Asthma and Health-Related Quality of Life

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ABSTRACT
The health-related quality of life (HRQoL) is assessed using instruments that have been validated scientifically. From the viewpoint of assessment, they are different from other clinical indices because the subjects themselves evaluate their own HRQoL (the patients in many clinical settings). As an index for evaluating health care services or outcomes, the HRQoL is as important as life expectancy. These instruments can be classified into generic and disease-specific instruments. There are numerous disease-specific instruments that can be used for patients with asthma, such as Juniper et al.'s Asthma Quality of Life Questionnaire (AQLQ), the Living with Asthma Questionnaire (LWAQ), the St. George's Respiratory Questionnaire (SGRQ), and Marks et al.'s Asthma Quality of Life Questionnaire (AQLQ). The characteristics of each instrument should be considered in the selection of specific HRQoL questionnaires for clinical research. Generally, the HRQoL is more disturbed in patients with severe asthma, and has been considered to be an important end-point in randomized controlled trials that involve asthma patients. We expect that further studies will also be performed in Japan.

KEY WORDS
Asthma Quality of Life Questionnaire (AQLQ), Health-Related Quality of Life (HRQoL), health status, Living with Asthma Questionnaire (LWAQ), Nottingham Health Profile (NHP), St. George's Respiratory Questionnaire (SGRQ)

INTRODUCTION
Unfortunately, the term quality of life (QoL) is frequently used as an abstract term in Japan. However, it is commonly accepted in the health care services and in relation to illness that QoL should be assessed using scientifically established instruments, mostly questionnaires. In general, the QoL is a comprehensive concept influenced by factors such as economic status, occupation, and housing, which are not directly related to the health status. In the fields of health care services or in relation to health or illness, the term health-related quality of life (HRQoL) is preferred.

It is a well-known fact that an immense amount of public resources is administered for health care services all over the world. However, healthcare providers are largely unaware that they are consuming public resources. Therefore, it is necessary to evaluate these health care services. Improvements in life expectancy and HRQoL can be considered as clinical indices for evaluating such an outcome. It would be ideal if all medical interventions improved both life expectancy and HRQoL. However, many practices are actually performed on the presumption of improving these indices, and are based on experience rather than scientific evidence. For assessing individual treatment efficacy such as the effect of a drug, it is necessary to consider the HRQoL assessment as an outcome in randomized controlled trials. Moreover, HRQoL assessment provides the fundamental data for economic evaluation, for example cost-utility analysis.

From the viewpoint of assessment, the subjects themselves assess their own HRQoL, and it has been shown that it is difficult for healthcare providers to predict the HRQoL, even considering other clinical or physiological information. In health care services, information obtained directly from subjects by interviews, self-reported questionnaires, or diaries is referred to as patient-reported outcomes (PROs) or self-reported outcomes. The term PROs is used from the viewpoint of assessment rather than the content. It also raises the issue that many indicators for illness
or health have been assessed by healthcare providers rather than by the patients themselves. The HRQoL is the best-known among the PROs.6

**METHODS OF ASSESSMENT AND GENERIC INSTRUMENTS**

The HRQoL is assessed by using self- or interviewer-administered questionnaires as instruments.7 Although various questionnaires have been advocated and used as instruments depending on the purpose of the assessment, the reliability, validity, and responsiveness of each questionnaire must be proven in order to know whether the HRQoL can be assessed scientifically. It usually requires a long-term patient approach to perform the scientific verification of an instrument.

The HRQoL in general should be assessed comprehensively, including several subscales. Each question in a questionnaire is called an item, and domains, dimensions or components, which often consist of multiple items, correspond to each subscale (which is referred to as a profile). The HRQoL should include components such as symptoms, functional capacity, psychological status and social interactions. Furthermore, there is also a viewpoint that components such as degrees of occupational and intellectual function, economic aspects, and overall satisfaction, should also be included. Depending on the specific purpose, components that should be included are determined, and their scores are calculated with or without weighting, and then instruments are created in order to express the measured results as numerical values.

When assessing the HRQoL in patients with a specific disease, either a generic or a disease-specific instrument can be selected depending on the purpose. The greatest advantage of the former is that it can be applied as an epidemiological approach. For example, assessment by a generic instrument is necessary for comparison between different diseases.

Generic instruments including the Sickness Impact Profile (SIP), Nottingham Health Profile (NHP), and SF (short-form)-36 of the Medical Outcomes Study (MOS) have all been administered to patients with asthma in the literature. The SIP has been used as the standard questionnaire amongst the generic instruments in the past.8,9 However, the clinical application of the SIP is complicated because it consists of many items, and it takes a long time to complete. Although the original purpose of the NHP developed in the United Kingdom was to assess perceived distress,10-12 it has been used by many researchers as a method to assess the HRQoL.13,14 The HRQoL assessment in the MOS, an international project developed around the United States, often uses a method with 36 items (short-form : SF-36).15 In studies on chronic diseases, the SF-36 is the most used generic instrument at the present.16 The Japanese version of the SF-36 was established by Fukuhara and colleagues based on an analysis of the responses obtained from a general population sample.17,18 The software for scoring is commercially available along with the Japanese standard values, and they are very convenient for end-users. The WHO first published the WHOQOL-100, a questionnaire with 100 items, and then the WHOQOL-BREF, an instrument with 26 items based on the former. The reliability and validity of the Japanese version has also been reported.

The author would like to introduce an example of using a generic instrument here.19 A comparison of the HRQoL assessed with the NHP is illustrated in Figure 1 for patients with asthma and chronic obstructive pulmonary disease (COPD), and HIV-infected persons. The NHP scores in the patients with the former two diseases were investigated previously by this author. The other scores were obtained from HIV-infected persons in Japan by Watanabe and coworkers (The QoL Research Group of the AIDS Clinical Center and eight Regional AIDS Treatment hospitals in Japan supported by a Research Grant from the Ministry of Health, Labour and Welfare of Japan).19 Since it is well-known that the HRQoL is adversely affected, COPD is a model disease for HRQoL research. Even though the figure does not account for age or gender, the NHP scores of the HIV-infected persons are more severely affected than those of the patients with asthma or COPD. In studies that compared the HRQoL of patients with asthma versus patients with COPD using generic instruments, the relative disturbance of patients with asthma is usually milder than that of patients with COPD. Moreover, in cross-sectional studies on patients with asthma, a deviation of the score distribution cannot be avoided when a generic instrument is used.

In order to be used for pharmaco-economic evaluation, including cost-utility analysis as well as quality-adjusted life year (QALY), a utility measure or a preference-based measure is necessary. Japanese versions of the EQ5D (EuroQol) and Health Utility Index (HUI) have been established for this purpose. Since there are also many reports using the EQ5D in chronic respiratory illnesses in western countries, there is a tendency to use it to measure outcomes for economic evaluation in randomized controlled trials in Europe and the United States.

**DISEASE-SPECIFIC INSTRUMENTS IN ASTHMA**

In respiratory illnesses, there have been many studies investigating the HRQoL of patients with asthma as well as COPD and lung cancers, and numerous disease-specific instruments have been published (Table 1). The American Thoracic Society has set up the Quality of Life Resource (http://www.atlsqol.org/) on its website, and listed instruments to assess the indices related to QoL and symptoms. For adults with
asthma, 6 generic instruments and 12 disease-specific instruments are listed. On the website operated by MAPI Research Institute, a non-profit organization with its headquarters in France, the Quality of Life Instruments Database (http://www.qolid.org/) can be found, which lists 20 disease-specific instruments for asthma in adults and children.

With respect to disease-specific instruments for asthma, the Asthma Quality of Life Questionnaire (AQLQ) published by Juniper and colleagues in 1992, which consists of 32 items, is the best known and most studied. Its responsiveness has also been reported. The AQLQ consists of four domains: Symptoms (12 items), Activity limitations (11 items), Emotional function (5 items), and exposure to environmental stimuli (4 items). This instrument is similar to the Chronic Respiratory Disease Questionnaire (CRQ), which is a disease-specific instrument for

Table 1  Examples of disease-specific instruments in asthma used to measure the health-related quality of life (HRQoL).

<table>
<thead>
<tr>
<th>Instrument</th>
<th>items</th>
<th>validity</th>
<th>responsiveness</th>
<th>Japanese version</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma Quality of Life Questionnaire-Juniper (AQLQ)</td>
<td>32</td>
<td>○</td>
<td>○</td>
<td>available</td>
</tr>
<tr>
<td>Standardized version of the AQLQ</td>
<td>32</td>
<td>○</td>
<td>○</td>
<td>?</td>
</tr>
<tr>
<td>Mini AQLQ</td>
<td>15</td>
<td>○</td>
<td>○</td>
<td>?</td>
</tr>
<tr>
<td>Living with Asthma Questionnaire (LWAQ)</td>
<td>68</td>
<td>○</td>
<td>○</td>
<td>available</td>
</tr>
<tr>
<td>Modified and shortened version of the LWAQ</td>
<td>27</td>
<td>○</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>St. George’s Respiratory Questionnaire (SGRQ)</td>
<td>50</td>
<td>○</td>
<td>○</td>
<td>available</td>
</tr>
<tr>
<td>Asthma Quality of Life Questionnaire-Marks (AQLQ)</td>
<td>20</td>
<td>○</td>
<td>○</td>
<td>?</td>
</tr>
<tr>
<td>Asthma Bother Profile (ABP)</td>
<td>22*</td>
<td>○</td>
<td>?</td>
<td>available</td>
</tr>
<tr>
<td>Airways Questionnaire 20 (AQ20)</td>
<td>20</td>
<td>○</td>
<td>○</td>
<td>available</td>
</tr>
</tbody>
</table>

* : 15 items in Japanese version ○—good, ?—unknown.
COPD developed at the same laboratory, and the response option to each item can be selected from a seven-point scale. Although the AQLQ was originally published as an interview form, it is more commonly used as a self-administered questionnaire today. The smallest change of score that is clinically significant is called the minimal clinical important difference (MCID). When using the total score of each domain divided by the number of items in the AQLQ, it has been reported that a difference of 0.5 is the MCID for a score of 7. The Japanese version of the AQLQ is supervised by the original authors.

In addition, each subject can select the kind of activity for five items from the domain “activity limitation”. In subsequent administrations, the same activity as in the previous questionnaire must be filled using the same items. This is classified as informed administration, and it is impossible to avoid the complication of preparing previous questionnaires. For this reason, a standardized version of the AQLQ with five fixed items in the domain “activity limitation” has been published. Moreover, Juniper and associates published the Mini Asthma Quality of Life Questionnaire (Mini AQLQ) in 1999. It is a self-administered short questionnaire with 15 items. This reduces the number of items in each domain, while keeping the four domains of the AQLQ. The Japanese versions of these revised AQLQs have not been reported.

On the other hand, the Living with Asthma Questionnaire (LWAQ) developed by Hyland and colleagues in the United Kingdom has been frequently used in European countries. It consists of 68 items with 11 subscales, and the response for each item can be selected from four options. The score is divided by the number of items, except for items in which the response is “not applicable”. The overall score is between 0 and 2, and increases as the severity of the HRQoL disturbance increases. The Japanese version has also been published.

When assessing the responsiveness of the LWAQ, there are three methods of comparison within each of the 11 domains, a comparison of the overall scores, and a comparison between 49 items of problem constructs and 19 items of evaluation constructs. A method of assessing the responsiveness by dividing an instrument into four or five subscales has also been reported.

Reid and colleagues reported the reliability and appropriateness of a modified and shortened version of
Comparison of the scores on the Impact component of the St. George’s Respiratory Questionnaire (SGRQ) between groups based on their asthma severity as defined by the following stepwise therapeutic regimen of the British Thoracic Society guidelines (1993); Step 1: occasional use of relief bronchodilators; Step 2: Step 1 plus low-dose inhaled corticosteroids, beclomethasone dipropionate (BDP-CFC) 200–800 μg or fluticasone propionate (FP) 100–400 μg daily; Step 3: Step 1 plus BDP at 800–2000 μg or FP 400–1000 μg daily; Step 4: Step 3 plus regular bronchodilators; and Step 5: Step 4 plus daily oral corticosteroids.

the Living with Asthma Questionnaire (ms-LWAQ), which is a modified version of the LWAQ originally created in the United Kingdom, to be more suitable for use in the United States and with a reduced number of items. It consists of 5 subscales: Consequences (10 items), Affect (6 items), Leisure (4 items), Seriousness (5 items), and Drugs (2 items).

The results of many studies that used the Asthma Quality of Life Questionnaire developed by Marks and coworkers in Australia have also been published, and the verification of the Japanese version was reported at a medical conference. In order to distinguish it from Juniper’s questionnaire with the same name, it is abbreviated in many ways, such as AQLQ-M.

The St. George’s Respiratory Questionnaire (SGRQ) developed by Jones and associates in the United Kingdom is often used in patients with asthma. The validity and responsiveness have been also confirmed in patients with asthma. The SGRQ is a self-administered questionnaire with a total of 50 items, and consists of 3 components: Symptoms (8 items), Activities (16 items), and Impacts (26 items). It is also possible to compute the total score. Since weighting is performed to calculate the score of the SGRQ, a manual with a computer is required for the calculation. In general, “Activities” may correspond to dyspnea and physical functions, and “Impacts” to the components related to psychological and social factors. It has been reported that the MCID is 4 for a score of 100.

Hyland and coworkers developed the Asthma Bother Profile (ABP), which consists of 15 “bother items” and 7 “management items”. Only “bother items” are used in the Japanese version, and it is a unidimensional instrument. This instrument has fewer items and can be self-reported easily. It should be used as a tool for patient evaluation in a clinical setting, but not as an index for the outcome of randomized clinical trials. Similarly, Barley and colleagues developed the Airways Questionnaire 20 (AQ 20) as a questionnaire for the health status of patients with asthma.

The Japanese Society of Allergology is developing a disease-specific instrument for patients with asthma in Japan. In these studies, Arioka and associates developed an instrument with a total of 66 items, including 29 items from the Functional Assessment of Cancer Therapy-General (FACT-G). The verification of its
reliability and validity has just been completed.

An instrument is expected to have three properties: whether it can discriminate between subjects (discriminative property), whether it can evaluate small important changes (evaluative property—responsiveness or sensitivity), and whether it can predict future results including the prognosis (predictive property). However, only limited results have been reported on comparative studies between the different instruments used in patients with asthma.

**RESEARCH RESULTS ON HRQoL IN ASTHMA**

The author would like to introduce the preliminary results of a cross-sectional study on the HRQoL of adult asthmatics. The SGRQ was administered in 314 consecutive patients who met the criteria of mild to severe, stable asthma in an outpatient clinic. The criteria for the patients with asthma were as follows: over 18 years old, a history of asthma symptoms, follow-up at the clinic for more than 6 months, good compliance with the clinical management based on the British Thoracic Society (BTS) guidelines published in 1993, including a daily measurement of their peak expiratory flow rate (PEFR), and received the same regimen for at least four weeks. We excluded patients with apparent comorbidities which may affect HRQoL. According to the BTS guidelines (1993), the treatments were defined into the following five steps: Step 1: occasional use of relief bronchodilators; Step 2: Step 1 plus low-dose inhaled corticosteroids, beclomethasone dipropionate (BDP-CFC) 200–800 μg or fluticasone propionate (FP) 100–400 μg daily; Step 3: Step 1 plus BDP at 800–2000 μg or FP 400–1000 μg daily; Step 4: Step 3 plus regular bronchodilators; and Step 5: Step 4 plus daily oral corticosteroids. No patients were given long-acting β agonist bronchodilators or any other inhaled corticosteroids except for BDP-CFC or FP dry powder inhalation in the present analysis. Of the 314 patients (150 men) (mean age: 49 yrs) with stable asthma, the number of patients treated by the Step 1, 2, 3, 4 and 5 regimens according to the BTS guidelines 1993 were: 7 (5 men), 74 (29), 151 (78), 62 (28) and 20 (10), respectively. The distributions of the scores from the 314 patients with stable asthma on the SGRQ are shown in Figures 2—4. The scores on the Activity and Impacts components and the total score on the SGRQ were similarly distributed, whereas the scores were more or less skewed towards the milder
end of the scale. The severity of asthma defined by a stepwise therapeutic regimen correlated significantly with the Activity and Impacts score, and the total score of the SGRQ. The total score on the SGRQ could be compared with that obtained from patients with COPD (Fig. 5). In patients with severe asthma, the pattern of their score distributions on the total score of the SGRQ was almost the same as the distribution in patients with COPD. Therefore, it is demonstrated that HRQoL disturbance is remarkable in patients with severe asthma, but less disturbed in mild asthma.

In general, the relationship between the scores of instruments that assess HRQoL in asthma patients and physiological indices is quite low regardless of whether it is evaluated cross-sectionally or longitudinally, and regardless of whether generic or disease-specific questionnaires are used. Many studies report that the correlation coefficient between the scores of each questionnaire and the FEV₁ or PEF values is around 0.3, and the relationship between airway responsiveness and the FEV₁ or PEF values is not significant. In other words, the factors that define the HRQoL in asthma patients still remain largely unclear.

Van der Molen and colleagues compared the discriminative properties of 2 generic questionnaires, the SF-36 and Psychological General Well Being (PGWB) index, and 2 disease-specific questionnaires, the AQLQ and LWAQ. They concluded that the discriminative property was best in the AQLQ, and then in the SF-36. Although there are some studies that compared the discriminative properties of different instruments, the results vary. It is more important to select an instrument based on research purposes, rather than because of its excellent discriminative property.

The assessment of the HRQoL of patients with asthma can be best applied in the assessment of treatment efficacy in randomized controlled trials. From the viewpoint of pharmaceuticals, the market for anti-asthmatics is large, and new medications have been continuously developed. Especially with the marketing competition of new inhaled steroids and leukotriene receptor antagonists in the 1990’s, instruments to assess HRQoL were used almost routinely as end-points in randomized controlled trials to evaluate the effectiveness of medications and other medical interventions in asthma patients. Although morning PEF values are currently being used as the primary end-points in clinical trials for asthma in most cases, disease-specific instruments for asthma with excellent responsiveness such as the AQLQ and LWAQ tend to be used as secondary end-points.

An important issue has been identified about following the changes in the HRQoL, i.e., responsiveness or sensitivity, by longitudinal examination with generic instruments. Although sufficient comparative studies between different instruments have not been performed, it is thought that generic instruments are less responsive than disease-specific instruments.

Ware and colleagues evaluated the responsiveness of the SF-36 in asthma as changes in randomized controlled trials, contrasting with Marks and colleague’s Asthma Quality of Life Questionnaire, which is a disease-specific instrument for asthma. They reported that the subscales “role-physical” and “physical functioning”, which represent real physical prob-
problems, showed significant changes.

Juniper and colleagues evaluated the effects of salmeterol (50 μg, inhaled twice daily), salbutamol (200 μg, inhaled 4 times daily), and placebo on the HRQoL in asthma, and the relationship with existing indices of evaluation.58 The trials were randomly-assigned, placebo-controlled, double-blinded, and crossed-over with 140 subjects, and were performed as a joint study at multiple facilities for 12 weeks with 4 weeks for each medication. During the period when salmeterol was administered, the AQLQ scores were significantly improved as compared with the scores during the periods of salbutamol or placebo administration; however, the score difference between salbutamol and placebo administration was small. The correlation coefficients of the changes in the overall AQLQ scores and the difference between morning and evening PEF values were 0.58 and 0.48, respectively, and there was a moderately significant relationship. The morning PEF values are currently used as primary end-points in clinical trials on asthma patients in most cases. The relationship between the change in morning PEF values and the changes in HRQoL scores seems to be higher on the AQLQ than on any other instruments. A correlation coefficient over 0.5 obtained in this clinical trial can be interpreted as being substantially high.

The question of which disease-specific instrument has the best responsiveness is related to the question of which instrument should be used for randomized controlled trials, and remains controversial. There are several studies that evaluated the AQLQ and LWAQ, which are disease-specific instruments, to test which shows better responsiveness. In the clinical trial to compare the effectiveness of salmeterol (50 μg, inhaled twice daily) and salbutamol (400 μg, inhaled twice daily), Rutten-van Molken and colleagues reported that there was no significant difference in the LWAQ scores, although the AQLQ scores were significantly improved in the group with salmeterol administration.59 However, in the controlled clinical trial to investigate the effectiveness of formoterol (24 μg, inhaled twice daily) against placebo, van der Molen and colleagues reported that the LWAQ scores were significantly improved although the AQLQ scores were not. This discrepancy between the two results probably arose because the subjects completed the questionnaires while looking at their own responses from the last administration of the questionnaire (informe administration) in the former study, while the subjects in the latter study did not look at their previous responses while completing the questionnaires. In our previous study using the Japanese version, the responsiveness, defined by the effect size or standardized response mean, of Juniper’s AQLQ was superior to that of the LWAQ, AQ20, SF-36, NHP or EQ5D.60,61

Hyland and colleagues have been focusing on the fact that symptoms are often evaluated in the form of diaries such as an asthma diary, and reported the appropriateness of the structured asthma QOL diary to assess HRQoL.62 They compared the QoL diary and LWAQ in clinical trials, and reported that the former had better responsiveness. Since diaries are a type of informed administration, it is expected that responses obtained through informed administration are related to improved responsiveness. However, there is criticism that this is not an appropriate use of the questionnaires.

In conclusion, the HRQoL is usually impaired in patients with moderate to severe asthma. An evaluation of health care services as well as medical intervention including pharmacotherapy should include the HRQoL disturbed by disease. There are many generic and asthma-specific instruments available, and specific instruments should be selected for the study purpose. Since it is thought that the responsiveness of the instruments is important in randomized-controlled trials, Juniper’s AQLQ may be preferred.

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