhibits good reliability and validity^[3-7]. This scale is ideally suited for

190 Chinese patients. In our study, no large differences were noted among the four results from the

191 anchor-based method and the distribution based-method. MCID (M) values obtained using the

192 anchor-based method were greater than values obtained from other methods. This result is potentially

193 attributed to the fact that the sample size was small, but it does not indicate that the results make no sense.

194 In Stephen's^[24] study, they studied MICD of different diseases, including 37 patients with lower extremity

195 ulcers, 27 with limb reconstruction, 25 with irritable bowel syndrome, and 25 with COPD. Two
196 disadvantages of the anchor-based method are noted. First, it was difficult to choose a representative anchor;
197 second, the sample size required to calculate MCID was much smaller than the sample size investigated in
198 this study. Researchers must include more participants to ensure that the sample is sufficient and
199 representative. Thus, the research costs were increased.

200 Effect size (ES) can be used to calculate MCID. ES calculations are simple, and nonprofessional
201 individuals can easily understand the method. Cohen ^[20] argued that an effect size (ES) between 0.2-0.49%
202 was small, 0.5-0.79% was medium, and greater than or equal to 0.8 was large. In our study, an effect size of
203 up to 0.5 is accepted by most people. An effect size of 0.2 indicates the smallest score change and this
204 finding was not very clinical significant. To allow the results to be recognized by many scholars and
205 clinicians and make the results more consistent with clinical practice, we chose the score changes of
206 ES=0.5 as significant MCID of domains and total scores in QLICD-CRF.

207 SEM and RCI do not depend on the sample size because the two indexes estimate the MCID through the
208 baseline standard deviation and reliability coefficient. The MCID obtained based on ES is more accepted,
209 and the calculation is also more convenient.

210 This study comprehensively evaluated the state of patients by combining patients' subjective feelings and
211 clinical indicators. This information could be useful to improve patient satisfaction and the doctor-patient
212 relationship. The current study primarily used a single anchor-based method to calculate the MCID of
213 different scales; then, an ROC curve was used to identify the most effective scale ^[25-29]. A few studies have
214 used multiple methods to calculate MCID. For example, Shulman MA used three distribution-based
215 methods (0.3 multiplied by SD, standard error of the measurement, and 5% range) and two anchor-based
216 methods (anchored to two patient-rated health status questions and separately to unplanned hospital

217 readmission) to estimate the MCID for the World Health Organization Disability Assessment Schedule 2.0
218 score converted to a percentage scale^[30]. Toussaint A used effect sizes (ES) and standardized response
219 means (SRM) of pre- and post-GAD-7 mean changes to calculate MCID for the Hamilton Rating Scale for
220 Depression (HRSD-24)^[31]. In this study, multiple methods were used to calculate the comprehensive MCID
221 according to the weights, and the advantages and disadvantages of various methods were considered.
222 Our study has also several limitations. First, the sample size was smaller compared with some other studies,
223 especially for the anchor-based method. Second, the subjects in this study were selected from the inpatient
224 population at hospitals. Additional studies are needed to assess the practicability of MCID evaluation in
225 other settings and populations, such as outpatients at a local clinic.

226 **4 Conclusions**

227 Every method has its limitations and advantages. The results of various methods are considered in the
228 weight method, so we recommend weight method to increase the acceptance of results. Finally, the
229 following MCIDs of QLICD-CRF are obtained: PHD 10, PSD 9, SOD 8, CGD 7, SPD 8, and TOT 7.

230

231 **Additional files**

232 **Abbreviations**

233 minimal clinically important differences (MCID)

234 the scale for Chronic Renal Failure under the system of the Quality of Life Instrument for Patients with
235 Chronic Diseases (QLICD-CRF).

236 Kidney Disease Quality of Life instrument (KDQOL)

237 The General Module for chronic diseases (QLICD-GM)

238 Physical domain (PHD)

- 239 Basic Physiological Functions (BPF)
- 240 Energy and Discomfort (EAD)
- 241 Independence (IND)
- 242 Psychological domain (PSD)
- 243 Will and Personality (WIP)
- 244 Emotion (EMO)
- 245 Social domain (SOD)
- 246 Interpersonal Communication (INC)
- 247 Social Support and Security (SSS)
- 248 Social Role (SOR)
- 249 Respiratory and circulation system symptom (RCS)
- 250 Musculoskeletal and Derma symptom (MDS)
- 251 Abnormal stool and urination (ASU)

252 **Declarations**

253 **-Ethics approval and consent to participate:**Our study was submitted to and approved by The ethics
254 committee of Kunming Medical College (currently known as Kunming Medical University) institutional
255 ethics committee and approved the study.the consent we obtained from study participants was written.

256 **- Consent for publication:** Not applicable.

257 **- Availability of data and materials:**If anyone would like to access data related to the study, please
258 contact corresponding author Chonghua Wan, email: wanchh@hotmail.com.

259 **- Competing interests:** The authors declare that they have no competing interests.

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263 recipient (Chonghua Wan) designed the study, performed the data collection and data analyses, and
264 extensively revised the manuscript.

265 - **Authors' Contributions:**XPH, ZY, and CHW designed the study. XPH, MW, XJF and CHW performed
266 the data collection. XPH, ZY, QAX and CHW performed data analyses. XPH drafted the manuscript. ZY
267 and CHW extensively revised the manuscript. All authors contributed to data interpretation. All authors
268 have read and approved the final manuscript.

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