Health-Related Utility of EQ-5D in Korean Adults With Chronic Urticaria: Mapping From Urticaria Outcome Measures

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ABSTRACT

Purpose: A need for useful measures reflective of the socio-economic burden of chronic urticaria (CU) has arisen. To obtain utility estimates for CU, we investigated EuroQol-5-Dimension (EQ-5D) indices according to urticaria control status and urticaria severity.

Methods: In this prospective observational study, we administered patient-oriented questionnaires on EQ-5D and urticaria outcomes, including Urticaria Activity Score over 7 days (UAS7), Urticaria Control Test (UCT), and CU-specific quality of life (CU-QOL). EQ-5D utility index scores were compared according to urticaria control status and disease severity. Conditional process analysis (CPA) was used to map EQ-5D utility scores from UAS7 and UCT.

Results: Greater EQ-5D utility values were obtained in patients with better urticaria control (0.91 ± 0.10 for well controlled CU, 0.84 ± 0.12 for partly controlled, 0.77 ± 0.14 for uncontrolled, \( P < 0.001 \)). According to CU severity, mean utility values were ranged from 0.746 (severe, UAS7 ≥ 28) to 0.860 (moderate), 0.878 (mild), and 0.953 (urticaria free). CPA suggested that UAS7 was directly correlated with UCT (regression coefficient, −0.251; 95% confidence interval [CI], −0.278, −0.223; \( P < 0.001 \)) and EQ-5D utility (−0.002; 95% CI, −0.003, −0.001; \( P = 0.007 \)) after controlling for age, sex, urticaria duration, and combined allergic diseases.

Conclusions: EQ-5D values increased with improvement in urticaria control and decreased with urticaria severity. A predictive model mapping EQ-5D utility from UAS7 and UCT scores suggested that EQ-5D can be useful for the pharmacoeconomic evaluation of individualized treatments for CU patients.

Keywords: Chronic urticaria; control; severity; symptoms; quality of life; EQ-5D; utility index

INTRODUCTION

Urticaria is characterized by sudden onset of itchy wheals and/or angioedema.1 Acute urticaria temporarily causes wheals for no longer than 6 weeks and appears upon exposure to food, drugs, infection, etc., remitting when the cause is eliminated.2 However, in about 50% of patients with chronic urticaria (CU), characterized by wheals for more than 6 weeks, the underlying cause is not identified, and its pathogenesis is not clearly established.1
substantially impairs the health-related quality of life (HR-QoL) of CU patients. Due to unpredictable exacerbation and difficulties in treatment, CU can negatively impact work and classroom productivity. Moreover, previous research has found that the prevalences of anxiety and depression are higher in CU patients. In economic models for evaluating cost-effectiveness and reimbursement decisions, utility measures are key parameters. The EuroQol 5-dimensional (EQ-5D) Questionnaire is a well-known preference-based instrument for assessing health in various diseases. The 5-level version of EQ-5D (EQ-5D-5L) consists of 5 questions on mobility, self-care, daily activity, pain/discomfort, and anxiety/depression, and is reported as 1 of 5 levels for each question. A EQ-5D-5L has recently been validated in the Korean population. However, no health state utilities for CU have been evaluated in Korea.

Thus, to investigate the impact of CU on health, the EQ-5D-5L was assessed and analyzed according to control status and severity of urticaria in Korean adults.

**MATERIALS AND METHODS**

**Study subjects**

This study was conducted as a prospective observational study through which to assess EQ-5D results and urticaria outcomes using patient-oriented questionnaires. In total, 416 observations were obtained from 163 CU patients (100 females and 63 males) enrolled to undergo EQ-5D assessment between January and June of 2018. In addition to demographic information on the patients, combined allergic diseases, urticaria severity, and control status were evaluated at each visit over the study period. All of the subjects provided written informed consent, and the study protocol was approved by the Institutional Review Board (IRB-MED-OBS-17-373).

**Measures**

EQ-5D-5L (0–1) and patient-oriented outcome measures of CU, including Urticaria Activity Score over 7 days (UAS7, 0–42), Urticaria Control Test (UCT, 0–16), and CU-specific quality of life (CU-QOL, 0–100), were assessed at each visit. The EQ-5D is a general measure of health outcomes utilized to depict the impact of different health states on quality of life. For the present study, EQ-5D index scores were generated using Korean population-based weights. The UAS is a validated daily symptom measure consisting of 2 components: itch severity score (0–6 for a day) and wheals score (0–6 for a day). The UAS7 is calculated by adding up UAS scores over 7 days. The CU-QOL consists of 17 items covering 4 domains: urticaria symptoms, emotional distress, food and environmental distress, and stigma. K-UCT is a Korean version of the UCT, which was developed originally in Germany as a tool to assess urticaria control status. For each patient, physicians assessed urticaria control status at each visit according to definitions described in a previous study. In brief, patients who had no wheals or itching during the treatment were classified as well-controlled CU. Patients whose urticaria symptoms had improved from a prior visit but were not completely controlled, were deemed to have partly controlled CU. When wheals or hives did not improve at all with medication, patients were classified as having uncontrolled CU.

**Statistical analyses**

Categorical data were compared using the $\chi^2$ test. Welch’s 2-sample $t$ test was used to compare 2 groups of continuous data, while analysis of variance was used to compare more
than 2 groups. The relationships between EQ-5D utility in CU patients and control status assessed by physicians, as well as UAS7, K-UCT, and CU-QOL, were evaluated by Pearson’s correlation coefficient.

To obtain a mapping algorithm for estimating EQ-5D index scores from the UAS7 and UCT, we applied conditional process analysis (CPA) using Hayes’s PROCESS program (model 4). CPA is a regression-based, path analytic approach using bias-corrected bootstrap confidence intervals (CIs) to test the significance of both direct and indirect effects and the influence of moderating variables on these effects. For the current study, we used moderated parallel mediation analyses to examine if the strength and direction of the direct and indirect effects of UAS7 on EQ-5D utility differed according to UCT scores and other covariates. Statistical analyses were conducted using IBM SPSS, version 25 for Windows (IBM SPSS Inc., Chicago, IL, USA).

RESULTS

Clinical characteristics of the study subjects

In total, 416 cross-sectional observations from 163 patients were analyzed. Female patients totaled 100 (61.3%) individuals. The mean age and disease duration of all 163 patients were 42.30 ± 12.25 and 3.79 ± 4.65 years, respectively. At the initial visit, the proportions of patients who were assessed as having well controlled, partly controlled, or uncontrolled CU were 34.4%, 39.3%, or 26.4%, respectively. Allergic diseases, including asthma, allergic rhinoconjunctivitis, atopic dermatitis (AD), food allergy, and drug allergy, were noted in 93 patients. The mean scores on CU-QOL, UAS7, and K-UCT at initial visits were 81.34 ± 19.90, 15.37 ± 10.00, and 11.70 ± 3.50, respectively (Table 1).

| Variables                               | CU (n = 163)   |
|-----------------------------------------|---------------|
| Female                                  | 100 (61.3%)   |
| Duration (yr)                           | 3.79 ± 4.65   |
| Mean age (yr)                           | 42.30 ± 12.25 |
| Onset age (yr)                          | 38.60 ± 13.00 |
| Mean duration of CU (mon)               | 3.80 ± 4.60   |
| Accompanying diseases                   | 93 (57.1%)    |
| Allergic conjunctivitis                 | 17 (10.4%)    |
| Atopic dermatitis                       | 11 (6.7%)     |
| Food allergy                            | 28 (17.2%)    |
| Drug allergy                            | 25 (15.3%)    |
| Asthma                                  | 2 (1.2%)      |
| Allergic rhinitis                       | 62 (38.0%)    |
| Family history of allergic diseases     | 78 (47.9%)    |
| Control status of CU assessed by physicians |                |
| Well controlled                         | 56 (34.4%)    |
| Partly controlled                       | 64 (39.3%)    |
| Uncontrolled                            | 43 (26.4%)    |
| UAS7 (0-42)                             | 15.37 ± 10.00 |
| UCT (0-16)                              | 11.70 ± 3.50  |
| CU-QOL (0-100)                          | 81.34 ± 19.90 |

Data are shown as mean ± standard deviation or number (%).

CU, chronic urticaria; UAS7, Urticaria Activity Score over 7 days; UCT, Urticaria Control Test; CU-QOL, chronic urticaria-specific quality of life.

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601
EQ-5D scores and disease control

The overall mean scores for EQ-5D and urticaria outcome measures in the study subjects according to disease control are shown in Table 2. Scores for EQ-5D-5L, CU-QOL, UAS7, and UCT were 0.86 ± 0.13, 75.08 ± 24.00, 17.51 ± 10.40, and 10.24 ± 3.90, respectively. The 461 observations were classified into 3 CU control states assessed by physicians: 173 showed well controlled CU, 173 partly controlled CU, and 70 uncontrolled CU. EQ-5D scores showed a marked difference according to the physician’s assessment of urticaria control status (0.91 ± 0.10 for well controlled CU, 0.84 ± 0.12 for partly controlled, 0.77 ± 0.14 for uncontrolled; \( P < 0.001 \), Table 2). Both CU-QOL (87.22 ± 17.11 vs. 70.39 ± 23.71 vs. 56.64 ± 23.98, \( P < 0.001 \)) and UCT (12.68 ± 2.88 vs. 9.46 ± 3.30 vs. 6.14 ± 3.35, \( P < 0.001 \)) values were significantly higher in patients with well controlled CU than in those with partly and uncontrolled CU. In contrast, UAS7 scores were found to be lower with well, partly, and uncontrolled CU, in that order (10.65 ± 9.13 vs. 20.39 ± 7.18 vs. 27.36 ± 8.41, \( P < 0.001 \)).

As a UCT score of ≥ 12 has been reported as a valid criterion for determining controlled CU, we compared EQ-5D utility scores according to UCT scores ≥ 12 or < 12. CU patients with UCT ≥ 12 showed significantly higher EQ-5D values than those with UCT < 12 (0.92 ± 0.10 vs. 0.81 ± 0.10, \( P < 0.001 \), Table 3). Among the 5 subdomains of EQ-5D, the pain/discomfort (59.4%) and anxiety/depression (44.0%) domains were remarkably impaired in CU patients across all urticaria control states. The daily activities domain was also found to be impaired in 119 (28.6%) patients with CU over the study period. Mobility and self-care domains, however, were generally preserved in CU patients. Patients with uncontrolled CU, defined as UCT < 12, were affected significantly in all 5 subdomains, compared to those with controlled CU (UCT ≥ 12). The daily activities, anxiety/depression, and pain/discomfort domains were found to be markedly affected in 41.4%, 59.5%, and 76.7% of patients with uncontrolled CU, respectively.

In comparison of EQ-5D utility according to urticaria severity as reflected in UAS7 scores, patients with greater UAS7 scores had lower EQ-5D utility (Fig. 1). In accordance with a recent report, we classified urticaria severity into 5 groups: 41 patients with UAS7 = 0, 40

| Table 2. Comparison of EQ-5D and urticaria outcome measures according to CU control states |
|-----------------------------------------------|----------|----------|----------------|------------------|----------|
|                                | Total (n = 416) | Well controlled (n = 173) | Partly controlled (n = 173) | Uncontrolled (n = 70) | \( P \) value |
|-----------------------------------------------|----------|----------|----------------|------------------|----------|
| EQ-5D-5L                                | 0.86 ± 0.13 | 0.91 ± 0.10 | 0.84 ± 0.12 | 0.77 ± 0.14 | < 0.001 |
| CU-QOL                                 | 75.08 ± 24.00 | 87.22 ± 17.11 | 70.39 ± 23.71 | 56.64 ± 23.98 | < 0.001 |
| UAS7                                   | 17.51 ± 10.40 | 10.65 ± 9.13 | 20.39 ± 7.18 | 27.36 ± 8.41 | < 0.001 |
| UCT                                     | 10.24 ± 3.90 | 12.68 ± 2.88 | 9.46 ± 3.30 | 6.14 ± 3.35 | < 0.001 |

Data are shown as mean ± standard deviation. CU, chronic urticaria; EQ-5D, EuroQol 5-dimension; EQ-5D-5L, EuroQol 5-dimension 5-level; CU-QOL, chronic urticaria-specific quality of life; UAS7, Urticaria Activity Score over 7 days; UCT, Urticaria Control Test.

| Table 3. Impairment in EQ-5D subdomains according to UCT levels |
|-----------------------------------------------|------------|----------------|------------------|----------|
| Impairment (%) in EQ-5D subdomain                     | Controlled CU (UCT ≥ 12) (n = 184) | Uncontrolled CU (UCT < 12) (n = 232) | \( P \) value |
|-----------------------------------------------|------------|----------------|------------------|----------|
| EQ-5D-5L index score                           | 0.92 ± 0.10 | 0.81 ± 0.10 | < 0.001          |
| Domain 1: mobility                             | 2 (1.1)         | 27 (11.6)          | < 0.001          |
| Domain 2: self-care                            | 0                           | 6 (2.6)             | 0.036           |
| Domain 3: daily activities                     | 23 (12.5)     | 96 (41.4)           | < 0.001          |
| Domain 4: pain/discomfort                      | 69 (37.5)     | 178 (76.7)          | < 0.001          |
| Domain 5: anxiety/depression                   | 45 (24.5)     | 138 (59.5)          | < 0.001          |

Data are shown as mean ± standard deviation or number (%). EQ-5D, EuroQol 5-dimension; EQ-5D-5L, EuroQol 5-dimension 5-level; CU, chronic urticaria; UCT, Urticaria Control Test.
with UAS7 = 1–6, 86 with UAS7 = 7–15, 176 with UAS7 = 16–27, and 73 with UAS7 = 28–42. The highest EQ-5D values were observed in patients with UAS7 = 0, while the lowest values were noted in those with UAS7 = 28–42.

Fig. 2 depicts correlations between EQ-5D utility and outcome measures for CU. EQ-5D utility was positively correlated with CU-QOL (correlation coefficient, 0.63; *P* < 0.001) and UCT (0.58; *P* < 0.001), whereas a significantly negative correlation was found between EQ-5D and UAS7 (−0.47; *P* < 0.001).

*Fig. 1.* Comparison of EQ-5D index scores according to UAS7 values. EQ-5D, EuroQOL 5-dimension; UAS7, Urticaria Activity Score over 7 days.

*Fig. 2.* Correlations between EQ-5D utility and outcome measures for chronic urticaria. EQ-5D, EuroQOL 5-dimension; CU-QoL, CU-specific quality of life; UAS7, Urticaria Activity Score over 7 days; UCT, Urticaria Control Test. *P* value < 0.001.
We attempted to construct a model with which to predict EQ-5D utility for CU patients using UAS7 and UCT through CPA (Fig. 3). The moderated-mediation CPA results for the relationships among UAS7, UCT, and EQ-5D are provided in Table 3. The total effects model explained 38.28% of the variation in EQ-5D utility ($F[6, 409] = 42.29$, $R^2 = 0.383$, $P < 0.001$), incorporating UAS7 and the addition of mediating variables, including UCT, age, sex, urticarial duration, and combined allergic diseases, on EQ-5D.

After controlling for age, sex, urticaria duration, and combined allergic diseases, UAS7 was directly correlated with UCT (regression coefficient, $-0.251$; 95% confidence interval [CI], $-0.278$, $-0.223$; $P < 0.001$) and EQ-5D utility ($-0.002$; 95% CI, $-0.003$, $-0.001$; $P = 0.007$) (Table 4). Among covariates, age and urticaria duration were not associated with EQ-5D utility in CU patients, whereas female sex ($-0.028$; 95% CI, $-0.049$, $-0.008$; $P = 0.008$) and the presence of comorbid allergic diseases ($-0.028$; 95% CI, $-0.048$, $-0.008$; $P = 0.007$) had a negative impact on EQ-5D (Table 4). However, age, sex, urticaria duration, and comorbid allergic diseases were not found to have a direct relationship with UCT in CU patients. As expected, a significant indirect relationship mediated by changes in UCT was observed between UAS7 and EQ-5D in a conditional process model.

**DISCUSSION**

The present results, for the first time, demonstrate that Korean adults with CU experience substantially worse health outcomes as evaluated by EQ-5D-5L. Impaired HR-QoL in CU...
patients was particularly associated with symptomatic discomfort, anxiety, and depression. Additionally, around one-third of cases was affected in their daily activities. Previous investigations from other countries have shown similar results to ours in that CU patients have higher odds of experiencing anxiety and sleep difficulties as well as impaired work productivity.\textsuperscript{14,15}

The EQ-5D is a generic, standardized instrument used to measure health outcomes across a wide range of diseases.\textsuperscript{7} Through population-based validation studies, researchers can obtain a single utility scale of preference-based index scores varying from 0 (death) to 1 (full health).\textsuperscript{6,7} In the present study, the mean generic HR-QoL score in Korean adults with CU was estimated at 0.86 by the EQ-5D-5L. Scores did, however, differ according to urticaria control states and urticaria activity. Similar to a previous study measuring HR-QoL in chronic spontaneous urticaria (CSU) patients using the EQ-5D-3L, lower EQ-5D utility scores were observed in patients with higher UAS7 and lower UCT scores. We found that the mean EQ-5D utility score for well controlled CU was 0.91, whereas those for partly controlled and uncontrolled CU were 0.84 and 0.77, respectively. Hawe \textit{et al}.\textsuperscript{13} reported mean utility scores of 0.86 for well controlled urticaria and 0.71 for severe urticaria. Because this previous study used pooled data from 3 phase 3 clinical trials of omalizumab for the treatment of patients with refractory CSU,\textsuperscript{13} the baseline health utility scores in their study subjects were, as would be expected, relatively lower than those in the present study population. Other explanations for this discrepancy may be related with regional, cultural, and ethnic differences between the study subjects. In addition, we used the EQ-5D-5L, which has been shown to provide measurement properties superior to those of the EQ-5D-3L,\textsuperscript{6} which was used by Hawe \textit{et al}.\textsuperscript{13}

The EQ-5D utility values in this study were in line with those reported in prior studies for patients with other immune-mediated chronic inflammatory skin diseases, such as AD\textsuperscript{16} and psoriasis.\textsuperscript{17} Although higher AD severity was correlated with poor EQ-5D utilities in both European and US patients, due to socio-demographic variations across countries, differences in HR-QoL for the same severity of the disease were noted.\textsuperscript{16} Subgroup analysis revealed that EQ-5D utility for severe AD with AD scores higher than 71 differed between European (0.42) and the US patients (0.56), even after adjusting for age, sex, smoking, body mass index, and disease duration.\textsuperscript{17} Therefore, to assess the burden of a specific disease and for pharmacoeconomic evaluation of disease-specific treatment, geographic and ethnic differences in a population should be considered. Nevertheless, health outcomes evaluated by EQ-5D-5L in patients with AD reflected better health outcomes in mild AD (0.88 ± 0.16) than in moderate-to-severe AD (0.70 ± 0.26), similar to the results in our study for health outcomes in CU patients (0.91 ± 0.10 for mild CU, 0.75 ± 0.20 for severe CU).

Recent studies have directly compared health outcomes between CU and psoriasis, although they used a 12-item short-form survey instrument in which physical and mental component scores were calculated.\textsuperscript{18,19} They confirmed that HR-QoL in CU patients is similar to that in moderate psoriasis. Meanwhile, CU patients reported a significantly greater impact in the daily activities and physical discomfort domains than psoriasis, for which the self-perception and social functioning domains were more greatly impacted.\textsuperscript{18,19}

As it can be difficult to collect data on the EQ-5D and HR-QoL in real-life practice, having a mapping algorithm available to transform CU-specific health outcomes into EQ-5D utility values may be very useful. In the present study, we confirmed that patient-oriented health outcomes, including UAS7 and UCT, as well as sex and combined allergic diseases were
significant determinants for EQ-5D utility values in adults with CU. CPA suggested that urticaria severity measured by UAS7 exerts direct and indirect effects on EQ-5D. From this, we derived a computational model with which to map scores from UAS7 and UCT to EQ-5D in CU patients.

There are several limitations to the present study. Although we collected CU-specific outcome measures and assessed urticaria control status repeatedly within a 6-month period of study, our study may have excluded some patients who were experiencing itchy wheals but not receiving treatment. Thus, patients with uncontrolled CU comprised less than one-third of the well- or partly-controlled CU groups. Another limitation was that a cross-validation test in another sample or in half of the original sample was not performed as the sample size was considered insufficient. Also, as some differences in the weights assigned to different EQ-5D dimensions were found across countries, the current mapping algorithm for predicting EQ-5D-5L utilities from UCT and UAS7 may not reflect the values of subjects in other countries. Last but not least, as CU is not a serious illness, very low levels of EQ-5D utility were not detected in the present study, thus our conditional process model would be limited in estimating lower end values.

There has been no pharmacoeconomic evaluation of therapeutic modalities for CU patients, such as anti-immunoglobulin E antibody, in Asian countries, including Korea. Results of the present study can provide the basis for facilitating cost utility analyses of medications for CU treatment in Asian populations. Furthermore, we have proposed a computational model of EQ-5D utility driven only by UAS7 and UCT. While the use of utilities derived directly from administering EQ-5D-5L, would be preferred, considering that both UAS7 and UCT are frequently evaluated in daily practice for CU patients, even without further clinical trials, the mapping algorithms can be used to generate utility estimates in future pharmacoeconomic evaluations of various treatment options for CU patients.

In conclusion, EQ-5D scores in CU were significantly associated with control status scores and disease activity. This study may be helpful for future modelling of quality-adjusted life years in pharmacoeconomic evaluation of CU.

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