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Original Article

Mapping naso-ocular symptom scores to EQ-5D-5L utility values in Japanese cedar pollinosis

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AR, allergic rhinitis; GBP, Great Britain Pond; ICER, incremental cost effectiveness ratio; JCP, Japanese cedar pollinosis; JPY, Japanese Yen; QALY, quality-adjusted life year; RS, rating scale; SLIT, sublingual immunotherapy; TOS, total ocular symptom score; TNS, total nasal symptom score; TSS, total naso-ocular symptom score; TTO, time trade-off

ABSTRACT

Background: The total naso-ocular symptom score (TSS) is widely used as an endpoint to evaluate the severity of seasonal allergic rhinitis. However, it is not a generic preference-based measure. We sought to develop an algorithm for mapping between the TSS and health utility in Japanese cedar pollinosis (JCP). We also performed a cost-utility analysis of sublingual immunotherapy (SLIT) for JCP by using this algorithm.

Methods: Patients with JCP filled out the TSS questionnaire and EQ-5D-5L simultaneously during the pollen season in 2019 and in 2020. We estimated a direct utility mapping model by regressing responses to individual TSS questions directly onto utility. The incremental cost-effectiveness ratio (ICER) of active SLIT to a placebo was determined by examining the drug expense and the estimated quality-adjusted life year (QALY) using a dataset from a double-blind placebo-controlled clinical trial.

Results: A total of 238 records were included for analysis. The estimated utility decreased with increasing severity of rhinitis. Patients with comorbid asthma showed lower utility. A negative and significant correlation was seen between the TSS and utility in both 2019 and 2020. The estimated equations were: $Y(\text{utility}) = -0.0161*X(\text{TSS}) + 1.005$ in non-asthmatic JCP patients. The ICER of active SLIT to the placebo was estimated to be 4,049,720 and 6,011,218 JPY/QALY in the first and second year, respectively.

Conclusions: It is possible to reasonably predict utility from the total naso-ocular symptom score by using regression models. In the estimated algorithm, pre-seasonal SLIT for JCP is cost-effective.

Introduction

Allergic rhinitis (AR), especially seasonal AR caused by pollen, is the most prevalent allergic disease, and its prevalence is on the rise. For example, the prevalence of Japanese cedar pollinosis (JCP), the most prevalent AR in Japan, increased from 16.2% in 1998, and 26.5% in 2008 to 38.8% in 2019 among Japanese otorhinolaryngologists and their families.[1,2] Although AR is not a lethal disease, it causes substantial burdens on not only the quality of life (QOL) of

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patients, but also the loss of work productivity and health resources.[1,3–5]

Analyses for the economic evaluation of health resources include cost-minimization analysis, cost-effectiveness analysis (CEA), cost-utility analysis (CUA), and cost-benefit analysis.[6] CEA evaluates two alternative treatments in relation to their associated costs and health outcomes.[7] In CEA, the additional cost per extra unit of effect between the intervention and control therapy is determined by the incremental cost-effectiveness ratio (ICER), where a low ICER indicates better cost-effectiveness of the new/alternative intervention.[7] CUA is a specific form of CEA in which the health utility of quality-adjusted life year (QALY) is used as a unit of effect.[7] QALY is a quantifiable measure of patient health that uses a scale from 0 (dead) to 1 (perfect health).[8] The CUA-based ICER is used to allocate healthcare resources, often using a threshold approach. In the setting of the National Institute for Health and Care Excellence (NICE) in the United Kingdom, the threshold below which interventions are generally considered to be cost-effective remains at 20,000 Great Britain pounds (GBP) per QALY.[9] In Japan, the willingness-to-pay value for one QALY was estimated to be 5 million Japanese yen (JPY).[10]

The most widely accepted method for determining utility from 0 (dead) to 1 (perfect health) is the EuroQoL-5D (EQ-5D) instrument.[11] The EQ-5D is the most widely used preference-based measure, and it includes five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, which have three response levels of severity from 1 (no problems) to 3 (extreme problems).[12] A value set to estimate utility from EQ-5D data was developed in Japan.[13] For example, if a subject reports level 1 of mobility (I have no problems in walking about), level 2 of self-care (I have some problems washing or dressing myself), level 3 of usual activities (I am unable to perform my usual activities), level 1 of pain/discomfort (I have no pain or discomfort), and level 1 of anxiety/depression (I am not anxious or depressed), the health utility is estimated as 0.661.

Using the EQ-5D, one report showed that the utility values were 0.89 and 0.97 for seasonal and perennial AR, respectively, in Japanese subjects.[14] However, estimation of utility by the EQ-5D is limited in AR, because EQ-5D is a generic and not disease-specific questionnaire, and since the original EQ-5D used only three levels of severity—for example, no, moderate, and extreme for pain/discomfort[12]—a ceiling effect was seen as the EQ-5D indicated that many AR patients showed perfect health (utility = 1).[14–16] To reduce the ceiling effect and improve the sensitivity, the EQ-5D-5L was developed (Table 1). Although the dimensions of EQ-5D-5L are identical to EQ-5D, the choice for answer is changed from the three-level system to a five-level system: none, slight, moderate, severe, and unable/extreme.[12] Although a permission is required to use EQ-5D-5L, determining utility converted from EQ-5D-5L data by using a value set is effectively and simply as compared with SF36, the well-known QOL questionnaire.[13,17]

The total naso-ocular symptom score (TSS) that examines five symptoms—sneezing, rhinorrhea, nasal congestion, itchy eyes, and watery eyes—is generally used as a primary endpoint in clinical trials of AR.[18,19] On the other hand, the EQ-5D is not often used in clinical trials, making it difficult to determine the QALY using data from the trials. When preference-based measures, such as the EQ-5D, are not used in a clinical trial, it is possible to "map" measures from disease-specific scores to preference-based utilities.[16] Although there have been several reports of mapping from disease-specific QOL scores to utility, little is known about mapping symptom scores to utility.[16,20]

In the present study, we investigated the mapping of the TSS to utility by simultaneously using a symptom score questionnaire and the EQ-5D-5L based on the Mapping onto Preference-based Measures Reporting Standards statement.[21] Using utility determined by a regression model, we analyzed the ICER of sublingual immunotherapy (SLIT) using a Japanese cedar extract drop to SLIT using a placebo to determine whether SLIT is cost-effective using the data from a double-blind placebo-controlled clinical trial.[22]

Table 1
EQ-5D-5L questionnaire.

Under each heading, Please check the ONE box that best describes your health TODAY.	
MOBILITY	
I have no problems in walking about	☐
I have slight problems in walking about	☐
I have moderate problems in walking about	☐
I have severe problems in walking about	☐
I am unable to walk about	☐
SELF-CARE	
I have no problems washing or dressing myself	☐
I have slight problems washing or dressing myself	☐
I have moderate problems washing or dressing myself	☐
I have severe problems washing or dressing myself	☐
I am unable to wash or dress myself	☐
USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)	
I have no problems doing my usual activities	☐
I have slight problems doing my usual activities	☐
I have moderate problems doing my usual activities	☐
I have severe problems doing my usual activities	☐
I am unable to do my usual activities	☐
PAIN/DISCOMFORT	
I have no pain or discomfort	☐
I have slight pain or discomfort	☐
I have moderate pain or discomfort	☐
I have severe pain or discomfort	☐
I have extreme pain or discomfort	☐
ANXIETY/DEPRESSION	
I am not anxious or depressed	☐
I am slightly anxious or depressed	☐
I am moderately anxious or depressed	☐
I am severely anxious or depressed	☐
I am extreamely anxious or depressed	☐

Methods

Patients

Patients with JCP without severe comorbid non-allergic diseases were enrolled from seven hospitals (International University of Health and Welfare Hospital, Okayama University Hospital, Kagawa Prefectural Central Hospital, Kagawa Rosai Hospital, Ibara City Hospital, Himeji Red Cross Hospital, and Himeji St. Mary's Hospital) in 2019 (n = 80) and 2020 (n = 166). Among all of the records, 8 records in 2020 (4.8%) were omitted, as they did not have complete and valid responses for the EQ-5D-5L, leaving a sample of 158 for the 2020 analysis. All patients had paroxysmal nasal symptoms, such as sneezing, rhinorrhea, and nasal congestion in the spring, and showed sensitization to Japanese cedar pollen by the skin prick test and/or the presence of serum specific immunoglobulin E as determined by ImmunoCAP (Phadia AB, Uppsala, Sweden). Five patients in 2019 and 21 patients in 2020 had concomitant asthma. A medical history of pollinosis was recorded in 234 patients; among them, 81 patients (35 in 2019 and 46 in 2020) did not receive any treatment for rhinitis at the time of answering the questionnaire, and the rest of the 153 patients received treatment for JCP (pharmacotherapy: n = 133; allergen immunotherapy: n = 13; surgery: n = 7). None of the patients had used systemic immunosuppressive

drugs, including oral steroids, during the pollen season. The detailed characteristics of the patients are shown in Table 2. Written informed consent was obtained from each subject, and the study was approved by the institutional review board of each hospital (13-B-322, 1903-042, 806, H30-19, H31-06, 36 and 019-65 at the International University of Health and Welfare Hospital, Okayama University Hospital, Kagawa Prefectural Central Hospital, Kagawa Rosai Hospital, Ibara City Hospital, Himeji Red Cross Hospital, and Himeji St. Mary's Hospital, and respectively).

Monitoring of symptoms, utility, and pollen dispersion

During the pollen season from January to April in 2019 and 2020, patients filled out a questionnaire for symptom scores and EQ-5D-5L simultaneously. The symptom scores were determined using a five-grade scale for the symptoms of sneezing, rhinorrhea, nasal congestion, eye itching, and watery eyes, which are usually used in clinical trials in Japan (Table 3).[1,19] The TSS is the sum of the scores of five individual symptoms that ranges from 0 to 20. The total nasal symptom score (TNS) is the sum of the scores of sneezing, rhinorrhea, and nasal congestion. The total ocular symptom score (TOS) is the sum of the scores of eye itching and watery eyes. The severity of AR was rated as none, mild, moderate, severe, and most severe based on the criteria in the practical guideline for the management of AR in Japan (PG-MARJ).[1] Utility was calculated by a Japanese version of the EQ-5D-5L value set.[23]

Table 2
Patients' characteristics.

		2019 (n = 80)	2020 (n = 158)
Age, mean ± SD, years (min–max)		46.7 ± 17.5 (18–79)	47.3 ± 17.8 (18–79)
Sex (male:female)		32:48	70:88
Concomitant allergic disease	None	63	84
	Asthma	5	21
	Atopic dermatitis	1	18
	Drug allergy	8	15
	Others	2	22
	Unknown	1	8
Treatment for JCP	None	35	46
	Early interventional pharmacotherapy	8	41
	Post-onset pharmacotherapy	30	54
	Allergen immunotherapy	3	10
	Surgery (eg. Laser vaporization)	4	3
	Unknown	0	4

Table 3
Correlation between individual symptom scores and utility.

	Year	r	95% CI	P
Sneezing	2019 + 2020	−0.419	−0.519 ~ −0.309	<0.001
	2019	−0.414	−0.581 ~ −0.214	<0.001
	2020	−0.441	−0.558 ~ −0.305	<0.001
Rhinorrhea	2019 + 2020	−0.400	−0.502 ~ −0.288	<0.001
	2019	−0.426	−0.590 ~ −0.227	<0.001
	2020	−0.413	−0.534 ~ −0.274	<0.001
Congestion	2019 + 2020	−0.440	−0.537 ~ −0.331	<0.001
	2019	−0.484	−0.636 ~ −0.295	<0.001
	2020	−0.422	−0.543 ~ −0.285	<0.001
Eye itching	2019 + 2020	−0.338	−0.446 ~ −0.220	<0.001
	2019	−0.365	−0.541 ~ −0.158	<0.001
	2020	−0.335	−0.466 ~ −0.188	<0.001
Watery eyes	2019 + 2020	−0.296	−0.408 ~ −0.176	<0.001
	2019	−0.316	−0.509 ~ −0.115	0.003
	2020	−0.286	−0.425 ~ −0.138	<0.001

Mapping algorithm

We estimated a direct utility mapping model by regressing responses to individual TSS questions directly onto utility. The linear regression analysis was estimated by GraphPad Prism 8 software (GraphPad, La Jolla, CA, USA). Any utilities predicted to be >1 were set to one.

Cost-utility analysis

CUA was performed using a dataset from a double-blind placebo-controlled clinical trial that was obtained from Torii Pharmaceutical Co. Ltd.[22] In brief, 267 and 264 subjects with JCP were randomly allocated to receive SLIT with a Japanese cedar extract drop (active SLIT) or a placebo (placebo SLIT), respectively, starting in October 2010. The SLIT group used one bottle with 200 Japanese allergy unit (JAU)/ml (421.1 JPY) for the first week, one bottle of 2000 JAU/ml (1006.8 JPY) for the second week, then a package of 2000 JAU/ml (100.8 JPY/package) daily after the third week. Daily nasal symptoms (sneezing, rhinorrhea, and nasal congestion) and ocular symptoms (eye itchiness and watery eyes) were recorded by electric daily from January 8 to April 30 in 2011 and 2012. Patients were allowed to use the following relief medications for unbearable symptoms: fexofenadine hydrochloride (60-mg tablets, 71.9 JPY/tablet in 2011), tramazoline hydrochloride (0.118% nasal solution in 10-ml bottles, 72 JPY/bottle), or ketotifen fumarate (0.05% ophthalmic solution in 5-ml bottles, 720.2 JPY/bottle). Data obtained during the pollen season were used for CUA. ICER was calculated by the following formula:

$$ICER = [(Cost_{active} - Cost_{placebo})/(QALY_{active} - QALY_{placebo})]$$

Statistical analysis

The t-test was used to compare data between two groups, and one-way analysis of variance (ANOVA) followed by Tukey's test was used for multiple comparisons. Correlation analyses were performed using Pearson correlation coefficient. P values of less than 0.05 were considered to be statistically significant. Statistical analyses were performed using GraphPad Prism 8 (GraphPad).

Results

Utility in JCP patients

In total, 80 and 158 patients provided complete EQ-5D-5L data in 2019 and 2020, respectively. In 2019, 1, 18, 20, 30, and 11 patients were rated as having none, mild, moderate, severe, and the most severe JCP.[1] One-way ANOVA revealed a significant difference in utility determined by the EQ-5D-5L among these groups ($P < 0.001$). Tukey's test further showed that utility was significantly lower in the most severe group as compared to the mild ($P < 0.001$), moderate ($P = 0.005$), and severe ($P = 0.011$) groups (Fig. 1A). Similar results were seen in 2020, in which 4, 61, 51, 27, and 15 patients were rated as having none, mild, moderate, severe, and the most severe JCP. A significant difference in utility was observed among these groups ($P < 0.001$). Tukey's test showed that utility was significantly lower in the most severe group as compared to the none ($P = 0.005$), mild ($P < 0.001$), and moderate ($P < 0.001$) groups. In addition, utility was also significantly lower in the severe group than in the none ($P = 0.013$), mild ($P < 0.001$), and moderate ($P = 0.001$) groups. On the other hand, utility did not differ between the severe and most severe groups in 2020 ($P = 0.933$; Fig. 1B). When we combined the data from the two years (n = 238), a more significant association was seen between

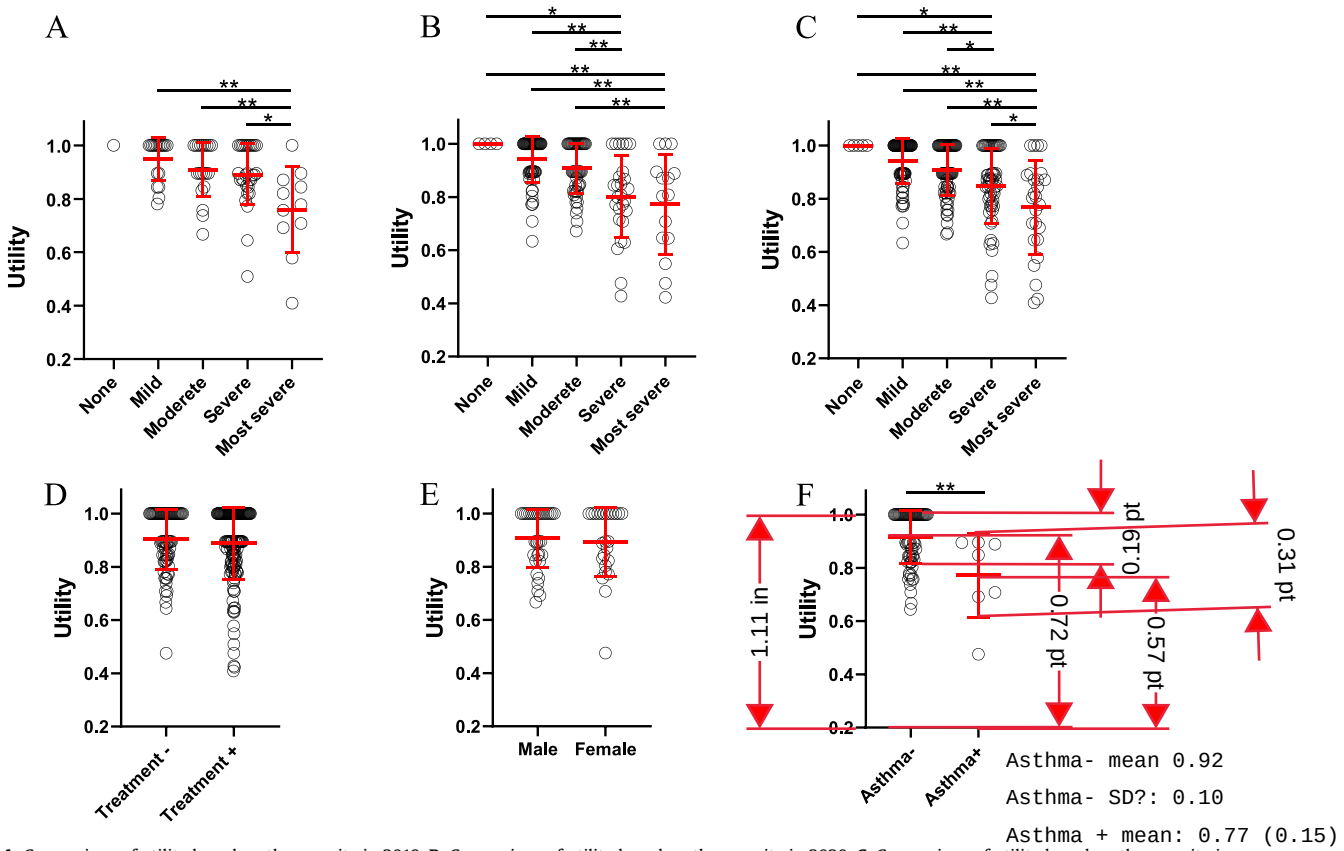

Fig. 1. Utility in JCP. **A:** Comparison of utility based on the severity in 2019. **B:** Comparison of utility based on the severity in 2020. **C:** Comparison of utility based on the severity in the combined data of 2019 and 2020. **D:** Comparison of utility in the presence or absence of treatment for JCP. **E:** Comparison of utility between male and female JCP patients. **F:** Comparison of utility between asthmatic and non-asthmatic patients. P values were determined by Tukey's test (A–C) and the t-test (D–F). *P < 0.05. **P < 0.01.

disease severity and utility; the utility values were 1.000 ± 0.000, 0.943 ± 0.085, 0.909 ± 0.095, 0.849 ± 0.142, and 0.767 ± 0.175 in the none, mild, moderate, severe, and most severe groups, respectively (Fig. 1C). Among the patients in the none, mild, moderate, severe, and most severe groups, 5 (100%), 50 (63.3%), 31 (43.7%), 17 (29.8%), and 4 (15.4%) patients, respectively, showed perfect health (utility = 1). No significant difference in the utility was seen between patients with and without treatment for JCP (P = 0.411; Fig. 1D). In the no-treatment group, no sex difference was seen in utility (P = 0.683; Fig. 1E). Seven patients in the no-treatment group had concomitant asthma; they showed significantly lower utility as compared to the confirmed non-asthmatic patients (n = 69, P = 0.001; Fig. 1F).

Correlation between symptom scores and utility

In 2019, a negative and significant correlation was seen between the TSS, which comprised five naso-ocular symptoms, and utility (r = −0.536 (95% confidence interval (CI): −0.676 to −0.359), P < 0.001; Fig. 2A). Similar results were seen in 2020 (r = −0.498 (95% CI: −0.607 to −0.370), P < 0.001; Fig. 2B). The significant negative correlation was still seen when we combined the data from the two years (r = −0.495 (95% CI: −0.585 to −0.392), P < 0.001; Fig. 2C). Both the TNS, which comprised three nasal symptoms, and the TOS, which comprised two ocular symptoms, also showed a significant negative correlation with utility; however, the TNS showed a stronger correlation (r = −0.499 (95% CI: −0.589 to −0.398) vs. r = −0.351 (95% CI: −0.458 to −0.234)) than the TOS in the combined data. All individual symptoms also showed a significant negative correlation with utility (P < 0.001, except for watery eyes in 2019, which had a P value of 0.003; Table 3).

Mapping algorithm

Linear regression modeling was applied to develop an algorithm for mapping the TSS to utility. Because the presence of asthma is a confounding factor of utility, we first developed a model in patients without comorbid asthma. In 2019, best-fit values for the slope and Y(utility)-intercept were −0.0167 (95% CI: −0.023 to −0.010) and 1.031 (95% CI: 0.974 to 1.088), respectively. Thus, the estimated equation for 2019 was: Y(utility) = −0.0167*X(TSS) + 1.031. A similar estimation was seen in 2020, for which the best-fit values for the slope and Y(utility)-intercept were −0.0175 (95% CI: −0.023 to −0.012) and 1.002 (95% CI: 0.965 to 1.039), respectively. When we combined the data of the two years (n= 203), the estimated equation was: Y(utility) = −0.0161*X(TSS) +1.005. In asthmatic patients (n=26), the estimated equation was: Y(utility)=−0.0181*X(TSS)+ 1.002 (Fig. 2D).

CUA of SLIT for JCP

We estimated the mean QALY in patients who received either active SLIT or placebo SLIT. Because none of the subjects had experienced an asthma attack within the previous 5 years, we chose to use the calculation formula for non-asthmatic patients. The estimated mean utility values in active and placebo SLIT patients in 2011 were 0.882 ± 0.056 and 0.864 ± 0.056, respectively, and they showed a significant difference (P < 0.001). JCP usually lasts for 3 months from late January to the end of April, and the

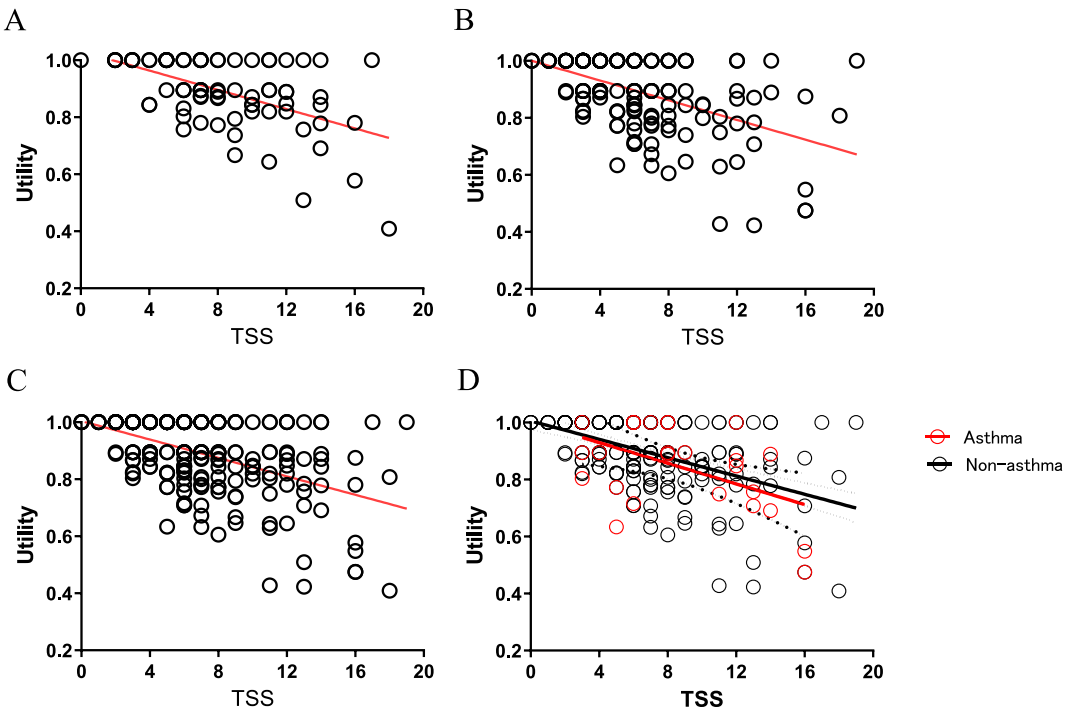

Fig. 2. Correlation between utility and the TSS. **A:** The correlation in 2019. **B:** The correlation in 2020. **C:** Combined data of 2019 and 2020. **D:** Correlation with the presence (red line) and absence (black line) of comorbid asthma.

mean estimated QALY in active and placebo SLIT patients in 2011 can be estimated to be 0.221 ± 0.014 and 0.216 ± 0.014, respectively.[24] Similar results were seen in 2012. Five patients in the active SLIT group showed a mean TSS below 0.005, so their calculated utility was above 1; we set the utility value as 1 for these patients. The estimated mean utility values in active and placebo SLIT patients in 2012 were 0.931 ± 0.053 and 0.908 ± 0.058, respectively, and they showed a significant difference ($P < 0.001$). The estimated mean QALY in the active and placebo SLIT patients in 2012 can be estimated to be 0.233 ± 0.013 and 0.227 ± 0.014, respectively.

When we assumed that SLIT was started on the first day of October 2010, patients receiving active SLIT used one 200-JAU/ml bottle, one 2000-JAU/ml bottle, and 198 2000-JAU/ml packs. The estimated cost for SLIT for the 2011 pollen season was 21,386.3 JPY. Drug costs of rescue medications were estimated to be 1686 and 2824 JPY for the active and placebo SLIT groups, respectively (Table 4). The ICER of active SLIT to placebo SLIT in the 2011 pollen season was estimated to be 4,049,720 JPY/QALY ([(21,386.3+1686.3)−(0+2824.0)]/(0.221 − 0.216)). After the end of the 2011 pollen season, patients receiving active SLIT used 363 of the 2000-JAU/ml packs until the end of the 2012 pollen season. The estimated cost for SLIT for the 2012 pollen season was 36,590.4 JPY. Drug costs for rescue medications during the 2012 pollen season were estimated to be 594.9 and 1073.0 JPY for the active and placebo SLIT groups, respectively. The ICER of active SLIT to placebo SLIT in the 2012 pollen season was estimated to be 6,011,217 JPY/QALY ([(36,590 + 549.9) − (0 + 1073.0)]/(0.233−0.227)).

Discussion

In the present study, we mapped symptom scores of JCP to utility using the EQ-5D-5L. We found that utility decreased with increasing severity of JCP, and linear regression modeling showed that the estimated equation is: Y(utility) = −0.0161*X(TSS) + 1.005 in non-asthmatic JCP patients. When we used this algorithm, CUA showed that SLIT with Japanese cedar pollen extract was cost-effective, because the ICER of active SLIT to placebo SLIT in 2011 (4.05 million JPY per QALY), but not 2012 (6.01 million JPY per QALY), was below 5 million JPY per QALY, the threshold for price adjustment downward in the Health Technology Assessment process in Japan.[25] This threshold can be used regardless of seriousness of illness. Rather, the threshold of 7.5 million JPY per QALY is used for pediatric or intractable and rare diseases in Japan.[26]

The EQ-5D-5L was developed to reduce the ceiling effect.[12] The present study showed that 44.4% of untreated JCP patients showed perfect health (utility = 1) according to the EQ-5D-5L. This rate is lower than that of a previous report performed in 2003 showing that perfect health was seen in 58% of untreated patient with seasonal AR in March.[14] Together with the finding that the annual amount of dispersed Japanese cedar pollen has been increasing gradually over time, this result suggests that the ceiling effect was lessened by using the EQ-5D-5L for JCP.[27]

The present study showed that the utility weight decreased with increasing severity of JCP; the utility values were 0.943, 0.909, 0.849, and 0.767 in the mild, moderate, severe, and most severe JCP groups, respectively. Tamayama *et al.* reported an association between the utility weights and the severity of JCP using rating scale (RS) and time trade-off (TTO) measurements.[28] They found that the utility weights in mild, moderate, severe, and severest (most severe) JCP were 0.82, 0.71, 0.56, and 0.43, respectively, with RS measurements, and 0.96, 0.94, 0.89, and 0.83, respectively, with TTO measurements. Our results were consistent with the results from TTO measurements. In fact, Tamayama *et al.* suggested that the lower weights seen with the RS measurements may be due to the known tendency for responders to be more inclined to mark responses at extreme ends of the scale.[28]

A few reports have demonstrated the mapping of the symptom scores of AR to utility. Dick *et al.* developed a two-part mapping algorithm by calculating disutility from data with daily symptom scores, daily medication scores, asthma symptom scores, and

Table 4
Cost-utility analysis of SLIT for JCP.

Year	Group	Utility	QALY	SLIT				Rescue medication				ICER to placebo (JPY/QALY)
				200 JAU bottle (421.1 JPY)	2000 JAU bottle (1006.8 JPY)	2000 JAU pack (100.8 JPY)	Cost for SLIT (JPY)	Fexofenadine tablet (71.9 JPY)	Tramazoline nasal drop (72 JPY/ 10 ml bottle)	Ketotifen eye drop (720.2 JPY/5 ml bottle)	Cost for rescue medication (JPY)	
2011	Placebo	0.864 ± 0.056	0.216 ± 0.014	0	0	0	0	12.3 ± 16.7	1.2 ± 1.8	2.6 ± 3.4	2824.0 ± 3456.8	
	Active	0.882 ± 0.056	0.221 ± 0.014	1	1	198	21,386.3	6.7 ± 4.9	0.8 ± 1.5	1.6 ± 2.7	1686.3 ± 2145.1	4,049,720
2012	Placebo	0.908 ± 0.058	0.227 ± 0.014	0	0	0	0	4.2 ± 10.1	0.4 ± 1.0	1.0 ± 2.1	1073.0 ± 2113.0	
	Active	0.931 ± 0.053	0.233 ± 0.013	0	0	363	36,590.4	1.9 ± 6.9	0.2 ± 0.8	0.6 ± 1.9	549.9 ± 1777.3	6,011,217

rhinoconjunctivitis QOL questionnaire (RQLQ) scores.[20] Because a negative and significant correlation was seen between symptom scores and utility, we mapped the TSS to utility by linear regression analysis. This simple mapping algorithm enabled us to perform CUA of clinical trials for AR, because the major endpoint in the trials was the symptom scores.

CUA of SLIT for AR has been investigated in several previous reports, especially grass pollen-induced AR. In earlier reports using a grass allergen tablet (Grazax®) in southern Europe, the mean utility determined by the EQ-5D(-3L) was 0.9626 in the Grazax® group and 0.9459 in the standard care group.[29] Based on the annual cost of SLIT with Grazax® ranging from €900 to €2900, the ICER was €13,870 per QALY in France, €20,690 per QALY in Italy, €20.955 per QALY in Austria, and €21,659 per QALY in Spain; all of these were below the cost-effectiveness threshold of the NICE of 20,000 GBP.[29] Similar results using the same tablet were seen in Northern Europe.[30] Similarly, the ICER of SLIT with Grazax® in combination with symptomatic medication to symptomatic medication alone was €12,168 per QALY in pediatric patients with grass pollen allergy.[9] SLIT with a house dust mite tablet for the treatment of house dust mite AR also showed cost-effectiveness as the ICER of SLIT plus allergy pharmacotherapy to placebo plus pharmacotherapy was €7519.[15] When we converted the TSS to utility using the proposed mapping algorithm in the present study and estimated the QALY based on the fact that JCP usually lasts for 3 months/year, the ICERs of active SLIT plus symptomatic medication to placebo plus symptomatic medication in the 2011 and 2012 pollen seasons were estimated to be 4,049,720 JPY and 6,011,217 JPY per QALY, respectively. These results suggest that pre-seasonal SLIT with the Japanese cedar extract drop is cost-effective for JCP, because the ICERs were below the cost-effectiveness threshold of the willing-to-pay value of 5 million JPY per QALY in Japan.[10] These results also suggest that pre-seasonal SLIT for JCP has similar cost-effectiveness to grass pollen tablet and house dust mite tablet.[15,29,30] Although the ICER of the whole-year SLIT to placebo exceeded the threshold of 5 million JPY per QALY, this treatment may achieve cost-effectiveness after discontinuation, because it is known that its efficacy can persist for at least 3 years after the discontinuation of allergen immunotherapy including JCP.[31,32]

There are limitations to this study. First, the sample size was relatively small when compared to previous reports investigating mapping.[16,20] This may have led to a weaker correlation ($r = -0.495$) between the TSS and QALY. Second, although the grading system of the TSS presented here is the same as that broadly used in clinical trials for AR in Japan, it is not common in other countries.[18,19] In the present study, we graded the naso-ocular symptoms of sneezing, rhinorrhea, nasal congestion, eye itching, and watery eyes using a five-grade scale based on the number of episodes of paroxysmal sneezing in a day, number of episodes of nose blowing in a day, duration of mouth breathing in a day, frequency of rubbing eyes in a day, and frequency of wiping tears in a day.[1,19] However, in other countries, the severity of symptoms is usually graded with a four-grade scale: no symptoms, mild symptoms (easily tolerated), moderate symptoms (bothersome, but tolerated), and sever symptoms (hard to tolerate and interferes with daily activities).[33] Third, it appears that the ceiling effect was observed even with the use of EQ-5D-5L. Although the ratio of patients showing perfect health (1 QALY) decreased with increasing severity of AR, 29.8% of the severe JCP group and 15.4% of the most severe JCP group showed perfect health. It is known that generic QOL questionnaires, especially those with small items, such as the SF-8, show low sensitivity as compared to disease-specific QOL questionnaires in AR.[34] Because AR is not a life-threatening disease, many patients with JCP may not pay so much attention to the items of EQ-5D-5L, including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.

Fourth, the SLIT data are relatively old. Currently, a Japanese cedar extract tablet with a higher content (5000 JAU) is used in SLIT for JCP.[35] In the future, CUA should be performed with this new formula.

In conclusion, we proposed a mapping algorithm that converts the TSS to QALY. Although a strong correlation was not seen between the TSS and QALY, this proposed algorithm may provide a basis for the economical evaluation of medical treatments, including clinical trials for AR.

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Conflict of interest

The authors have no conflict of interest to declare.

Authors' contributions

HK, and MO designed the study and wrote the manuscript. KK, THar, YH, SM and THig contributed to data sampling of EQ-5D-5L questionnaire and patients' information. AO and MA contributed to data management and statistical analysis. YO contributed to data collection of sublingual immunotherapy. SI contributed to cost-utility analysis.

References

1. Okubo K, Kurono Y, Ichimura K, Enomoto T, Okamoto Y, Kawauchi H, et al. Japanese guidelines for allergic rhinitis 2020. *Allergol Int* 2020;**69**:331–45.
2. Matsabura A, Sakashita M, Gotoh M, Kawashima K, Matsuoka B, Kondou S, et al. [National epidemiological survey of nasal allergies 2019 (Comparison with 1998, 2008): breaking news-for otolaryngologists and their families]. *Nippon Jibiinkoka Gakkai Kaiho Tokyo* 2020;**123**:485–90 (in Japanese).
3. Lamb CE, Ratner PH, Johnson CE, Ambegaonkar AJ, Joshi AV, Day D, et al. Economic impact of workplace productivity losses due to allergic rhinitis compared with select medical conditions in the United States from an employer perspective. *Curr Med Res Opin* 2006;**22**:1203–10.
4. Vandenplas O, Vinnikov D, Blanc PD, Agache I, Bachert C, Bewick M, et al. Impact of rhinitis on work productivity: a systematic review. *J Allergy Clin Immunol Pract* 2018;**6**:1274–86.
5. Cardell LO, Olsson P, Andersson M, Welin KO, Svensson J, Tennvall GR, et al. TOTALL: high cost of allergic rhinitis-a national Swedish population-based questionnaire study. *NPJ Prim Care Respir Med* 2016;**26**:15082.
6. Halmai LA, Neilson AR, Kilonzo M. Economic evaluation of interventions for the treatment of asthma in children: a systematic review. *Pediatr Allergy Immunol* 2020;**31**:150–7.
7. Ronaldson S, Taylor M, Bech PG, Shenton R, Bufe A. Economic evaluation of SQ-standardized grass allergy immunotherapy tablet (Grazax) in children. *Clinicoecon Outcomes Res* 2014;**6**:187–96.
8. Coons SJ, Rao S, Keininger DL, Hays RD. A comparative review of generic quality-of-life instruments. *Pharmacoeconomics* 2000;**17**:13–35.
9. Owen L, Pennigton B, Fischer A, Jeong K. The cost-effectiveness of public health interventions examined by NICE from 2011 to 2016. *J Public Health (Oxf)* 2018;**40**:557–66.
10. Shiroiwa T, Sung YK, Fukuda T, Lang HC, Bae SC, Tsutani K. International survey on willingness-to-pay (WTP) for one additional QALY gained: what is the threshold of cost effectiveness? *Health Econ* 2010;**19**:422–37.
11. Poole CD, Bannister CA, Andreasen JN, Andersen JS, Currie CJ. Estimation of health-related utility (EQ-5D index) in subjects with seasonal allergic rhinoconjunctivitis to evaluate health gain associated with sublingual grass allergen immunotherapy. *Health Qual Life Outcomes* 2014;**12**:99.
12. Mukuria C, Rowen D, Harnan S, Rawdin A, Wong R, Ara R, et al. An updated systematic review of studies mapping (or cross-walking) measures of health-related quality of life to generic preference-based measures to generate utility values. *Appl Health Econ Health Policy* 2019;**17**:295–313.
13. Tuchiya A, Ikeda S, Ikegami N, Nishmura S, Sakai I, Fukuda T, et al. Estimating an EQ-5D population value set: the case of Japan. *Health Econ* 2002;**11**:341–53.
14. Monden A, Ogino S. [The evaluation of the utility values for allergic rhinitis using EQ-5D]. *[J Jap Soc Immunol Allergy Otorhinolaryngol]* 2005;**23**:15–8 (in Japanese).
15. Green W, Kleine-Tebbe J, Klimek L, Hahn-Pedersen J, Andreasen JN, Taylor. Cost-effectiveness of SQR HDM SLIT-tablet in addition to pharmacotherapy for the treatment of house dust mite allergic rhinitis in Germany. *Clinicoecon Outcomes Res* 2017;**9**:77–84.
16. Dick K, Briggs A, Ohsfeldt R, Grand TS, Buchs S. A quality-of-life mapping fuction developed from a grass pollen sublingual immunotherapy trial to a tree pollen sublingual immunotherapy trial. *J Med Econ* 2020;**23**:64–9.
17. Yu ST, Chang HY, Yao KP, Lin YH, Hurng BS. Validity of EQ-5D in general population of Taiwan: results of the 2009 National Health Interview and Drug Abuse Survey in Taiwan. *Qual Life Res* 2015;**24**:2541–8.
18. Caimmi D, Calderon MA, Bousquet M, Demoly P. Allergen immunotherapy outcomes and unmet needs: a critical review. *Immunol Allergy Clin North Am* 2016;**36**:181–9.
19. Okubo K, Okano M, Sato N, Tamaki Y, Suzuki H, Uddin A, et al. Add-on omalizumab for inadequately controlled severe pollinosis despite standard-of-care: a randomized study. *J Allergy Clin Immunol Pract* 2020;**8**:3130–40.
20. Dick K, Briggs A, Brandi H. Application of a mapping function to estimate utilities for ragweed allergen immunotherapy trials. *Pharmacoecon Open* 2020;**4**:649–55.
21. Petou S, Rivero-Arias O, Dakin H, Longworth L, Oppe M, Hround R, et al. The MAPS reporting statement for studies mapping onto generic preference-based outcome measures: explanation and elaboration. *Pharmacoeconomics* 2015;**33**:993–1011.
22. Okamoto Y, Okubo K, Yonekura S, Hashiguchi K, Goto M, Otsuka T, et al. Efficacy and safety of sublingual immunotherapy for two seasons in patients with Japanese cedar pollinosis. *Int Arch Allergy Immunol* 2015;**166**:177–88.
23. Shiroiwa T, Ikeda S, Noto S, Igarashi A, Fukuda T, Saito S, et al. Comparison of value set based on DCE and/or TTO data: Scoring for EQ-5D-5L health states in Japan. *Value Health* 2016;**19**:648–54.
24. Osada T, Okano M. Japanese cedar/cypress pollinosis updated: new allergen, cross-reactivity, and treatment. *Allergol Int* 2021;**70**:281–90.
25. Kamae I, Thwaites R, Hamada A, Fernandez JL. Health technology assessment in Japan: a work in progress. *J Med Econ* 2020;**23**:317–22.
26. Shiroiwa T. Cost-effectiveness evaluation for pricing medicines and devices: a new value-based price adjustment system in Japan. *Int J Technol Assess Health Care* 2020;**36**:270–6.
27. Kishikawa R, Koto E. Effect of climate change on allergenic airborne pollen in Japan. *Immunol Allergy Clin N Am* 2021;**41**:111–25.
28. Tamayama K, Kondo M, Shono A, Okubo I. Utility weights for allergic rhinitis based on a community survey with a time trade-off technique in Japan. *Allergol Int* 2009;**58**:201–7.
29. Canonica GW, Poulsen PB, Vestenbeak U. Cost-effectiveness of Grazax for prevention of grass pollen induced rhinoconjunctivitis in Southern Europe. *Respir Med* 2007;**101**:1885–94.
30. Bachert C, Vestenbeak U, Christensen J, Griffiths UK, Poulsen PB. Cost-effectiveness of grass allergen tablet (GRAZAX) for the prevention of seasonal allergic rhinoconjunctivitis – a Northern European perspective. *Clin Exp Allergy* 2007;**37**:772–9.
31. Penagos M, Durham SR. Duration of allergen immunotherapy for inhalant allergy. *Curr Opin Allergy Clin Immunol* 2019;**19**:594–605.
32. Yonekura S, Gotoh M, Kaneko S, Maekawa Y, Okubo K, Okamoto Y. Disease-modifying effect of Japanese cedar pollen sublingual immunotherapy tablets. *J Allergy Clin Immunol Pract* 2021;**9**:4103–16.e14.
33. Blaiss M, Maloney J, Nolte H, Gawchik S, Yao R, Skoner DP. Efficacy and safety of timothy grass allergen immunotherapy tablets in North American children and adolescents. *J Allergy Clin Immunol* 2011;**127**:64–71.
34. Fujii T, Ogino S, Arimoto H, Irifune M, Iwata N, Ookawachi I, et al. [Quality of life in patients with Japanese cedar pollinosis: using the SF-8 health status questionnaire (Japanese version)]. *Arerugi* 2006;**55**:1288–94 (in Japanese).
35. Gotoh M, Yonekura S, Imai T, Kaneko S, Hirokawa E, Konno A, et al. Long-term efficacy and dose-finding trial of Japanese cedar pollen sublingual immunotherapy tablet. *J Allergy Clin Immunol Pract* 2019;**7**:1787–97.