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Original Article

Examination of the cut-off values for a questionnaire used to evaluate asthma control in Japanese asthma patients

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ACQ, asthma control questionnaire;

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asthma control survey; PEF, peak expiratory

flow; QOL, quality of life; ROC, receiver

operating characteristic

ABSTRACT

Background: The Japan Asthma Control Survey (JACS) questionnaire, developed as a tool for measuring asthma control levels in Japanese asthma patients, was previously tested for its reliability and validity. However, many of the patients enrolled in the original validation study had mild asthma; thus a re-evaluation including severe cases was required to calculate more reliable cut-off values.

Methods: Pooled analysis of data from the original validation study and the subsequent medication guidance study including adult patients with severe asthma was conducted to calculate the JACS questionnaire cut-off values and to assess their sensitivity and specificity for identifying “well-controlled”, “not well-controlled”, and “poorly controlled” asthma as described in the Asthma Prevention and Management Guideline 2015 (JGL2015). The data were from 353 patients with mild to severe persistent asthma classified according to JGL2015.

Results: The JACS questionnaire cut-off values were 8.0 (sensitivity, 67.9%; specificity, 81.9%) for “well-controlled” and “not well-controlled” and 4.8 (sensitivity, 85.3%; specificity, 53.3%) for “not well-controlled” and “poorly controlled”.

Conclusions: JACS cut-off values can be expected to be more useful for evaluating asthma control status in clinical practice and clinical research, thus improving asthma treatment, in Japan. This analysis was the original validation study (UMIN000016589) and the subsequent medication guidance study (UMIN000024353).

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Introduction

Bronchial asthma is primarily characterized by chronic airway inflammation and symptoms related to variable airway narrowing (wheezing and breathing difficulty) and cough. The goals of asthma treatment are to resolve the patient's symptoms without adverse drug reactions, enable them to live their daily lives as normally as possible, and maintain respiratory functions to prevent exacerbation and death from asthma in the future.¹

The Ministry of Health, Labor and Welfare (MHLW) in Japan is currently promoting a campaign to prevent “asthma-associated death.”¹ According to Monthly Vital Statistics Reports of the MHLW

in Japan for 2016, approximately 1450 people died of asthma.² Although the number of asthma deaths is decreasing year by year, further promotion of this campaign will be needed to achieve the goal of “no death associated with asthma.”

To reduce death from asthma, it is crucial to completely control asthma over the long-term. The useful tests for assessing asthma control status include spirometry and the peak flow test, as well as questionnaires such as the asthma control questionnaire (ACQ)^{3,4} and asthma control test (ACT).^{5,6} However, these questionnaires were developed outside Japan, translated into Japanese, and validated in Japan, but does not adopt the Japanese Asthma Prevention and Management Guideline 2015 (JGL2015)¹ criteria for cut-off values; thus these are most likely incompatible with JGL2015.¹ Therefore, on the basis of the social environment and way of life in Japan, we first developed the Japan Asthma Control Survey (JACS) questionnaire with VAS scale that allows optimal measurement of the overall asthma control status including assessments of physical functions, psychology, and asthma symptoms, and then conducted a validation study (Study 1) of the questionnaire (Table 1).

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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?

The results demonstrated that the JACS questionnaire and ACQ have similar reliability and validity.⁷

In the present examination, we performed pooled analysis of the JACS scores from the validation study (Study 1) and a separate observational study on medication (use) guidance (Study 2; conducted between October 2016 and March 2017) (Table 2), and then calculated cut-off values for “well-controlled (well),” “not well-controlled (not well),” and “poorly controlled (poor)” asthma as described in the JGL2015.¹

Methods

Patients and methods

Table 2 shows the number of patients, eligibility criteria, outcomes, evaluation time points, and study periods in Study 1 and Study 2, which were used for calculating cut-off values in the present examination.

Two groups of patients were included: adult patients with mild to severe persistent bronchial asthma who required Step 2 or higher treatment and visited the study centers as outpatients between October 2015 and March 2016, in Study 1; and patients who were diagnosed with not well-controlled or poorly controlled

asthma as defined in the JGL 2015 and who visited the study centers between October 2016 and March 2017, in Study 2. Patients were excluded from the study for the following reasons: evident chronic obstructive pulmonary disease (COPD); respiratory infection; diseases that could affect responses on the questionnaire; and unsuitability for enrollment in the study as judged by the investigator. Patients enrolled in the study completed the JACS questionnaire, ACQ, and Mini AQLQ on Weeks 0 and 4. The asthma control status was assessed by respiratory specialists in accordance with the JGL2015.

To calculate cut-off values, we conducted a pooled analysis of data (including JGL2015 asthma control status, data from the JACS questionnaire, ACQ, and Mini AQLQ) for 353 patients in Study 1 and Study 2.

Ethics

Study 1 was approved by the Ethics Committee of Adachi Kyosai Hospital (approval number 2142), and Study 2 was approved by the Ethics Committee of Nihonbashi Sakura Clinic (approval number 3160192). In the protocol of Study 2, analyses using the pooled data to calculate JACS cut-off values from Studies 1 and 2 were pre-defined. Ethics committee of Nihonbashi Sakura Clinic reviewed

Table 2
Overview of studies used for calculating cut-off values.

	Validation study (Study 1)	Study on medication guidance (Study 2)
Study name (UMIN No.)	Clinical research on preparation of bronchial asthma questionnaire in Japan (UMIN000016589)	Effect of medication guidance on the level of control in patients with partly controlled or uncontrolled asthma despite ICS/LABA treatment (UMIN000024353)
No. of patients	Observational study 226	Observational study 127
Subject	- Patients with bronchial asthma (patients diagnosed with mild to severe persistent in JGL 2015: severity classification in consideration of the current treatment) - Age ≥ 20 years at consent to the study - Patients in Step 2 or higher of asthma treatment defined by JGL 2015	- Patients with bronchial asthma (patients diagnosed with mild to severe persistent in JGL 2015: severity classification in consideration of the current treatment) - Aged ≥ 20 and < 80 years - Not well-controlled (≥ 2 items applicable) or poorly controlled patients in JGL2015
Outcome	1) Evaluation of reliability of the questionnaire (1) Reproducibility (2) Internal consistency 2) Evaluation of validity of the questionnaire (1) Factor validity (2) Criterion-related validity (Correlation between JACS score and ACQ or MiniAQLQ) 3) Evaluation of sensitivity and responsiveness (1) Sensitivity (2) Responsiveness	1) Control status: JGL, GINA 2015 2) Questionnaire/Inquiry (1) JACS questionnaire (2) ACQ (3) MiniAQLQ 3) Respiratory function test (1) FEV1, (2) % FEV1, (3) FEV1 %, (4) V ($\cdot$) 25, (5) V ($\cdot$) 50, (6) V ($\cdot$) 50/V ($\cdot$) 25, (7) MMF 4) Inhalation method
Time point of evaluation	Weeks 0 and 4	Weeks 0 and 4
Study Period	Between October 2015 and March 2016	Between October 2016 and March 2017

Table 3

Patient background.

No. of patients (%)		Total	Validation study (Study 1)	Study on medication guidance (Study 2)
Total		353	226	127
Gender	Male	130 (36.8)	79 (35.0)	51 (40.2)
	Female	223 (63.2)	147 (65.0)	76 (59.8)
Age	Years (mean $\pm$ SD)	53.9 $\pm$ 14.9	53.1 $\pm$ 15.4	55.3 $\pm$ 14.0
Disease duration	Months (mean $\pm$ SD)	155.1 $\pm$ 169.6	135.9 $\pm$ 165.6	188.7 $\pm$ 171.9
Disease type	Atopic	183 (51.8)	114 (50.4)	69 (54.3)
	Non-atopic	115 (32.6)	85 (37.6)	30 (23.6)
	Combined	55 (15.6)	27 (11.9)	28 (22.0)
Severity	Mild persistent	93 (26.3)	81 (35.8)	12 (9.4)
	Moderate persistent	169 (47.9)	101 (44.7)	68 (53.5)
	Severe persistent	91 (25.8)	44 (19.5)	47 (37.0)
Treatment step	Step 2	126 (35.7)	97 (42.9)	29 (22.8)
	Step 3	163 (46.2)	99 (43.8)	64 (50.4)
	Step 4	64 (18.1)	30 (13.3)	34 (26.8)
JGL control status (0 W)	Well-controlled	131 (37.1)	131 (58.0)	0 (0.0)
	Not well-controlled	177 (50.1)	79 (35.0)	98 (77.2)
	Poorly controlled	45 (12.7)	16 (7.1)	29 (22.8)
Complications	Allergic disease	233 (66.0)	137 (60.6)	96 (75.6)
	Allergic rhinitis	213 (60.3)	128 (56.6)	85 (66.9)
	Atopic dermatitis	22 (6.2)	12 (5.3)	10 (7.9)
	Chronic sinusitis	54 (15.3)	23 (10.2)	31 (24.4)
	Others	19 (5.4)	4 (1.8)	15 (11.8)
Concomitant drug	ICS	27 (7.6)	27 (11.9)	0 (0.0)
	ICS/LABA	328 (92.9)	201 (88.9)	127 (100.0)
	LABA	6 (1.7)	2 (0.9)	4 (3.1)
	LTRA	166 (47.0)	107 (47.3)	59 (46.5)
	Theophylline	72 (20.4)	33 (14.6)	39 (30.7)
	Anticholinergics	40 (11.3)	12 (5.3)	28 (22.0)
	Oral steroids	23 (6.5)	16 (7.1)	7 (5.5)
	Others	112 (31.7)	43 (19.0)	69 (54.3)
	Smoking history	Yes	58 (16.4)	40 (31.5)

and approved the suitability of calculating cut-off values using the pooled data.

Both Study 1 and Study 2 were conducted in accordance with the Declaration of Helsinki (revised in October 2013) and “Ethical Guidelines for Medical and Health Research Involving Human Subjects” amended on 22 December 2014. Patients were given written informed consent forms approved by the Ethics Committees, were fully informed about the study in writing, and then freely signed their consent forms.

Assessments and statistical analysis

With the JGL2015-based asthma control status as the dependent variable and the JACS total score and subscores as the independent variable, the ROC curve^{8,9} was plotted, and then the cut-off values

of JACS total score, the sensitivity, specificity, and AUC with 95% confidence intervals (CIs) were calculated and ROC curve was plotted for JGL2015-based control status pairs, e.g. well-controlled vs not well-controlled and not well-controlled vs poorly controlled. Also, odds ratio, sensitivity,¹⁰ specificity,¹⁰ positive predictive value (PPV),¹¹ negative predictive value (NPV),¹¹ % correctly classified, and area under the ROC were determined. In addition, the cut-off values for the JACS subscore scores (symptom, activity, emotion, and treatment) were calculated.

In Study 1, the correlation between the JACS score and ACQ5/ACQ6 scores for asthma control status and the correlation between the JACS score and Mini AQLQ¹² score for quality of life (QOL) was tested to validate the reliability of the JACS questionnaire. However, in the present examination, the correlation between scores was assessed for patients with a broader range of background.

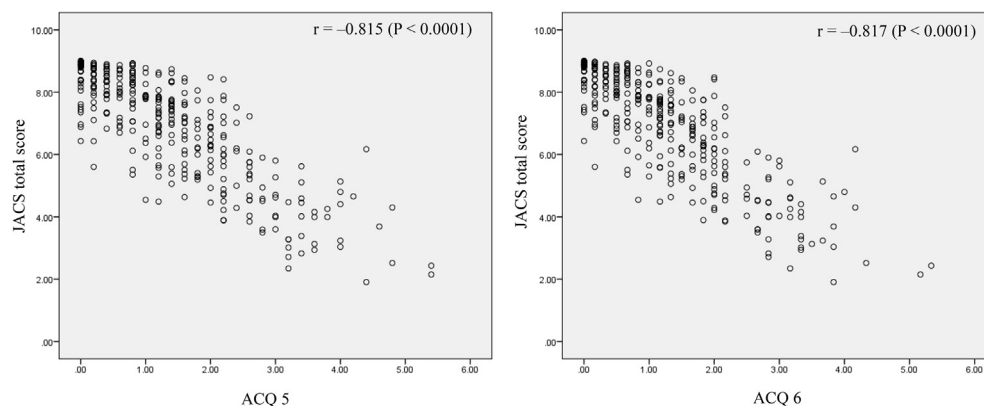


Fig. 1. Correlation between JACS and ACQ scores. Assessed using the Spearman rank correlation coefficient.

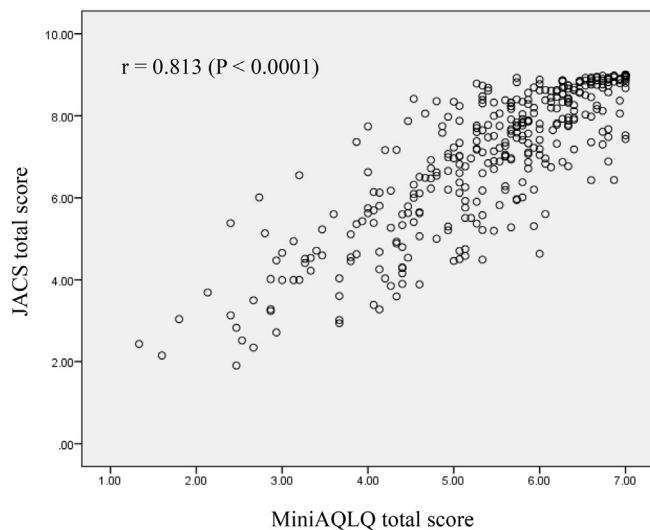


Fig. 2. Correlation between JACS and MiniAQLQ scores. Assessed using the Spearman rank correlation coefficient.

The correlation between the JACS questionnaire and ACQ5/ACQ6 and the correlation between the JACS questionnaire and Mini AQLQ were tested by using Spearman rank correlation coefficient (r).

Results

The background characteristics of the 353 patients whose data were used for cut-off value calculation is shown in Table 3. The JGL2015 asthma control status of patients differed markedly between Study 1 and Study 2. There were 131 well-controlled, 79 not well-controlled, and 16 poorly controlled patients in Study 1, and 0 well-controlled, 98 not-well-controlled, and 29 poorly

controlled patients in Study 2. Combining the patients in both studies produced a population consisting of 131 well-controlled, 177 not well-controlled, and 45 poorly controlled patients.

The correlation coefficients between the JACS score and ACQ5 score, the JACS score and ACQ6 score, and the JACS score and MiniAQLQ score were $r = -0.815$ ($P < 0.0001$), -0.817 ($P < 0.0001$), and 0.813 ($P < 0.0001$), respectively, indicating a significant correlation of the JACS score with all of the other scores (Fig. 1, 2).

The JACS total score cut-off values for JGL2015 asthma control status were calculated to be 8.0 (sensitivity, 67.9%; specificity, 81.9%; AUC, 0.789) for well-controlled vs not well-controlled and 4.8 (sensitivity, 85.3%; specificity, 53.3%; AUC, 0.698) for not well-controlled vs poorly controlled. The ROC curve is presented in Figure 3.

The JACS total scores for asthma control status were >8.0 for well-controlled, >4.8 and ≤ 8 for not well-controlled, and ≤ 4.8 for poorly controlled. Odds ratio, sensitivity, specificity, positive predictive value, negative predictive value, % correctly classified, and area under ROC are listed by cut point in Table 4 for well-controlled vs not well-controlled and for not well-controlled vs poorly controlled.

The JACS subscale score cut-off values, as well as the sensitivity, specificity, AUC for the cut-off values, and the range of JACS subscale scores were calculated as the JACS total score, and presented in Table 5.

Discussion

In the present pooled analysis, we determined cut-off values for the JACS questionnaire, a tool for measuring asthma control, and ranges for asthma control status according to the JGL2015.

Study 1 included patients with step 2 or higher asthma treatment as defined in the JGL2015, thus enrolled many patients with lower severity asthma. To calculate more reliable cut-off values, we pooled the data from Study 2 (which included patients with not well-controlled and poorly controlled asthma) and the data from

Criterion for cut-off value calculation	Cut-off value	the range of JACS total score			Sensitivity (%)	Specificity (%)	AUC (95% CI)
		Well-controlled	Not well-controlled	Poorly controlled			
Well-controlled vs not well-controlled	8.0	>8.0	>4.8 and ≤ 8.0	≤ 4.8	67.9	81.9	0.789 (0.738, 0.840)
Not well-controlled vs poorly controlled	4.8				85.3	53.3	0.698 (0.607, 0.788)

ROC curve

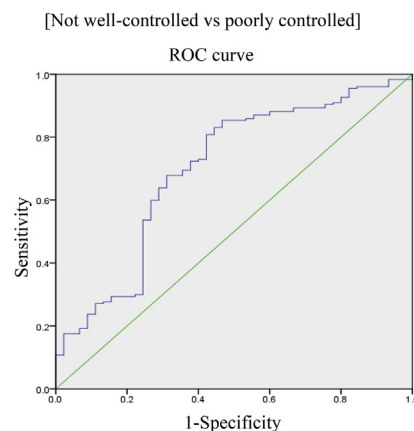
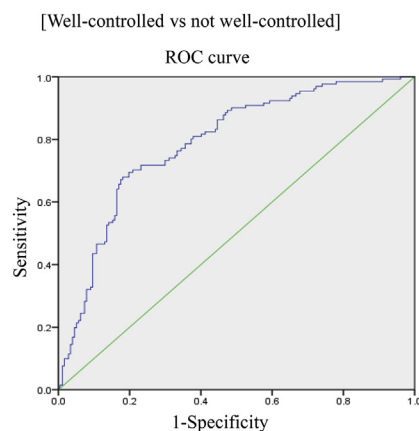


Fig. 3. JACS cut-off values.

Table 4

Summary of various cut point scores.

Cut point score	Odds ratio	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	% Correctly classified	Area under ROC
Various JACS cut point scores in patients with JGL asthma control status of “well controlled (n = 131)” vs “not well controlled (n = 177)”							
≥ 2	—	100	0.6	42.7	100	42.9	0.503
≥ 3	—	100	2.8	43.2	100	44.2	0.514
≥ 4	12.037	99.2	8.5	44.5	93.8	47.1	0.539
≥ 5	13.163	98.5	16.9	46.7	93.8	51.6	0.577
≥ 6	8.634	94.7	32.8	51.0	89.2	59.1	0.637
≥ 7	7.273	86.3	53.7	57.9	84.1	67.5	0.700
≥ 8	9.602	67.9	81.9	73.6	77.5	76.0	0.749
≥ 8.5	7.247	46.6	89.3	76.3	69.3	71.1	0.679
Various JACS cut point scores in patients with JGL asthma control status of “not well controlled (n = 177)” vs “poorly controlled (n = 45)”							
≥ 2	—	99.4	0	79.6	0.0	79.3	0.497
≥ 3	2.457	97.2	6.7	80.4	37.5	78.8	0.519
≥ 4	2.700	91.5	20.0	81.8	37.5	77.0	0.558
≥ 4.5	3.714	88.1	33.3	83.9	41.7	77.0	0.607
≥ 5	6.125	83.1	55.6	88.0	45.5	77.5	0.693
≥ 5.5	3.897	74.0	57.8	87.3	36.1	70.7	0.659
≥ 6	4.543	67.2	68.9	89.5	34.8	67.6	0.681
≥ 7	2.668	46.3	75.6	88.2	26.4	52.3	0.609
≥ 8	3.090	18.1	93.3	91.4	22.5	33.3	0.557

Study 1. The pooled population consisted of 131 well-controlled, 177 not well-controlled, and 45 poorly controlled patients.

Although the reliability and validity of the JACS questionnaire were evaluated in Study 1, no JACS scores reflecting asthma status had been defined. In the present examination, we determined more reliable cut-off values for the JACS total score and ranges for asthma control status according to the JGL2015, which we consider to be extremely valuable in the future use of the JACS questionnaire.

The ACQ and ACT scores for asthma control status have already been described along with their cut-off values in the JGL 2015. However, the ACQ and ACT questionnaires do not use JGL2015 criteria to define asthma control status. The ACQ employs asthma diary data and the following gold standard criteria⁴: frequency of β_2 stimulant use, peak expiratory flow (PEF) value, night sleep disturbances, exacerbation requiring oral steroids, emergency visits to the hospital, and adverse drug reactions. The ACT uses history, physical examination, and FEV₁-value-based specialist rating of asthma control (five-stage scale ranging from not controlled at all to completely controlled).⁶ For these reasons, the assessment of asthma control by respiratory specialists in Japan has differed depending on JGL2015 vs gold standard (such as ACQ or ACT) criteria usage. In Japan, the use of the JACS questionnaire is expected to reduce such discrepancies and allow more appropriate evaluation, with possible higher specificity and correlation with JGL 2015 compared with ACQ or ACT.

The “well-controlled” asthma control status in JGL2015 indicates that patients have no asthma symptoms, no limited activities and no exacerbation, with sufficient respiratory functions,

whereas the JACS total score of >8.0 , the cut-off value for “well-controlled,” suggests that patients with such score have some asthma symptoms. The discrepancy in symptom between the JGL2015-based and the JACS total score-based status is likely to be due to the fact that symptoms were not so obvious for patients to report them to their physicians, but patients became conscious of their own symptoms when looking at the VAS scale of the JACS questionnaire.

Table 4 summarizes the cut points for well-controlled vs not well-controlled and not well-controlled vs poorly controlled asthma. For example, at the cut point score of ≥ 8 for well-controlled vs not well-controlled asthma, the following parameters were defined: (1) odds ratio, or ratio of the total number of well-controlled and not well-controlled patients with cut point ≥ 8 to the total number of well-controlled and not well-controlled patients with cut point <8 ; (2) sensitivity, or percent of patients with cut point ≥ 8 among well-controlled patients; (3) specificity, or percent of patients with cut point <8 among not well-controlled patients; (4) positive predictive value, or percent of well-controlled patients among patients with cut point ≥ 8 ; (5) negative predictive value, or percent of not well-controlled patients among patients with cut point <8 ; (6) % correctly classified, or percent of well-controlled patients with cut point ≥ 8 plus not well-controlled patients with cut point <8 among a total of 308 patients with well-controlled or not well-controlled asthma; (7) area under the ROC, or measure of discrimination between well-controlled and not well-controlled patients by area under ROC for the cut point ≥ 8 . The area under ROC ranges from 0 to 1, with 1 meaning that patients with one

Table 5

JACS subscale cut-off values.

Subscale	Criterion for cut-off value calculation	Cut-off value	the range of JACS subscale scores			Sensitivity (%)	Specificity (%)	AUC (95% CI)
			Well-controlled	Not well-controlled	Poorly controlled			
Symptom	Well-controlled vs not well controlled	7.7	>7.7	>5.6 and ≤ 7.7	≤ 5.6	78.6	67.8	0.791 (0.740, 0.841)
	Not well-controlled vs poorly controlled	5.6				67.8	64.4	0.689 (0.607, 0.770)
Activity	Well-controlled vs not well controlled	7.5	>7.5	>5.1 and ≤ 7.5	≤ 5.1	80.2	65.5	0.765 (0.712, 0.818)
	Not well-controlled vs poorly controlled	5.1				75.7	55.6	0.680 (0.592, 0.768)
Emotion	Well-controlled vs not well controlled	7.8	>7.8	>5.4 and ≤ 7.8	≤ 5.4	74.1	70.1	0.751 (0.696, 0.805)
	Not well-controlled vs poorly controlled	5.4				74.0	55.6	0.651 (0.558, 0.745)
Treatment	Well-controlled vs not well controlled	8.9	>8.9	>8.3 and ≤ 8.9	≤ 8.3	40.5	75.1	0.566 (0.501, 0.630)
	Not well-controlled vs poorly controlled	8.3				57.6	57.8	0.551 (0.449, 0.654)

asthma control status can be completely discriminated from patients with the second asthma control status, and 0.5 meaning that discriminating one status from the other is completely random. Table 4 indicates that ≥ 8 is the best cut point for discriminating well-controlled from not well-controlled asthma.

In Table 4, the negative predictive value for not well-controlled and poorly controlled is 45.5%, not high, even at the cut point of ≥ 5 which is close to the cut-off value. This indicates that poorly controlled patients accounted for only 45.5% of patients with cut point < 5 . In the present evaluation using the JACS questionnaire, patients might have reported symptoms in the questionnaire but they failed to report to their physicians.

In calculation of the cut-off values for the JACS subscales, AUC values for symptoms were 0.791 for “well-controlled” vs “not well-controlled” and 0.689 for “not well-controlled” vs “poorly controlled,” indicating that AUC for symptoms most accurately reflects the JGL2015-based asthma control status. Next to the AUC for symptoms, AUC for activity and emotion was also accurate. Conversely, the AUC cut-off values for treatment were less accurate: 0.566 for “well-controlled” vs “not well-controlled” and 0.551 for “not well-controlled” vs “poorly controlled.” This may be probably due to its poor validity, as the internal consistency, etc. in the validation study (Study 1). The present calculation of the cut-off values for the subscales in the JACS questionnaire will allow for evaluation of asthma control status by scale which cannot be evaluated by the JACS total score.

Limitations

In Study 2 entitled “Effect of medication guidance on the level of control in patients with partly controlled or poorly controlled asthma despite ICS/LABA treatment,” the primary outcome was how medication guidance affects asthma control status, QOL, and respiratory functions in patients with asthma symptoms despite inhaled ICS/LABA treatment. The results of Study 2 has not been published; however, the JACS cut-off values remained to be addressed, and hence we have first published the present results in this article. In addition, not well-controlled patients were included in Study 2, which would yield a bias. Thus, we thought that the distribution of the asthma control level status in the Japanese patients may well be reflected by pooling the data of Studies 1 and 2.

Conclusions

The JACS cut-off value was 8.0 for well-controlled vs not well-controlled JGL2015-based asthma control status and 4.8 for not well-controlled vs poorly controlled JGL2015-based asthma control status, indicating that the range of JACS total scores was > 8.0 for well-controlled, > 4.8 and ≤ 8.0 for not well-controlled, and ≤ 4.8 for poorly controlled asthma. The cut-off values and JACS score ranges determined in the present examination can be expected to enhance asthma control assessment in clinical practice and clinical research involving Japanese asthma patients and improve asthma treatment in Japan.

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Conflict of interest

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

Authors' contributions

The corresponding author, YT, had full access to all of the data in this study and takes complete responsibility for the integrity of the 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. Although the data management and statistical analysis were conducted by a contract research organization, explanation for the data was conducted by all authors.

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