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Development of a Communication Tool between Patients and Physicians for Recognizing COPD Exacerbations in Japan

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ABSTRACT

In Japan, exacerbations are underreported compared with other countries, possibly due in part to a failure to recognize them. This study aimed to create a simple chronic obstructive pulmonary disease (COPD) Exacerbation Recognition Tool (CERT-J) specifically for Japanese patients. Patients ≥40 years with confirmed COPD or asthma-COPD overlap were included. Focus groups were held to identify words and phrases used by patients to describe symptoms associated with an exacerbation, resulting in candidate items being identified. Following cognitive debriefing, the items were refined based on item frequency, level of endorsement and effect of demographic factors. Exploratory factor analysis (EFA) was then performed to inform an expert panel's choice of items to form the new tool. A total of 41 patients were included in the focus groups and nine patients performed the cognitive debrief. Following this, the expert panel identified 26 items for testing in a further 100 patients (mean age 72 years, forced expiratory volume in 1 s 54.8% predicted and 1.8 exacerbations in the preceding 12 months). Eleven items were associated with breathlessness or activity limitation and seven of these were the most frequently endorsed. EFA identified four factors, with one (breathlessness) being dominant. The expert panel recommended that the CERT-J should include six items: breathlessness and activity limitation (3 items), cough (1 item) and phlegm (2 items). The final CERT-J should benefit patients with COPD by providing them with an increased understanding and recognition of exacerbations.

Clinical Trial Registration: GSK K.K (jRCT1080224526).

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KEYWORDS
Patient-reported outcome; focus group discussion; CERT; cognitive debriefing; factor analysis; communication tool

Introduction

Reducing the risk of exacerbations is one of the key goals in the management of chronic obstructive pulmonary disease (COPD), alongside reducing symptoms [1, 2]. Exacerbations are clinically important as they negatively impact health status, and are associated with lung function decline, as well as increased risk of cardiovascular events, and increased mortality and healthcare utilization [1–9]. Consequently, greater understanding and recognition of exacerbations is important to improve patient outcomes [10]. COPD exacerbations in Japan appear to be underreported, with rates shown to be as much as five-times higher compared with exacerbations that are reported [11]. Following an exacerbation, patients in Japan may be more likely to delay seeking treatment to see if their symptoms resolve spontaneously, resulting in underreporting of COPD exacerbations [12]. This may also be due to a lack of understanding of what an exacerbation is, its importance, and the ability to recognize an event or explain it appropriately to doctors [10, 13].

Current tools that aid communication between patients and physicians include the COPD Assessment Test (CAT), but whilst CAT scores do change with an exacerbation [14], it was not designed to detect exacerbations or educate patients about exacerbations [15]. The EXACT is a validated daily diary specifically designed to detect and quantify exacerbation severity in COPD [16–18], but it is a daily diary and so is more suited to research than clinical practice [16–18]. A COPD Exacerbation Recognition Tool (CERT) has been published recently as an aid to help patients recognize and report exacerbations in China [19] but, like the other

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instruments, it was developed in other countries and languages and requires translation and validation in Japan, so it may not adequately reflect the choice of items that Japanese patients would make or their understanding of them. For this reason, we performed a study to identify the words and phrases commonly used by Japanese patients with COPD and Asthma-COPD Overlap (ACO) to describe the symptomatic characteristics of the onset of an exacerbation and create a practical Japan-specific CERT (CERT-J).

Materials and methods

This multicenter study (GSK K.K. [jRCT1080224526]) consisted of three components with a total study duration spanning 20 months from February 2019 to October 2020: Parts 1 and 2 were qualitative phases with recruitment targets of 45 and 9 participants, respectively. Part 3 was a quantitative phase (supporting information Figure S1), with a recruitment target of 100 participants, recruited from hospitals/clinics with certified respiratory specialists in Japan (supporting information Table S1). The study was conducted in accordance with applicable local regulations, and the principles stated in the Declaration of Helsinki. All study documents were reviewed and approved by ethics committees at each investigational site and all patients provided written, informed consent.

Population

Patients ≥40 years of age with COPD or ACO confirmed using spirometry according to the 2016 Global Initiative for Chronic Obstructive Lung Disease diagnostic criteria. As a large proportion of patients in Japan are diagnosed with ACO on the basis of clinical features of both asthma and COPD, particularly a history of exacerbations [20], patients with a physician's diagnosis of ACO were also enrolled. Participants who had experienced an exacerbation within the last 12 months were included. Interviews were performed in the stable state, as in the development of the EXACT daily diary that was designed to detect the onset of exacerbations [16, 17]. Eligibility criteria are reported in Supplementary Materials. Patients who participated in a focus group in Part 1 were ineligible to participate in Part 2, and patients participating in either Part 1 or 2 were ineligible for Part 3 of the study.

Part 1: item elicitation

Words and phrases commonly used by Japanese patients to describe the symptomatic characteristics of the onset of a COPD exacerbation were elicited during nine focus groups consisting of 3–6 patients. Composition of the focus groups was assessed to ensure the inclusion of at least one female participant and more recently exacerbating participants per site. The focus groups were audio-recorded, transcribed verbatim and entered into ATLAS.ti (ATLAS.ti Scientific Software Development GmbH, Berlin, Germany). Words and phrases provided by patients were highlighted and grouped into key themes and relationships. Following this, an expert panel recommended the items for cognitive debriefing.

Part 2: cognitive debriefing

Nine one-to-one cognitive debriefing interviews were performed to discuss the wording and phrasing of questions identified in Part 1; further details are included in Supplementary Materials. Audio recordings and notes from all interviews were reviewed to judge how the patients understood each question. Following this, the wording of some items was modified, and an expert panel was consulted to finalize the items to be taken forward as a questionnaire in Part 3.

Part 3: item reduction

The objective was to select items to form the CERT-J from those identified in Parts 1 and 2. Candidate items selected from Part 2 were assembled into a 26-item self-administered questionnaire which presented each item with appropriate response options (supporting information Table S2), with further details included in Supplementary Materials. Item reduction took into account the frequency and level of endorsement and floor and ceiling effects. Items endorsed by <50% of patients were removed, unless considered to be a critical clinical indicator. Following removal of items with poor endorsement, tests of association were performed between item responses and a range of demographic variables, items with a correlation of $p < 0.05$ being flagged for possible exclusion.

Prior to exploratory factor analysis (EFA), item-item Pearson correlations were calculated to identify pairs of items that were strongly correlated (≥80% shared variance) to assess the degree of redundancy within the item set. EFA with promax rotation was used and eigenvalues >1.0 and inspection of the scree plot were used to identify the optimum number of factors. Items with the highest factor loadings and response rates were used singly, or two related items were combined, to create five potential CERT-J versions each with a different combination of items.

Tests of the sensitivity and specificity of these five versions were performed using a surrogate marker for the presence of an exacerbation that was defined as the presence of three or more out of seven frequently reported items being positive. An expert panel then reviewed the performance of these five versions to finalize the content of the CERT-J.

All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Patient population

A total of 150 patients were included: Part 1, $n = 41$; Part 2, $n = 9$; Part 3, $n = 100$. Patient baseline demographics and clinical characteristics are shown in Table 1. The majority

Table 1. Patient demographics and clinical characteristics.

	Part 1 ($N = 41$)	Part 2 ($N = 9$)	Part 3 ($N = 100$)
Age, years, mean (range)	74.1 (57–94)	75.4 (56–90)	72.3 (45–88)
Male, n (%)	35 (85.4)	7 (77.8)	85 (85.0)
Education background, n (%)			
Elementary/Jr. High School	19 (46.3)	0 (0.0)	30 (30.0)
High School	12 (29.3)	6 (66.7)	54 (54.0)
Jr. College/Technical Jr. College	1 (2.4)	1 (11.1)	5 (5.0)
University/Grad School	9 (22.0)	2 (22.2)	11 (11.0)
Geographical area[a], n (%)			
Urban	23 (56.1)	6 (66.7)	44 (44.0)
Rural	18 (43.9)	3 (33.3)	56 (56.0)
Smoking status, n (%)			
Current	12 (29.3)	3 (33.3)	66 (66.0)
Former	29 (70.7)	6 (66.7)	34 (34.0)
Smoking, pack-years (range)	56.0 (10–148)	49.4 (18–90)	63.9 (10–165)
Disease duration, n (%)			
1–<5 years[b]	15 (36.6)	3 (33.3)	42 (42.0)
5–<10 years	20 (48.8)	4 (44.4)	27 (27.0)
10–<15 years	6 (14.6)	1 (11.1)	22 (22.0)
≥15 years	NR	1 (11.1)	9 (9.0)
FEV_1 % predicted (range)	45.4 (1–79)	58.3 (26–83)	54.8 (16–116)
CAT score (range)	17.0 (1–39)	13.7 (6–23)	15.6 (0–36)
COPD exacerbations in last 12 months, mean (range)	1.6 (1–5)	1.9 (1–6)	1.8 (1–10)
Requiring hospitalization, mean (range)	0.8 (0–2)	0.4 (0–2)	0.6 (0–5)

[a] Urban was defined as ordinance-designated cities/core cities, rural was defined as other than urban.

[b] Includes patients whose disease duration was less than 1 year.

CAT, COPD assessment test; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 s; NR, not reported.

(78–85%) were male and mean age ranged from 72 to 75 years. Educational attainment was relatively low. Patients had a mean of 1.6–1.8 exacerbations in the previous year, and a mean of 0.6–0.8 exacerbations requiring hospitalization.

Parts 1 and 2: item elicitation and cognitive debriefing

Words and phrases related to items associated with difficulty breathing and activity were mentioned most commonly (Figure 1). Following cognitive debriefing and re-wording of some items, 26 items were taken forward for testing in Part 3. These covered cough (2 items), breathlessness (12 items), activity limitation (6 items), and phlegm (6 items).

Part 3: quantitative study and establishment of final COPD exacerbation tool

Questionnaire responses

Endorsement rates to the 26 items were ranked using two response groupings (supporting information Tables S2 and S3); the distribution was consistent across both groupings (Figure 2 and supporting information Figure S2).

Items relating to breathing difficulty highly ranked in both grouping (supporting information Table S3). Sixteen items had a response rate >50% and were selected for further analysis, with one exception: Item 25 (sputum color) was not included even though it had a high response rate (60%) because some patients always have yellow, green or brown phlegm even when stable. Subsequently, Item 24 (change in phlegm color) with a response rate of 49%, was chosen because it reflects the fact that change in sputum color can occur at exacerbation onset.

Demographic associations

The responses to the 16 surviving items were correlated with a range of demographic factors including: age, sex, height, living area, education, smoking status, smoking pack years, disease duration. All 128 correlations between these demographics and the selected 16 items were weak or very weak (Spearman rho values were 0.00–0.331) (supporting information Table S4). The correlations were significant at $p < 0.05$ in 15 comparisons, but there was no correction for multiplicity of testing and a Bonferroni correction would require $p < 0.0004$ for significance. None of the comparisons had a p-value lower than this. Seven correlations at $p < 0.05$ were with duration of disease, which may be an indirect measure of severity, so an association would be expected. Overall, this analysis suggested a low level of bias in the patients' responses to these items, so none were removed.

Factor analysis

Prior to factor analysis, item-item Spearman's rank correlations showed strong correlations (>80%) between six pairs of items concerning breathlessness or difficulty breathing with different types of activity (e.g. "breathlessness on long distance walks" and "wheezing on long distance walks"). This suggested that they measured closely related concepts and possible redundancy (supporting information Table S5).

The EFA Scree plot (Figure 3) showed one dominant factor, but four factors had eigenvalues >1.0, so 2-factor and 4-factor solutions were examined more closely.

With the 2-factor solution, the proportion of eigenvalues attributable to each factor was: Factor 1 ("breathlessness and activity limitation") 82.2% and Factor 2 ("cough and phlegm") 17.8%. With the 4-factor solution, the proportions were: Factor 1 ("breathlessness with activity") 78.0%; Factor 2 ("limitation of social activity") 9.7%; Factor 3 ("cough and

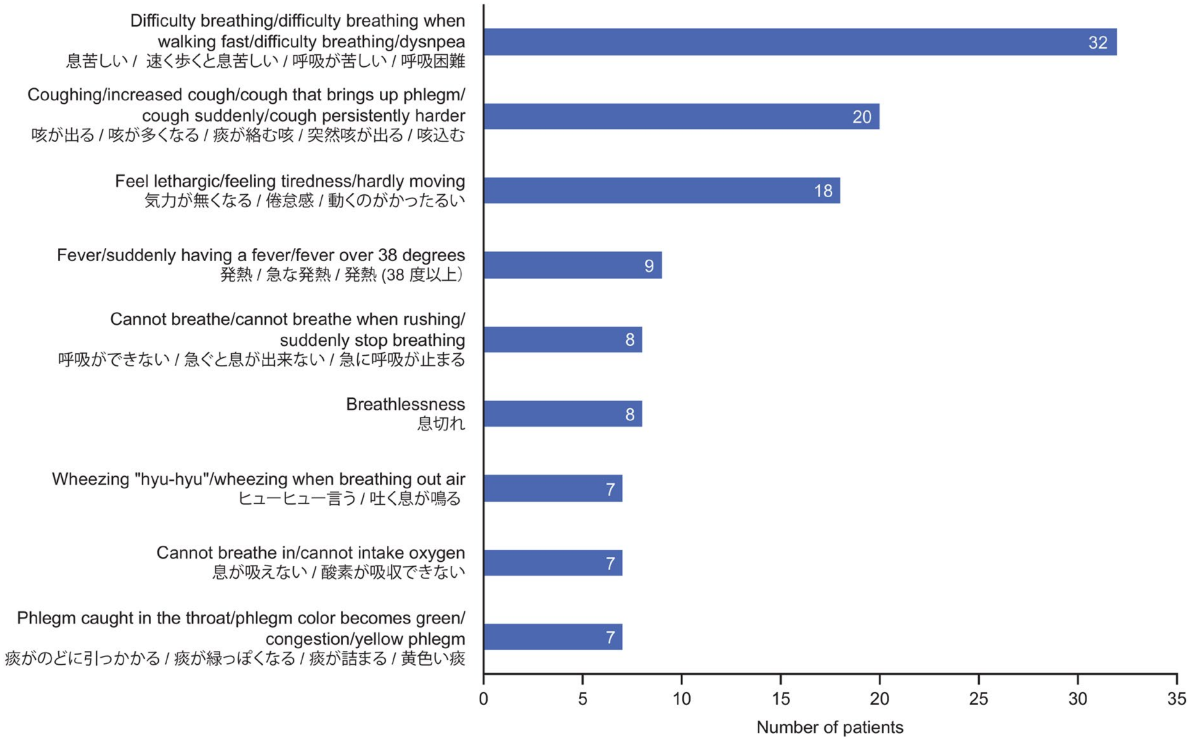


Figure 1. Focus groups: frequency of the most common words or phrases considered to be important to patients in describing exacerbations to others[a] ($n = 41$). [a]Duplicate responses were included.

phlegm") 9.2%; Factor 4 ("difficulty breathing walking up stairs") 4.0%. The 4-factor solution was chosen because it separated the concepts more clearly (Table 2).

Tests of sensitivity and specificity

Based on the factor structure and item loadings, the most representative items within each factor were used to create an eight-item list of candidate items for the CERT-J (supporting information Table S6). From this list, five different combinations were created using items that were used unchanged or combined with a closely related item into a single item. The sensitivity of these five combinations ranged between 79.5–100%, depending on the number of items that would need to be positive for an exacerbation alert to be triggered; specificity ranged from 6.3 to 75.0% (supporting information Table S7). The greater the number of positive items required to identify an exacerbation, the greater the specificity, but the lower the sensitivity.

Expert panel meeting

An expert panel reviewed the five candidate versions of the CERT and recommended Version 5 (the only six-item version) because it had a good combination of sensitivity (91.8%) and specificity (56.3%) when using a requirement for three items to be positive. This version included: amount of cough; daily or social activity limitation due to difficulty breathing; difficulty with breathing going up stairs; breathlessness walking long distances, increased frequency of phlegm; increased volume of phlegm; change in phlegm color. Japanese and English wording can be seen in Figure 4.

Discussion

This study has developed the first communication tool for COPD exacerbations to be used between patients and physicians in Japan. It has six items that cover cough, breathlessness, activity limitation, and phlegm. These items are similar to those identified in the recently published CERT developed in China [19].

The study suggests that Japanese patients may be more ready to report worsening breathlessness and its effect on activity than items about worsening cough and sputum, as shown by the high number of items concerning breathlessness reported by patients in the focus groups and the clear dominance of the breathlessness-activity factor in the EFA. Whilst this suggests that changes in cough and sputum with an exacerbation are rated as less important by Japanese patients, chronic bronchitis is present in Japan [21, 22]. Patients with COPD may also limit their movement [23] lowering their breathlessness and thereby their perceived need to seek medical attention. To ensure that the CERT permits the possibility of a valid exacerbation alert being triggered in the absence of significant worsening of breathlessness or activity, the expert panel ensured that items relating to cough and phlegm were included in the final six-item version.

The CERT developed in China used a similar methodology [19], but otherwise the two studies were independent. The EFA results were very similar between the two studies because the dominant factor in the CERT-J analysis contained breathlessness and disturbance to activity, accounting for 82.2% of the variance using a 2-factor solution that combined breathlessness and activity in a single factor, compared with 79.1% in the CERT developed in China

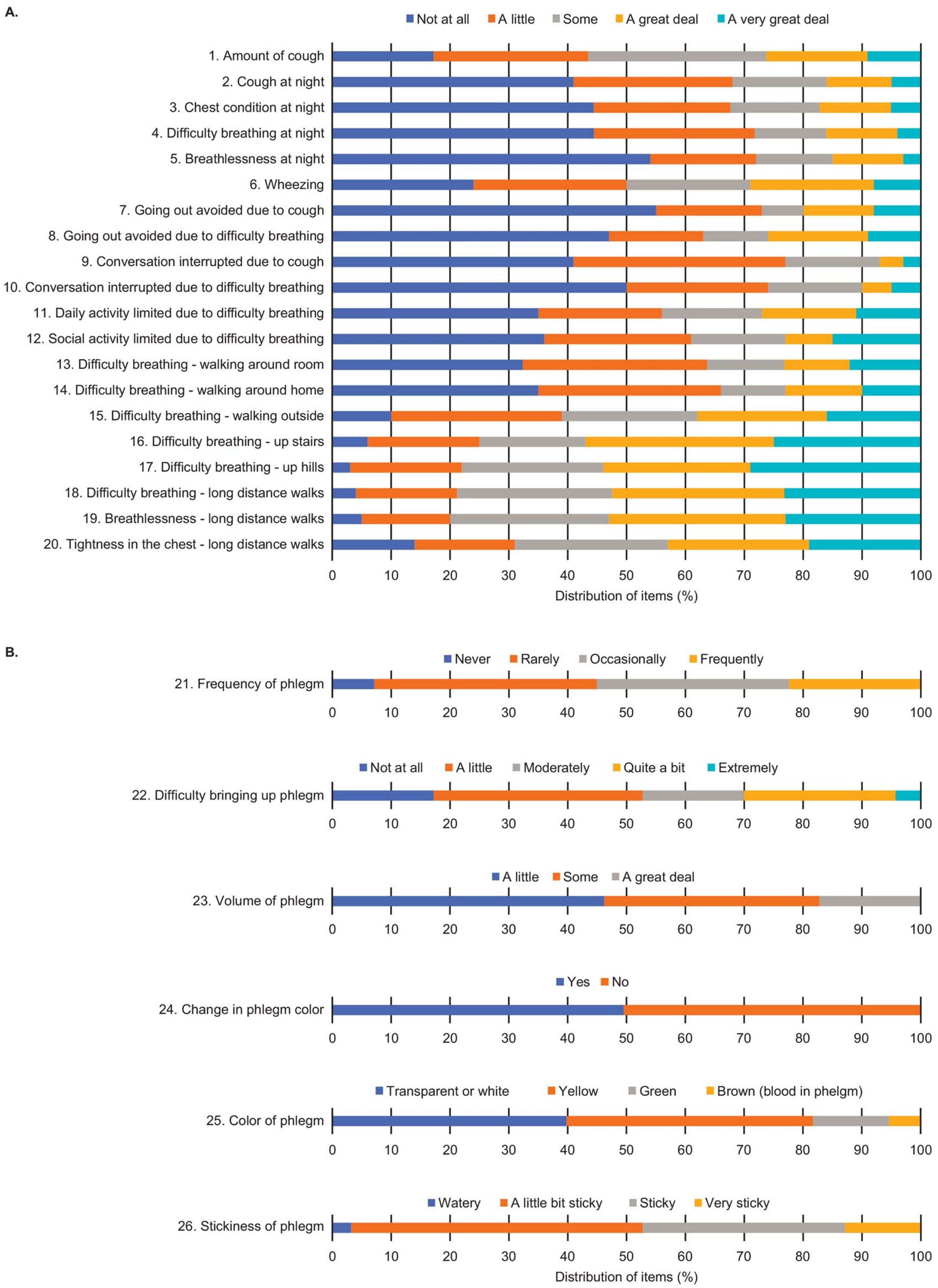


Figure 2. Part 3 questionnaire responses: demonstrating distribution of (A) Items 1–20 and (B) Items 21–26. Items 22 to 26 were questions about phlegm that were only completed by patients who selected "rarely", "occasionally", or "frequently" to item 21.

[19]. Cough and sputum accounted for 17.8% of the variance in the 2-factor results of Part 3 of this study and 20.9% in CERT in China [19]. The consistency of these observations suggest that the experience of a COPD exacerbation is similar in different countries and gives clear support to the conclusion that patients characterize exacerbations more through the effects of breathlessness and activity limitation than through worsening cough and sputum.

The CERT-J should be used by patients when they experience a worsening of symptoms including cough, breathlessness, activity limitation, and phlegm, to enable earlier detection of exacerbations. It was critical to ensure that it was simple to use so that patients will be able to connect with their physicians and access timely treatment in routine clinical practice. Whilst other tools such as the CAT exist to aid communication between patients and physicians, it does not educate

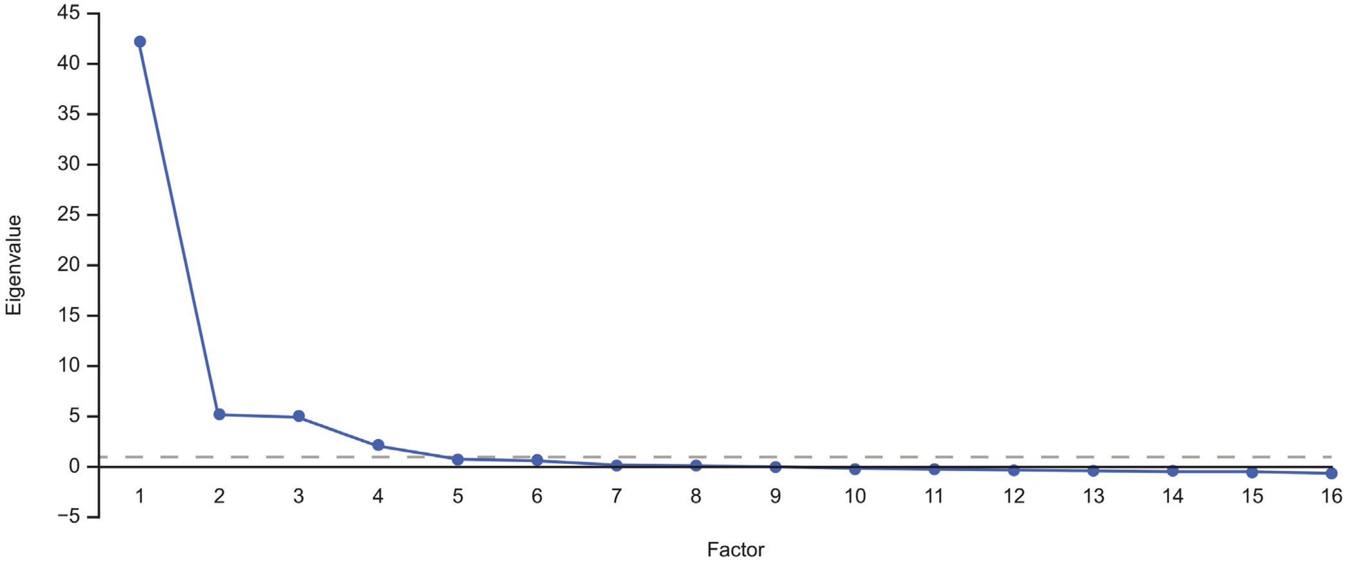


Figure 3. Scree plot from factor analysis.

Table 2. Factor loadings after rotation.

Item number and description of each item[a]	Factor 1	Factor 2	Factor 3	Factor 4	Response rate (%)
19. Breathlessness: long-distance walks	**1.05**	−0.06	0.00	−0.03	80.0
18. Difficulty breathing: long-distance walks	**0.87**	0.13	−0.07	−0.02	78.8
20. Tightness in the chest: long distance walks	**0.81**	0.03	0.13	−0.02	69.0
17. Difficulty breathing: up hills	**0.67**	0.11	0.04	0.13	78.0
12. Social activity limited due to difficulty breathing[c]	0.07	**0.96**	−0.05	−0.03	48.0
11. Daily activity limited due to difficulty breathing[c]	0.17	**0.76**	−0.12	0.03	48.0
8. Going out avoided due to difficulty breathing	0.02	**0.76**	0.09	0.01	37.0
15. Difficulty breathing: walking outside[d]	0.46	**0.48**	−0.07	0.01	80.0
6. Wheezing	0.01	**0.41**	0.38	−0.02	50.0
21. Frequency of phlegm	−0.05	0.06	**0.84**	0.00	55.1
23. Volume of phlegm	0.03	0.03	**0.75**	−0.02	53.8
26. Stickiness of phlegm	0.13	0.08	**0.61**	0.01	47.3
1. Amount of cough	−0.14	−0.07	**0.61**	0.03	56.6
22. Difficulty bringing up phlegm	0.10	0.11	**0.51**	0.03	47.3
24. Change in phlegm color	0.08	−0.18	**0.48**	−0.03	49.5
16. Difficulty breathing: up stairs[d]	0.33	0.13	0.00	**0.62**	80.0

Note: Values in bold indicate factor loading >0.4. The Ultra-Heywood option was used for four-factor analysis.

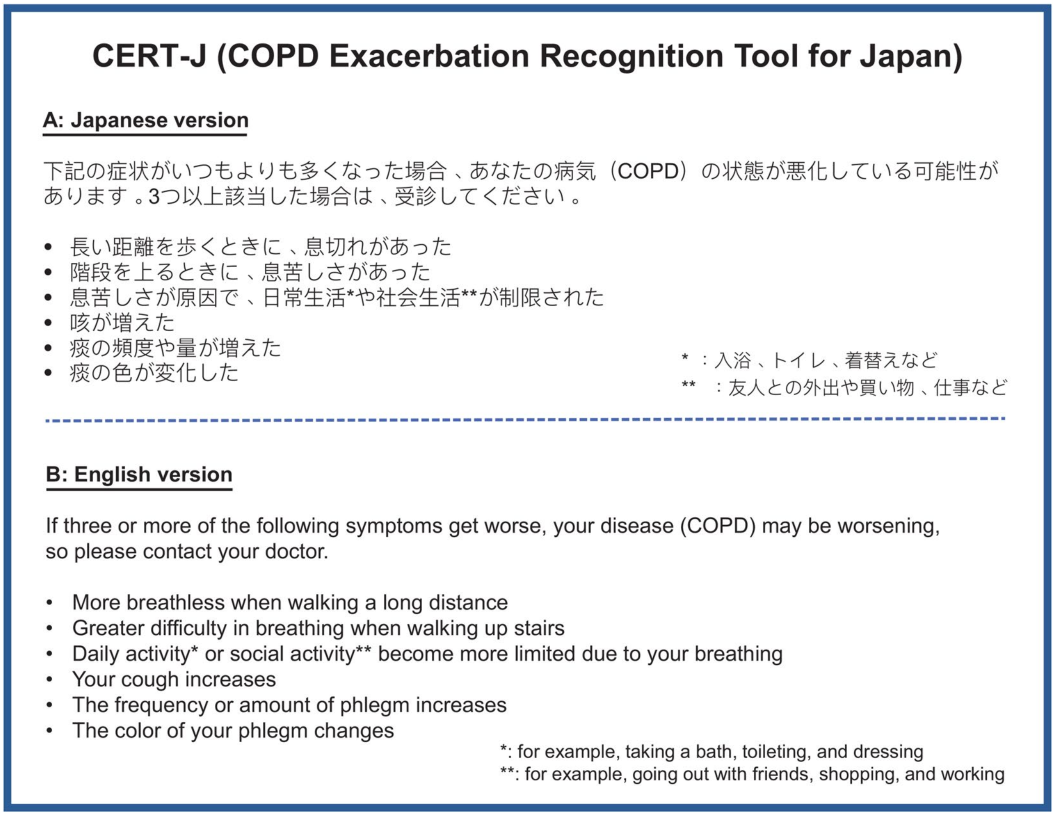
[a] 96 samples without any missing items were included; [b] Response rates were calculated based on the population who provided responses with the first grouping; [c] Response rates were calculated from patients selected "moderately, quite a bit, extremely" in Q11 and/or Q12; [d] Response rates were calculated from patients selected "moderately, quite a bit, extremely" in Q15 and/or Q16.

patients about exacerbations; it is designed to measure the impact of COPD on health-related quality of life. The EXACT diary is not suited for education or routine clinical practice since it is a tool for use in clinical research studies [15–18]. CERT-J is designed to help patients recognize symptoms of an exacerbation, to improve exacerbation reporting rates in Japan [11, 12, 24] and subsequently improve outcomes [25, 26].

In terms of practical application, the CERT-J could be used in clinical practice as part of a COPD education program to support patients recognize and identify exacerbations earlier, to enable timely treatment. This may be achieved best by incorporating it into a COPD exacerbation action plan, as part of COPD self-management interventions, which have been shown to improve health-related quality of life [27].

The analysis of this study was robust, and the findings are compatible with other studies, but a key limitation is the definition of exacerbators versus non exacerbators for the sensitivity and specificity testing. This would have required a very large study that sampled patients during an exacerbation and patients without an exacerbation. That was beyond the scope of this study. Another factor is the requirement, common to the development of all tools and questionnaires like this, for decisions to be made by the developers and their advisory panels. We attempted to mitigate this by testing the response rates and sensitivity and specificity of five different possible versions for the CERT-J and showed that they had very similar behavior. The final decision to use the six-item version was based on clinical judgment by disease-area experts.

Strengths of this study include the fact that the CERT-J was developed with patient focus groups and cognitive de-briefing interviews to ensure that the included items would be recognized and understood by patients. Furthermore, a large patient population was used to assess performance of the candidate items and an expert panel reviewed five versions of the CERT for specificity and sensitivity coupled with their clinical experience.



CERT-J (COPD Exacerbation Recognition Tool for Japan)

A: Japanese version

下記の症状がいつもよりも多くなった場合、あなたの病気（COPD）の状態が悪化している可能性があります。3つ以上該当した場合は、受診してください。

- 長い距離を歩くときに、息切れがあった
- 階段を上るときに、息苦しさがあった
- 息苦しさが原因で、日常生活*や社会生活**が制限された
- 咳が増えた
- 痰の頻度や量が増えた
- 痰の色が変化した

*：入浴、トイレ、着替えなど
**：友人との外出や買い物、仕事など

B: English version

If three or more of the following symptoms get worse, your disease (COPD) may be worsening, so please contact your doctor.

- More breathless when walking a long distance
- Greater difficulty in breathing when walking up stairs
- Daily activity* or social activity** become more limited due to your breathing
- Your cough increases
- The frequency or amount of phlegm increases
- The color of your phlegm changes

*: for example, taking a bath, toileting, and dressing
**: for example, going out with friends, shopping, and working

Figure 4. Final CERT-J.
CERT-J, COPD Exacerbation Recognition Tool in Japan; COPD, chronic obstructive pulmonary disease.

Conclusion

The CERT-J was designed to aid patients in recognizing, and subsequently reporting, COPD exacerbations. It confirmed the importance of worsening breathlessness at the onset of an exacerbation, but that worsening cough and sputum are important factors that patients should be aware of and should report to physicians.

Acknowledgments

We would like to pay our gratitude and our respects to our colleague, respiratory specialist and Visiting Professor Shu Hashimoto who passed away in July of 2022. He was a dedicated professor in the Department of Internal Medicine, Nihon University, Division of Respiratory Medicine, Tokyo, Japan, and as the leader of the study expert panel, had made significant contributions to the conception and design of this study, and the analysis and interpretation of the data.

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Authors’ contributions

All authors made substantial contributions to conception and design, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Paul Jones, Keiko Sato, Eri Sasaki, Osamu Hataji, Toru Oga, Yoshimi Suzukamo, Bruce Crawford and Yoko Sakai contributed to the conception and design of the study. Osamu Hataji contributed to the acquisition of data. All authors contributed to the data analysis and interpretation.

Disclosure statement

The corresponding author had full access to all the data and the final responsibility to submit for publication. Kenichi Hashimoto and Paul Jones are employees of GSK and hold stocks/shares. Eri Sasaki is an employee of GSK. Takeo Ishii and Keiko Sato are former employees of GSK and holds stocks/shares. Toru Oga, Osamu Hataji and Yoshimi Suzukamo have no conflicts of interest to declare. Bruce Crawford and Yoko Sakai are former employees of Syneos Health. Syneos Health received funding from GSK to conduct the study, and were involved in Part 1 and 2 interviews, Part 3 site monitoring, analysis of the study, and study report. Employees of Syneos Health were not paid for manuscript development.

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Consent for publication

All authors have provided final approval of the published version of the manuscript.

Data availability

Due to the nature of this research, participants of this study did not agree for their data to be shared publicly, so supporting data is not available.

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