Evaluating Health-related Quality of Life in Asthma

Osamu Nishiyama1, Hiroyuki Taniguchi1, Yasuhiro Kondoh1 and Tomoki Kimura1

ABSTRACT
Recently, in the field of asthma, there has been a substantial number of clinical trials which include health-related quality of life (HRQoL) as one of the outcomes. These studies employ two types of instruments for assessing HRQoL, generic and disease-specific instruments each being used individually or in combination. It has been proposed that treatments for patients aimed at increasing longevity, prevention of future morbidity, or making patients feel better. To achieve the last purpose, it is considered that HRQoL should be evaluated. Moreover, there are several reports demonstrating only weak to moderate correlations between physiological variables and HRQoL in patients with asthma. This is another reason for the importance of direct evaluation of HRQoL in conjunction with the conventional clinical indices. Pharmacological interventions based on guidelines seem to improve not only pulmonary function but also HRQoL in patients with asthma. However, all managements do not necessarily improve HRQoL, therefore assessing HRQoL is strongly recommended in clinical trials. However, the benefit of including HRQoL in evaluation of patients management is still unknown. It is valid that evaluation of HRQoL in clinical practice can both reveal patients problems that were not spontaneously identified by patients themselves and allow physicians focus on specific problems. Until such data are available, the benefit of assessing HRQoL in clinical practice will remain uncertain. Although conducting more clinical trials that prove efficacy in clinical practice is required, consideration of HRQoL in patients has recently been recognized as an important topic in the asthma field. It can be said that outcomes in health care for asthma will shift from the physiological aspect to humanistic aspect.

KEY WORDS
asthma, health status, health-related, instrument, quality of life

INTRODUCTION
Health-related quality of life (HRQoL), in other words health status, is become an emerging concept in this decade.1 Various questionnaires have been developed in many areas to evaluate HRQoL, especially in chronic diseases. However, measuring HRQoL is not prevalent in most interventional clinical research and clinical practice, especially not in Japan. In this respect, the concept of measuring HRQoL in asthma seems to be leading the field. Recently, many clinical researchers and general practitioners are recognizing the importance of HRQoL as an outcome of evaluating asthma. In this review article, the basic concept of HRQoL, a variety of measurement instruments, the characteristics of HRQoL in adult patients with asthma, reported impacts of treatments of asthma on HRQoL, and estimated future direction of measuring HRQoL in asthma will be discussed.

THE CONCEPT OF HEALTH-RELATED QUALITY OF LIFE
Quality of life involves all valued aspects of life. There are several perspectives of life that are not generally considered as directly related to health, including income, freedom, and quality of the environment. Although they may affect health, these aspects are usually distant from health or medical concerns. The HRQoL is the concept of quality of life, which includes aspects of life directly associated with health. HRQoL usually includes symptoms, moods, functional activities, however, it excludes such variables as income, freedom, and environment.1 When treating patients, clinicians focus on HRQoL, although al-
most all aspects of life can be health related. HRQoL, health status, and functional status are often used interchangeably to refer to similar concepts.

It has been proposed that treatments for patients are offered for the purpose of increasing longevity, offering prevention of morbidity, or simply for making patients feel better. Although the first two of these three endpoints are relatively easy to measure, the last one is somewhat difficult. Therefore, clinicians have been substituting physiological variables for measuring the third. However, the importance of direct measurement of patients’ feelings directly related to health has been noted recently, so the concept of HRQoL was developed.2

Measuring HRQoL is important in chronic diseases because physiological variables, such as those from laboratory tests and pulmonary function tests, usually have poor correlations with functional capacity and well-being, the areas in which patients are most interested.1 Another reason for the importance of measuring HRQoL is the commonly observed phenomena that two patients with the same clinical and physiological variables often have different responses. For example, some patients may continue to work without major depression, others may quit their jobs and develop depressive symptoms.1

**VARIETY OF MEASUREMENT INSTRUMENTS**

HRQoL is usually evaluated using several measurement instruments. More common instruments are questionnaires consisting of multiple items or questions. There are some instruments that evaluate HRQoL using a global scale and there are others using a visual analogue scale. There are also several modes of administration of the instruments such as interviews, telephone calls, self-interviews, and surrogate respondents.1 However, the most important thing when evaluating HRQoL for patients is to use instruments that are proven to be valid, reliable, and responsive.1 The use of an instrument which does not have proven validity should be avoided.

There are two major types of instruments used to evaluate HRQoL in chronic diseases, generic and disease specific instruments (Table 1). Generic instruments attempt to measure all the important aspects of HRQoL. The advantages of generic instruments include the capacity to evaluate a variety of diseases and the flexibility to be used in any population. Furthermore, comparisons of HRQoL in many underlying conditions can be made. However, unresponsiveness to changes in specific condition is a disadvantage.

The second type of instrument is the disease specific instrument. This instrument involves only important aspects of HRQoL in specific diseases. The advantage of using specific instruments is superiority in responsiveness and discriminating ability.

Recently, HRQoL measures have been frequently chosen as primary and secondary outcomes in clinical trials. Generic and specific instruments are used individually and in combination. Treatments that are effective for physiological variables and mortality do not necessarily have beneficial effects on HRQoL, however evaluation of HRQoL in clinical trial is considered to be important.

**CHARACTERISTICS OF HRQOL IN ADULT PATIENTS WITH ASTHMA**

Patients with asthma are bothered by the symptoms themselves, such as shortness of breath, chest tightness, wheeze, and cough, and clinicians usually focus on these asthma symptoms. However, in addition, many patients have problems other than asthma symptoms, including disability in physical and daily activities, handicaps in work, and mental problems. Therefore, HRQoL must be measured with conventional indices to obtain a complete picture of a patient’s health.11

There have been some reports that revealed the characteristics of HRQoL in asthma.6,8,10,12,14 Only weak to moderate correlation between clinical physiological measures and HRQoL were demonstrated.15,16 This is one of the reasons for importance of obtaining HRQoL for patients in conjunction with the conventional clinical indices. However, correlation between changes in physiological measures and changes in HRQoL scores assessed with the Asthma Quality of Life Questionnaire (AQLQ) are reportedly somewhat stronger.6,17 Therefore, HRQoL may reflect changes in asthma control more than physiological measures at one point. Although correlation between physiologic measures and HRQoL are weak to moderate, controlling peak expiratory flow (PEF) over 80% of predicted value is significantly associated with better HRQoL.18

As for symptoms, there have been several studies demonstrating relationships with HRQoL. Relatively strong relationships were found between overall and

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**Table 1** Examples of generic and asthma specific instruments for health-related quality of life

<table>
<thead>
<tr>
<th>Generic instruments</th>
<th>Asthma specific instruments</th>
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<tbody>
<tr>
<td>Sickness Impact Profile (SIP)3</td>
<td>Asthma Quality of Life Questionnaire (AQLQ)6,7</td>
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<tr>
<td>Short-form 36 (SF-36)4</td>
<td>Living with Asthma Questionnaire (LWAQ)8</td>
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<tr>
<td>EuroQOL5</td>
<td>St. George’s Respiratory Questionnaire (SGRQ)9</td>
</tr>
<tr>
<td>Airways Questionnaire 20 (AQ20)10</td>
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symptom score for the AQLQ and both morning and daytime symptoms, however, there were only moderate relationships between scores for other domains and morning and daytime symptom score. In an analysis using a generic instrument, the Sickness Impact Profile (SIP), significant correlations between nighttime and daytime symptoms and overall HRQoL score, as well as limited but significant association between those symptoms and scores for all other domains were observed. Although both HRQoL scores assessed with generic and disease-specific instruments were significantly influenced by symptoms, the latter is reported to be better for discriminating patients with asthma. In addition to symptoms, a number of aggregate measures have been used to define severity in patients with asthma. An inverse relationship has been found between HRQoL and severity using these aggregate indicators. Aggregate scales seem to be more accurate predictors for HRQoL than single indicators of severity in patients with asthma. Strong relationships have been found between aggregate severity scales and score for specific instruments. Symptoms evaluated with visual analogue scale (VAS) have been reported to be strongly correlated with HRQoL assessed with the AQLQ. In another report, a significant correlation was found between the number of problems associated with asthma control and HRQoL assessed with the short-form 36 (SF-36), the AQLQ, and the St. George’s Respiratory Questionnaire (SGRQ).

It has been reported that clinical predictors of HRQoL for patients with asthma depend on the severity of the disease. Although intensity of shortness of breath and rescue β₂-agonist use are reportedly independent predictors of HRQoL for patients with mild asthma, only intensity of shortness of breath independently predicts HRQoL for moderate to severe asthma.

Although several factors can influence HRQoL for patients with asthma, there have been inconsistent reports about age. It is true that HRQoL is also impaired in elderly patients, however, some studies demonstrated that older adults have poorer HRQoL and others indicated that they are less distressed by their asthma than are younger adults. In terms of gender, although several studies reported no gender difference in HRQoL in patients with asthma, others have demonstrated significant gender effects. According to those reports, men with asthma generally have significantly better HRQoL. There are also some reports that revealed a correlation between higher education and better HRQoL for patients with asthma.

In comparison of generic and disease-specific HRQoL instruments, it is reported that scores assessed with the SF-36 and the AQLQ were highly correlated, and that both instruments had strong discriminative properties and were able to characterize patients with moderate asthma. Other reports revealed that the changes in the scores assessed with the SGRQ, a disease-specific instrument, are slightly better than those assessed with the 15D, a generic instrument, with the changes in clinical variables. In comparing the two disease-specific instruments, the SGRQ and the AQLQ, each measure is comparable to another, with the exception of the SGRQ symptoms score which shows less responsiveness. The AQLQ is also reported to be more responsive than the Living with Asthma Questionnaire (LWAQ) and Airways Questionnaire 20 (AQ20).

IMPACTS OF TREATMENTS FORASTHMA ON HRQOL

When considering treatment effects on HRQoL, there are two methods to test the effects. One is an evaluation observing statistically significant improvements in comparison to placebo or baseline values. Another is a minimal clinically important difference (MCID), which is the minimal difference patients perceive as meaningful. For example, a MCID on the AQLQ is determined as 0.5 and that on the SGRQ is 4.6 Statistically significant change in HRQoL is not necessarily a clinically meaningful change. Therefore, presentation of clinical trial results in this manner is more meaningful and easier to interpret.

When evaluating treatment effects on HRQoL, difference of instruments used should be considered. Generic instruments tend to be less sensitive than disease-specific instruments. Disease-specific instruments, heavily weighed in the symptom domain of HRQoL, will be more sensitive to interventions targeted on symptom improvement. Therefore, physicians should be aware of the characteristics of the instruments used.

There have been sizable reports that evaluate the treatment effects on HRQoL in patients with asthma. It is reasonable to expect that treatments effective for symptoms and pulmonary function will also produce improvements in HRQoL. Inhaled corticosteroid (ICS) plays a key role in the treatment of patients with asthma. ICSs including budesonide, fluticasone, and beclomethasone generally control asthma and improve HRQoL in many clinical studies. Long-acting β₂-agonists (LABA) including salmeterol and formoterol also improve HRQoL in patients with asthma when added to baseline use of inhaled corticosteroids. Leukotriene-receptor antagonist, such as montelukast, zafirlukast, and zileuton, have favorable effects on HRQoL. The difference in HRQoL between patients who use β₂-agonists on a PRN basis and patients who use it regularly is not inconsistent. Some other pharmacological interventions, such as nedocromil sodium and omalizumab, an anti-IgE an-
tobody,62,63 were also proven to improve HRQoL in patients with asthma. Patch formulation of tulobuterol recently available in Japan, which releases its active ingredients in a sustained fashion,64 can improve HRQoL in patients with asthma, however, there is still no direct evidence. In general, guideline-based asthma treatments improve HRQoL.65 However, physicians must be aware that most medications can improve physiological variables such as pulmonary function, but sometimes they can worsen HRQoL. These kind of adverse effects on HRQoL are reported in patients with chronic obstructive pulmonary disease.66

In terms of education, reported results are inconsistent.67-69 Some reports showed efficacy in patients with moderate-to-severe asthma.68,69 Pharmacist advise is also effective for improving HRQoL in patients with asthma.70 However, in these new fields, some further studies are needed to confirm these effects.

**FUTURE DIRECTION OF MEASURING HRQOL IN ASTHMA**

Substantial numbers of clinical trials that include HRQoL as one of the outcomes have been reported in this decade. However, whether including evaluation of HRQoL benefits patients management is still unknown. It is valid that evaluation of HRQoL in clinical practice can reveal patients’ problems that are not spontaneously identified by patients and let physicians more closely focus on problems. It is interesting to compare HRQoL-based treatment with guideline-based treatment for testing the efficacy of evaluating HRQoL in patients with asthma. Until such data are available, the benefit of using these HRQoL questionnaires in clinical practice is uncertain.

Predicting value of HRQoL in patients with asthma is another issue. Although self-reported lifestyle restriction from asthma can predict the frequency of visiting the emergency room,71 it is unknown whether HRQoL predicts the frequency of emergency room visits and admissions. Furthermore, changes in HRQoL during longer periods should be investigated. Recently, an instrument to evaluate HRQoL during an acute asthma exacerbation was developed.72 Elucidating meaning and benefits of assessing HRQoL in the acute phase is a new issue.

Although conducting clinical trials that demonstrate their efficacy in clinical practice is required, consideration of patients’ HRQoL has been recognized as more important in the asthma field. It can be said that outcomes in health care for asthma are shifting from the physiological aspect to the humanistic aspect.73

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