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Original article

Development of a questionnaire to evaluate asthma control in Japanese asthma patients

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Abbreviations:

ACT, asthma control test; ACQ, asthma control questionnaire; AIRJ, asthma insights and reality in Japan; AQLQ, asthma quality of life questionnaire; COPD, chronic obstructive pulmonary disease; ICC, intra-class correlation coefficients; JACS, Japan asthma control survey; PEF, peak expiratory flow; QOL, quality of life; VAS, visual analogue scale

ABSTRACT

Background: The asthma control questionnaires used in Japan are Japanese translations of those developed outside Japan, and have some limitations; a questionnaire designed to optimally evaluate asthma control levels for Japanese may be necessary. The present study was conducted to validate the Japan Asthma Control Survey (JACS) questionnaire in Japanese asthma patients.

Methods: A total of 226 adult patients with mild to severe persistent asthma were enrolled and responded to the JACS questionnaire, asthma control questionnaire (ACQ), and Mini asthma quality of life questionnaire (Mini AQLQ) at Weeks 0 and 4. The reliability, validity, and sensitivity/responsiveness of the JACS questionnaire were evaluated.

Results: The intra-class correlation coefficients (ICCs) were within the range of 0.55–0.75 for all JACS scores, indicating moderate/substantial reproducibility. For internal consistency, Cronbach's alpha coefficients ranged from 0.76 to 0.92 in total and subscale scores, which were greater than the lower limit of internal consistency. As for factor validity, the cumulative contribution ratio of four main factors was 0.66. For criterion-related validity, the correlation coefficients between the JACS total score and ACQ5, ACQ6, and Mini AQLQ scores were –0.78, –0.78, and 0.77, respectively, showing a significant correlation ($p < 0.0001$).

Conclusions: The JACS questionnaire was validated in terms of reliability and validity. It will be necessary to evaluate the therapeutic efficacy measured by the JACS questionnaire and calculate cutoff values for the asthma control status in a higher number of patients.

Clinical Trial registration: UMIN000016589

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Introduction

Bronchial asthma is a respiratory disease characterized by clinical symptoms such as recurring cough, wheezing, and breathing difficulty, which may have varying degrees of impact on the patients' lives, and this impact is more pronounced among people with severe or poorly controlled asthma.

In the treatment of asthma, the establishment of management methods through the introduction of inhaled corticosteroids and the refinement of the Asthma Prevention and Management

Guideline has dramatically improved long-term control of asthma,¹ enabling patients live their daily lives as healthy people do. However, the findings of Asthma Insights and Reality in Japan (AIRJ) in 2011, a fact-finding survey of asthma patients in Japan, showed that the goals proposed in the guidelines for asthma had not been fully achieved due to poor adherence.² Furthermore, pathological phenotypes based on cluster analysis have recently been identified to obtain an objective view of a variety of clinical presentations of asthma,³ but a treatment choice according to each phenotype has not yet been established and recent population survey conducted by the Ministry of Health, Labour and Welfare in 2015 reported that 1511 people had died of asthma,⁴ highlighting that the goal of “no death associated with asthma” had not been achieved. The goal of asthma treatment to accomplish is no death by asthma. At present, although treatment for severe asthma has been conducted by

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antibody-targeted medicines, the use of these medicines will incur the escalation of medical costs.

Poor asthma control, as exemplified by unscheduled hospital visits due to persistent symptoms or exacerbation of asthma, impairs the quality of life (QOL) of asthma patients by adversely affecting daily living, limiting activities, and even increasing psychological burden.

More than one questionnaire has been developed to evaluate QOL and control level for asthma patients, and the representative questionnaires had been the Asthma Control Questionnaire (ACQ)^{5,6} and Asthma Control Test (ACT),⁷ both of which had been translated into Japanese. These questionnaires have been conveniently used as the most common measures for evaluating asthma control status in daily clinical practice. However, the questionnaires used in Japan are Japanese translations of those developed outside Japan, and have some limitations, including a failure to verify whether the questionnaire is optimum for Japanese, and evaluations of asthma control based exclusively on symptoms. Also, based on these questionnaires alone it is possible that levels of partially uncontrolled asthma had not been detected. Therefore, a questionnaire designed to optimally evaluate asthma control status in Japanese, with their physical functions and psychology taken into account, may be necessary to contribute to the accomplishment of “no death by asthma.”

As a part of the development of a new questionnaire “Japan Asthma Control Survey (JACS) questionnaire”, an original tool for measuring asthma control levels in Japanese asthma patients, the present study was conducted to validate the JACS questionnaire.

Methods

Questionnaire generation process

Item selection

Items to be included in the questionnaire were mainly extracted based on expert opinions. Redundancy was avoided by combining multiple items into one, and the number of items was reduced from 25 to 16 by several expert meetings. The first questionnaire was produced for pilot testing.

Pilot studies 1 and 2

To evaluate the reliability and validity of the prototype questionnaires, pilot studies 1 and 2 were performed. A total of 30 outpatients with asthma were enrolled for each pilot study between February and July 2015. Inclusion/exclusion criteria and patient background for each pilot study are shown in [Supplementary Table 1, 2](#). All patients completed three questionnaires in Japanese (JACS, ACQ, and Mini Asthma Quality of Life Questionnaire [Mini AQLQ]), and the reliability and validity of the JACS questionnaire were evaluated based on factor analysis, internal consistency reliability, and correlation between JACS and ACQ, and Mini AQLQ.

In pilot study 1, a prototype questionnaire with 16 items was evaluated. Based on factor analysis of the data, the questionnaire was revised to 15 questionnaire items, and these were classified into four subscales (symptom: 4 items, emotion: 4 items, treatment: 2 items, activity: 5 items). This revised version with 15 items was used in pilot study 2. The total score and four subscales were found to be reliable, with Cronbach's alpha coefficients of 0.92 for the total score, and 0.85, 0.81, 0.95, and 0.90 for each subscale. In addition, validity was established based on correlation between the JACS and ACQ ($r = -0.61$, $p = 0.0003$) as well as JACS and Mini AQLQ ($r = 0.80$, $p < 0.0001$, [Supplementary Fig. 1, 2](#)). In this pilot study, reliability and validity of the preliminary JACS questionnaire were suggested. In the present validation study, the 15-item

questionnaire based on the visual analogue scale (VAS) ([Table 1](#)), which was used in pilot study 2, was used as the JACS questionnaire. Original JACS questionnaire is shown in [Supplementary Methods](#).

Validation study

Study design

This study was a multi-center, prospective, observational study. [Figure 1](#) shows the study design and patient enrollment.

Patients and methods

Adult patients with mild to severe persistent bronchial asthma who visited the study centers on an outpatient basis between October 2015 and February 2016 were included in the study if they were in Step 2 or higher of asthma treatment as defined in the Asthma Prevention and Management Guideline 2015.⁸ The following patients were excluded from the study: patients with evident chronic obstructive pulmonary disease (COPD); patients with respiratory infection; patients with diseases that may affect their responses to the questionnaire; and patients who were judged unsuitable for enrollment in the study by the investigator. Patients enrolled in the study responded to the JACS questionnaire, ACQ, and Mini AQLQ at Weeks 0 and 4. We used ACQ and Mini AQLQ in Japanese. The asthma control status was assessed by respiratory specialists in accordance with the Japanese asthma prevention and management guidelines (JGL 2015).⁸

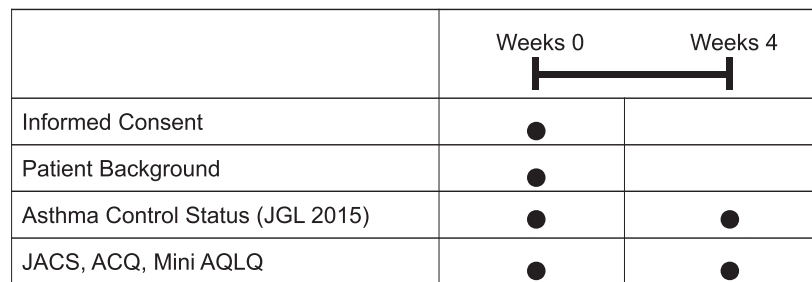
Ethics

Prior to participation in the pilot studies and this validation study, all patients were fully informed of this study and gave

Table 1
JACS questionnaire.

No.	Subscale	Questionnaire
1	Symptom	Did you experience breathlessness or a hard time breathing because of asthma?
2	Symptom	Did you experience wheezing or crowing when you breathe?
3	Activity	Did you suffer from coughing?
4	Symptom	Did you have symptoms (such as wheezing, crowing, short breath, chest discomfort or chest pain) during bedtime or at the time of awakening because of asthma?
5	Emotion	Did you become anxious because of night sleep disturbances caused by asthma?
6	Activity	Did you stay indoors because of weather or to avoid polluted air, pollen dust, or yellow sand dust?
7	Emotion	Do you feel intense physical activities (such as quick action, exercise, or running) are difficult because of asthma?
8	Activity	Did you have activity limitations at work or at home because of asthma?
9	Activity	Was your daily life disturbed by persisting symptoms despite the current asthma treatment?
10	Activity	Did dust, cigarette smoke, cold air, exhaust fumes, or drinking evoke asthma symptoms?
11	Emotion	Have you been frustrated or disappointed at things going wrong because of asthma?
12	Emotion	Do you feel your asthma is not socially understood at places such as work-site or school?
13	Treatment	Do you think you take medicine regularly as instructed every day?
14	Treatment	Do you think you inhale medicine in a correct way as instructed every day?
15	Symptom	How many times a day did you inhale the drug to dilate your bronchial tubes when you felt difficulty in breathing?

These questionnaires were translated by authors and specialists of this area in English from Japanese original version.



< Inclusion Criteria >

- (1) Patients with asthma (mild persistent - severe persistent)
- (2) Age ≥ 20 years
- (3) Patients in Step 2-4 defined by the Asthma Prevention and Management Guideline 2015
- (4) Patients who voluntarily provide written informed consent form after having been fully informed about and understand the requirements of study participation
- (5) Patients who have no problem of communication

< Exclusion Criteria >

- (1) Patients with apparent chronic obstructive pulmonary disease (COPD)
- (2) Patients with respiratory infection
- (3) Patients with diseases that may affect answers to the questionnaire
- (4) Patients who were judged unsuitable for enrollment in the study by the investigator

Fig. 1. Study design and patient enrollment.

written consent based on their own free will. The protocol of the pilot studies and this validation study was approved by the Ethics Committee of Adachi Kyosai Hospital (approval number 2142), and the study was conducted in accordance with the ethical and scientific principles of the Declaration of Helsinki (revised in 2013), Japanese Ethical Guidelines for Clinical Studies (amended on 22 December 2014), and relevant laws. Patient anonymity was preserved using methods approved by the Ethics Committee.

Outcomes

For the JACS questionnaire, reliability (reproducibility and internal consistency), validity (factor validity and criterion-related validity), sensitivity/responsiveness were investigated.

Statistical analysis

For the JACS questionnaire, a response to each question was measured on the VAS in units of centimeters, and the distance was used as the score for the question (0–9.0 cm). In addition, the questions were classified into four subscales, and mean values were calculated for subscale and total scores.

For patient background characteristics, question and subscale scores in the JACS questionnaire, ACQ (ACQ5 and ACQ6), and Mini AQLQ at each visit, and physician-assessed asthma control status, the mean and standard deviation were calculated for numerical and ordinal variables. Frequency was calculated for ordinal and nominal variables. In addition, descriptive statistics were calculated by control status (from well-controlled to well-controlled, from well-controlled to not well-controlled, from not well-controlled to well-controlled, and from not well-controlled to not well-controlled; from Week 0 to Week 4, respectively).

Reliability was assessed in patients with no change in the physician-assessed control status. For reproducibility, intra-class correlation coefficients (ICCs) were calculated for question and subscale scores, with reproducibility assessed as fair for 0.21–0.40, moderate for 0.41–0.60, substantial for 0.61–0.80, and almost perfect for 0.81–1.00. For internal consistency, Cronbach's alpha coefficients were calculated for subscale scores at Week 0, with an alpha of 0.7 or greater assessed as internally consistent.

For factor validity, factor analysis was performed to determine the factor structure (Week 0 of the validation study). Varimax rotation was used to determine the factor loading matrix and the cumulative contribution ratio. The initial value for communality was set by the principal factor method using the squared multiple correlation coefficient. A scree plot was used with an eigenvalue of 1 or greater to determine the number of factors. For criterion-related validity, correlation coefficients (Spearman rank correlation coefficients) between JACS scores and ACQ (ACQ5 and ACQ6) scores, and between JACS scores and Mini AQLQ scores were calculated (Week 0 of the validation study). Scatter plots of

Table 2
Patient background.

No. of patients	226		
Gender	Male	79	(35.0%)
	Female	147	(65.0%)
Age	53 $\pm$ 15 (years)		
Disease type	Atopic	114	(50.4%)
	Non-atopic	85	(37.6%)
	Combined	27	(12.0%)
Severity	Mild persistent	81	(35.8%)
	Moderate persistent	101	(44.7%)
	Severe persistent	44	(19.5%)
Treatment step	Step 2	97	(42.9%)
	Step 3	99	(43.8%)
	Step 4	30	(13.3%)
Complications	Yes	137	(60.6%)
(Allergic disease)	No	89	(39.4%)
Smoking history	Current smoker	18	(8.0%)
	Ex-smoker/Never smoker	208	(92.0%)
Asthma control	Well-controlled	131	(58.0%)
	Not well-controlled	95	(42.0%)
Asthma medication	ICS	27	(12.0%)
	ICS/LABA	201	(88.9%)
	LABA	2	(0.9%)
	LTRA	107	(47.4%)
	Theophylline	33	(14.6%)
	Anticholinergic	12	(5.3%)
	Oral steroid	16	(7.1%)
	Others	43	(19.0%)

correlation were presented with the relevant regression line for total scores.

For sensitivity, descriptive statistics were calculated for JACS scores in patients with not well-controlled and those with well-controlled as assessed by the physician at Week 0, and were compared between the two patient groups by Wilcoxon rank sum test.

For responsiveness, JACS scores were compared between Week 0 and Week 4 by Wilcoxon signed rank sum test in each of the following two patient groups: patients with well-controlled at Week 0 and not well-controlled at Week 4 as assessed by the physician, and those with not well-controlled at Week 0 and well-controlled at Week 4.

Patients enrolled in the study from whom the questionnaires were collected on at least one occasion were included in the analyses. Statistical analyses were performed using SAS for Windows, version 9.3 or later.

Results

Patient characteristics

A total of 226 asthma patients were enrolled at 20 study centers, and 222 patients completed the study. Patient background characteristics are shown in Table 2.

The physician-assessed asthma control status did not change from Week 0 to Week 4 in 174 patients (from well-controlled to well-controlled: 116 patients, from not well-controlled to not well-controlled: 58 patients) and changed in 48 patients (from well-controlled to not well-controlled: 14 patients, from not well-controlled to well-controlled: 34 patients). Among patients with data only at Week 0, the control status was well-controlled in 1 patient and not well-controlled in 3 patients.

Change in JACS scores

For the JACS questionnaire, changes in question scores over time are shown in Figure 2. For all questions, scores tended to increase from Week 0 to Week 4.

Table 3
Reliability for each subscale.

		ICC (n = 172)	Cronbach's alpha (n = 226)
Total score		0.75	0.92
Subscale score	Symptom	0.75	0.89
	Emotion	0.73	0.76
	Treatment	0.55	0.87
	Activity	0.74	0.82

ICC, intra-class correlation coefficient.

Table 4
Factor analysis.

Question	Subscale	Factor 1	Factor 2	Factor 3	Factor 4
1	Symptom	0.58	0.50	0.39	0.11
2		0.52	0.44	0.44	0.03
4		0.38	0.83	0.25	0.12
15		0.46	0.44	0.34	−0.03
5	Emotion	0.24	0.73	0.45	0.08
7		0.26	0.14	0.65	0.01
11		0.66	0.35	0.34	−0.05
12		0.62	0.16	0.26	0.05
13	Treatment	0.05	0.04	−0.03	0.87
14		0.04	0.12	0.04	0.89
3	Activity	0.48	0.57	0.09	0.19
6		0.22	0.24	0.63	0.01
8		0.50	0.27	0.57	−0.02
9		0.51	0.42	0.45	0.02
10		0.57	0.35	0.25	0.20
Cumulative contribution ratio		0.20	0.39	0.55	0.66

Gray columns indicate factor loadings for each subscale.

Reliability (reproducibility and internal consistency)

The ICCs for the JACS total and subscale scores are shown in Table 3. In patients with no change in the control status from Week 0 to Week 4, the ICCs were within the range of 0.55–0.75 for all JACS subscale and total scores, indicating moderate (0.41–0.60) or substantial (0.61–0.80) reproducibility. For internal consistency, Cronbach's alpha coefficients ranged from 0.76 to 0.92 (Table 3), which were greater than 0.7, the lower limit of internal consistency.

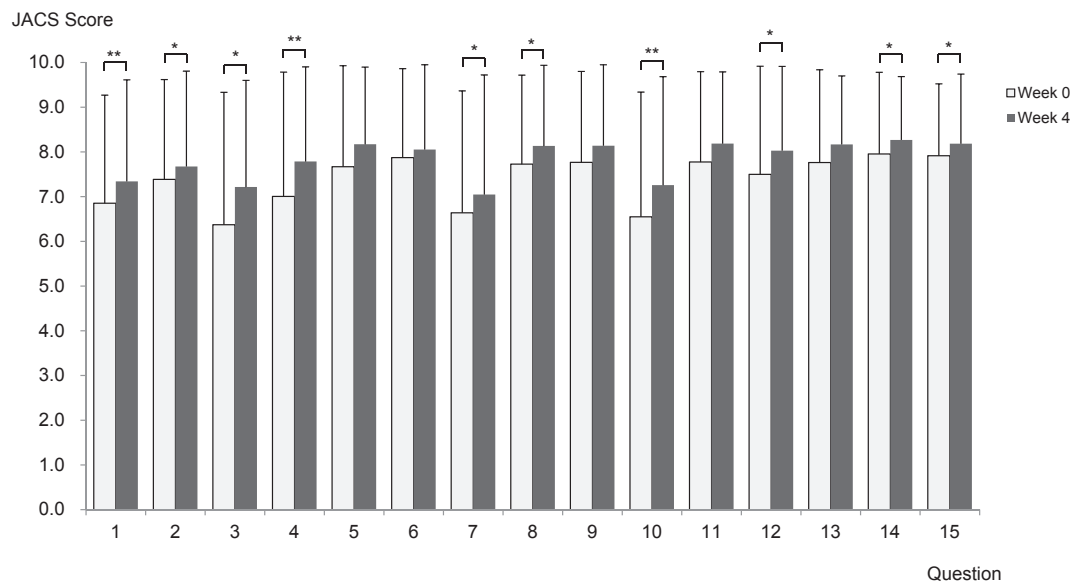


Fig. 2. JACS score for each question. Wilcoxon rank sum test (* $p < 0.05$, ** $p < 0.01$).

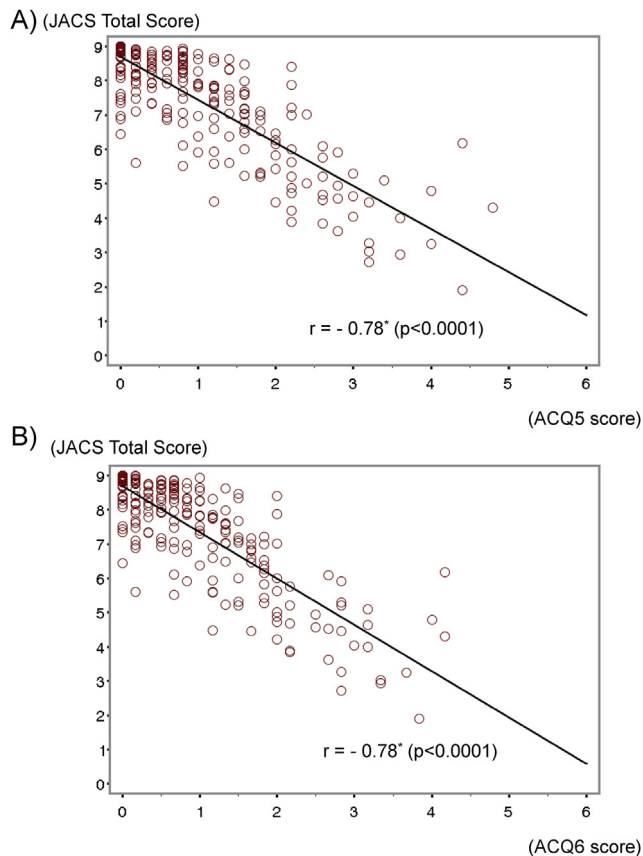


Fig. 3. Correlation between JACS and ACQ. **A)** ACQ5, **B)** ACQ6. *Spearman rank correlation coefficient.

Validity (factor validity and criterion-related validity)

For factor validity assessed by factor analysis, factor loadings after varimax rotation are shown in Table 4. Four subscales were detected by factor analysis and the cumulative contribution ratio of four main factors was 0.66.

For criterion-related validity, the correlation coefficients between the JACS total score and ACQ5, ACQ6, and Mini AQLQ scores were -0.78 , -0.78 , and 0.77 , respectively, showing that the JACS total score was significantly correlated with all these scores ($p < 0.0001$) (Fig. 3, 4).

Sensitivity and responsiveness

In the assessment of sensitivity, the total score was 8.1 ± 1.0 in patients with well-controlled ($n = 131$) and 6.4 ± 1.7 in patients with not well-controlled ($n = 95$) at Week 0, with a significant difference between the two patient groups ($p < 0.0001$).

Table 5

Sensitivity and responsiveness.

Sensitivity	Well controlled ($n = 131$) 8.1 ± 1.0	Not well controlled ($n = 95$) 6.4 ± 1.7	p value
Responsiveness; Asthma control			
Well controlled $\rightarrow$ Not well controlled ($n = 14$)	8.0 ± 0.9	7.8 ± 1.0	0.3258
Not well controlled $\rightarrow$ Well controlled ($n = 34$)	6.7 ± 1.3	8.1 ± 1.0	<0.0001

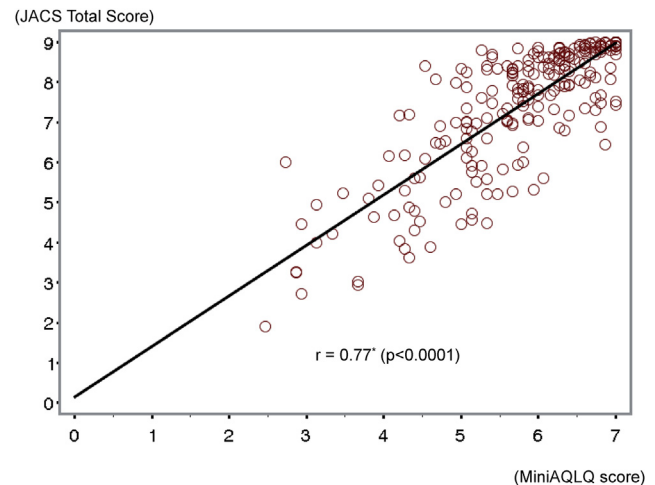


Fig. 4. Correlation between JACS and Mini AQLQ. *Spearman rank correlation coefficient.

In the assessment of responsiveness, the total score significantly increased from 6.7 ± 1.3 to 8.1 ± 1.0 in patients with not well-controlled at Week 0 and well-controlled at Week 4 ($n = 34$) ($p < 0.0001$). The total score tended to decrease from 8.0 ± 0.9 to 7.8 ± 1.0 ($p = 0.33$) in patients with well-controlled at Week 0 and not well-controlled at Week 4 ($n = 14$), although the number of these patients was small (Table 5).

Discussion

Conventional questionnaires, including the ACQ and ACT, which have been translated into many languages and widely used worldwide, have the advantage that a great deal of data has been accumulated and asthma control can be compared among countries. In addition, the ACQ and ACT, consisting of as few as five to seven multiple-choice questions, are highly convenient in terms of administration and interpretation of the results.

The present study was conducted as part of the development of a new JACS questionnaire, an original tool for evaluating the asthma control status. Some of the characteristics and superiority of the JACS questionnaire can be described as follows: Firstly, the JACS questionnaire is a tool originally developed for measuring asthma control levels in Japanese asthma patients, whereas the ACQ and ACT were developed outside Japan. For example, a question regarding the influence of yellow sand dust on patient behavior is included in the JACS questionnaire, which is a problem specific to the Japanese and East Asian asthma patients. Secondly, the number of questions is 15, which is considered to be the maximum volume enabling clinical use, and covers not only asthma symptoms, but also takes into account 3 other subscales of emotion, treatment, and

activity which are not employed in the conventional questionnaires, such as the ACQ and ACT. Among the JACS questions, in addition to asthma symptoms, several questions related to patient feelings about the symptoms are asked. Question No. 5, for example, is 'Did you become anxious because of night sleep disturbances caused by asthma?' instead of 'Did you have night sleep disturbances caused by asthma?', and this question is included in the subscale of emotion. These subscales are considered helpful both for physicians and patients to clearly recognize problems to be solved in the control of asthma. Thirdly, the VAS question style, which was developed by Hayes MH,⁹ was selected. VAS appears to be a reliable tool in the assessment of patients' perception of asthma symptoms in the real life study.¹⁰ The validity of VAS in the measurement of asthma symptoms was previously documented in both experimental and clinical studies.^{11–13} In the present study as well, VAS is expected to be useful for capturing more subtle changes through non-stepwise evaluations.¹⁴ Finally, in many cases it is necessary to obtain permission from the copyright holder when we would like to use a questionnaire, but anyone can use the JACS questionnaire without permission in cases of academic research.

The four subscales were admitted in this analysis. Factor 1, 2, 3 and 4 shows "Symptom", "Activity", "Emotion" and "Treatment" respectively. The procedure to calculate the subscales was in reference to the method of SF-36, widely used in the evaluation of HRQOL. In the validation of the Japanese version of SF-36, the eight domains were not clearly divided up "physical" and "mental" components. For example, "Role emotional" contributed to physical component but "Role emotional" was classified to mental component.¹⁵ Relationship between subscale and domain of JACS had an equally poor loading as SF-36. In the present study, we classified the questions into factors taking into account the fitting of reliability and suitability of question content for each subscale. For example, if Question 4 belongs to Factor 2, the Cronbach's alpha and ICC of Factor 1 and 2 are similar to before the change, so we decided that the current classification was suitable as subscale. Accordingly, this loading factor analysis was appropriate and the cumulative contribution ratio was also satisfied.

In addition, Jia CE *et al.* reported significant differences between ACT and ACQ in the assessment of controlled and not well-controlled asthma. Meanwhile, neither the ACT nor ACQ are useful for assessing uncontrolled asthma, because the ACT has poor accuracy, and the cutoff point for the ACQ has not yet been established.¹⁶ Furthermore, the ACQ has two cutoff points that best discriminate "well-controlled (≤ 0.75)" and "not well-controlled (≥ 1.5)" asthma,¹⁷ which often makes it difficult to evaluate the asthma control status when the ACQ score lies between the two cutoff points.¹⁸ On the other hand, relatively good correlation between JACS and ACQ score was observed. When the cutoff point of JACS is calculated in the future, the aspect of equivalence to the ACQ cutoff point between $0.75 <$ and < 1.5 will remain as a problem to consider. The aim of the present study was to validate the JACS questionnaire. In the future, we plan to conduct further study to examine the significance of the JACS questionnaire, including obtainment of the cutoff scores for well controlled, not well-controlled, and uncontrolled asthma. We conducted a validation study of JACS questionnaire in Japanese, and expect that JACS could be used in the clinical research of patients with asthma.

Limitations

The present study validated the JACS questionnaire only in Japanese asthma patients. In order to make it an international index of the asthma control status, validation studies in various languages and races are required as is the case with the ACQ and ACT.

Similar to the ACQ, for which a validation study was conducted in 50 patients, and the ACT, for which a validation study was conducted in 471 patients, the JACS questionnaire was validated in terms of reliability and validity, but failed to calculate cutoff values for the control status because of insufficient number of samples, requiring further clinical studies. In addition, since 131 (58%) of the 226 patients studied already had well-controlled at the start of the study, it is necessary to increase the number of patients with not well-controlled in future studies. Of 222 patients evaluated for the control status at both the start and end of the study, moreover, well-controlled was maintained in 116 patients, and not well-controlled was maintained in 58 patients, resulting in a limited availability of patients in whom changes in the control status might be captured by the JACS questionnaire.

Since scores improved from the start to the end of the study for all questions as a result of response shift, it may be necessary to consider adjusting scores.

Conclusions

The JACS questionnaire was validated in terms of reliability and validity. However, because many of the patients had well-controlled asthma, there were not enough cases to calculate the cutoff score. As the cutoff score of ACQ was calculated in another large-scale study after being validated, it is necessary for the development of the JACS questionnaire to not only calculate the cutoff score, but also to examine responsiveness to treatment intervention in a higher number of patients.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.alit.2017.06.013>.

Conflict of interest

YT received honoraria from AstraZeneca, Kyorin Pharmaceutical, Astellas Pharma, Teijin Pharma, GlaxoSmithKline and Ono Pharmaceutical, grant/research funding from Astellas Pharma and Kyorin Pharmaceutical. SH received honoraria from Astellas Pharma, Novartis Pharma, AstraZeneca, Boehringer Ingelheim, Kyorin Pharmaceutical, Teijin Pharma, Sanofi, Torii Pharmaceutical and MSD. HT received honoraria from Kyorin Pharmaceutical, Boehringer Ingelheim, AstraZeneca and Astellas Pharma.

Authors' contributions

YT had full access to all of the data in this study and takes complete responsibility for the integrity of data and the accuracy of the data analysis. All authors designed the study, contributed to data collection, and interpretation of the results. YT wrote the manuscript and all authors read and approved the final manuscript. The data management and statistical analysis were conducted and supported by CRO (Contract Research Organization).

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