Psychometric Validation of a Japanese Version of the emPHasis-10 Questionnaire, a Patient-Reported Outcome Measure for Pulmonary Hypertension — Multicenter Study in Japan —

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Background: The emPHasis-10 questionnaire is a disease-specific patient-reported outcome assessment of quality of life (QOL) in pulmonary hypertension (PH). The aim of this study was to psychometrically validate a linguistically validated Japanese version of the emPHasis-10.

Methods and Results: Japanese patients with PH (age ≥18 years) and no change in functional status, or initiation or change in PH-specific treatment during the past 3 months were recruited from 5 institutions from August 2018 to July 2019. A set of questionnaires was administered twice. The validity and reliability of the emPHasis-10 were assessed using the data of 76 patients. On concurrent validity analysis, a moderate-to-strong correlation was seen with the total score of all 5 external criteria (the Minnesota Living with Heart Failure modified for PH [MLHFO-PH], Hospital Anxiety and Depression Scale, Dyspnea-12 questionnaire, European Quality of Life-5 Dimensions questionnaire [EQ-5D], and 6-min walk test), with a notably strong correlation with the MLHFO-PH (0.77) and EQ-5D (–0.64). On known-group validity, a linear increasing trend of the emPHasis-10 score was observed across 4 World Health Organization functional status groups (Jonckheere-Terpstra test, 1-sided, P<0.001). Intraclass correlation coefficient for test-retest reliability was 0.86, and the Cronbach's α for internal consistency was 0.89.

Conclusions: The Japanese emPHasis-10 questionnaire is psychometrically valid to evaluate QOL in Japanese PH patients in a clinical setting.

Key Words: emPHasis-10; Japanese population; Patient-reported outcome; Psychometric validation; Pulmonary hypertension

Pulmonary hypertension (PH) is a condition in which the pulmonary artery pressure is increased due to various causes. It often progresses to right heart failure (HF), eventually leading to death. Although breathlessness and fatigue are the main symptoms, quality of life (QOL) is significantly impaired because of the impact on this disease not only on the physical aspect but also on the mental aspect. Advancement in medical therapy for pulmonary arterial hypertension (PAH), which improves the long-term prognosis of PH, has been observed over the past decade. In the treatment of PH, improving QOL through proper management is essential.

The emPHasis-10 questionnaire is a unidimensional, disease-specific patient-reported outcome (PRO) assessment of QOL in patients with PH, developed through joint research by the University of Manchester and the Pulmonary Hypertension Association UK, organized by patients with PH. It consists of 10 questions on the important compo-
Table 1. PH Patient Clinical Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total (n=76)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>56.5±15.2</td>
</tr>
<tr>
<td>Sex, female</td>
<td>61 (80.3)</td>
</tr>
<tr>
<td>Classification of pulmonary hypertension</td>
<td></td>
</tr>
<tr>
<td>PAH</td>
<td></td>
</tr>
<tr>
<td>Idiopathic PAH</td>
<td>31 (40.8)</td>
</tr>
<tr>
<td>Heritable PAH</td>
<td>2 (2.6)</td>
</tr>
<tr>
<td>Associated PAH</td>
<td></td>
</tr>
<tr>
<td>Connective tissue disease</td>
<td>9 (11.8)</td>
</tr>
<tr>
<td>Portal hypertension</td>
<td>4 (5.3)</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>7 (9.2)</td>
</tr>
<tr>
<td>PVOD and/or PCH</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>CTEPH</td>
<td>22 (29.0)</td>
</tr>
<tr>
<td>WHO functional class (n=75)</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>II</td>
<td>52 (69.3)</td>
</tr>
<tr>
<td>III</td>
<td>20 (26.7)</td>
</tr>
<tr>
<td>IV</td>
<td>2 (2.7)</td>
</tr>
<tr>
<td>6-min walk test (n=74) (m)</td>
<td>403.9±128.4</td>
</tr>
</tbody>
</table>

Table 2. emPHasis-10 Concurrent Validity: Correlations With Other Scales

<table>
<thead>
<tr>
<th>External criteria</th>
<th>Spearman rank correlation coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLHFQ-PH</td>
<td>0.77</td>
</tr>
<tr>
<td>HADS</td>
<td>0.52</td>
</tr>
<tr>
<td>Anxiety</td>
<td>0.42</td>
</tr>
<tr>
<td>Depression</td>
<td>0.53</td>
</tr>
<tr>
<td>D-12</td>
<td>0.36</td>
</tr>
<tr>
<td>Total</td>
<td>0.35</td>
</tr>
<tr>
<td>Physical</td>
<td>0.31</td>
</tr>
<tr>
<td>Affective</td>
<td>0.24</td>
</tr>
<tr>
<td>EQ-5D</td>
<td>-0.64</td>
</tr>
<tr>
<td>6-min walk test</td>
<td>-0.38</td>
</tr>
</tbody>
</table>

Data given as n (%) or mean±SD. Percentages may not sum up to 100% due to rounding. CTEPH, chronic thromboembolic pulmonary hypertension; PAH, pulmonary arterial hypertension; PCH, pulmonary capillary hemangiomatosis; PVOD, pulmonary veno-occlusive disease; WHO, World Health Organization.

Methods

Participants
We recruited native Japanese speaking patients with PH aged ≥18 years, with no change in World Health Organization (WHO) functional class and no initiation or change in PH-specific treatment for the past 3 months prior to recruitment. Patients were excluded when WHO functional class was expected to change or PH-specific treatment was expected to start or change during this study, or when patients were unable to understand and respond to the questionnaire due to comorbidities.

Data Collection
After ethics approval was obtained at each institution, recruitment was conducted from August 2018 to July 2019 at the following 5 institutions across Japan: International University of Health and Welfare Mitah Hospital; Kyorin University Hospital; Hokkaido University Hospital; Kyushu University Hospital; and Chiba University Hospital. This study was conducted in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects. Written informed consent was obtained from each eligible participant at the time of recruitment. The study was registered under UMIN-CTR (UMIN000033788).

Measures
The participating physicians collected data on participant demographic and clinical characteristics and asked participants to complete the questionnaires on site. A set of questionnaires was administered twice: on the day the participants provided informed consent (first questionnaire); and between 7 and 30 days after the first questionnaire (second questionnaire).

Regarding clinical characteristics, clinical classification of PH, WHO functional class, and 6-min walk test (6MWT) carried out ≤6 months before recruitment, were recorded.

The first questionnaire included the following self-administered questionnaires: the Japanese emPHasis-10; Minnesota Living with Heart Failure modified for PH (MLHFQ-PH); Dyspnea-12 (D-12) questionnaire; and the European Quality of Life-5 Dimensions questionnaire (EQ-5D) questionnaire.

MLHFQ-PH The MLHFQ-PH is a 21-item questionnaire originally developed as the MLHFQ. The MLHFQ has been widely used in a large body of research to measure health-related QOL in patients with HF. A Japanese version of the MLHFQ has also been developed. The psychometric properties of the MLHFQ (after its modification for patients with PH by replacing the term “heart failure” with “PH”) have been previously demonstrated. Each item is
The validity of the emPHasis-10 was assessed based on concurrent validity and known-group validity. For concurrent validity, associations with the external criteria (i.e., MLHFQ-PH; D-12 total, physical, and affective scores; HADS total, anxiety, and depression scores; EQ-5D; and 6MWT) were examined using Spearman’s rank correlation coefficient. Scales measuring similar concepts to the emPHasis-10 were expected to be moderately–highly correlated, whereas those measuring different concepts were expected to be poorly correlated. The correlation coefficient was interpreted as follows: 0.1, weak; 0.3, moderate; and 0.5, strong.

For known-group validity, the emPHasis-10 total scores were calculated for different groups of participants based on WHO functional classification. A linear trend was tested across groups with different levels of functional status using the Jonckheere-Terpstra test, with a 1-sided significance level of 0.05. It was hypothesized that the participant groups with a higher (worse) functional status would have a higher emPHasis-10 score.

Reliability was assessed by examining test-retest reliability and internal consistency. Test-retest reliability was measured as the extent to which responses to the emPHasis-10 agree between 2 time points in participants with stable conditions, using the intraclass correlation coefficient (ICC). A coefficient ≥0.7 was considered sufficient to confirm test-retest reliability. For internal consistency, the extent to which items in the emPHasis-10 were correlated with each other was calculated using Cronbach’s α coefficient. Cronbach’s α ≥0.7 was considered to indicate internally consistent scale.

Unanswered questionnaire items were treated as missing data. All analyses were performed using SAS version 9.4 or later (SAS Institute, Cary, NC, USA).
Results

Demographic and Clinical Characteristics
A total of 76 patients participated in the study. Participant demographic and clinical characteristics are summarized in Table 1. Mean (±SD) age was 56.2±15.2 years, and the majority of patients were women (80.3%). The most common PH classifications were idiopathic PAH and chronic thromboembolic PH, accounting for 40.8% and 29.0%, respectively. The majority of the participants were at WHO functional class II (69.3%), and the mean (±SD) 6MWT was 403.9±128.4 m.

Validity
On concurrent validity, a moderate-to-strong correlation was observed in the total and subscale scores of all the external criteria except for the affective aspects in D-12 (0.24; Table 2). Particularly, correlations were notably strong with the MLHFQ-PH (0.77) and EQ-5D (−0.64). On known-group validity, the mean (±SE) emPHasis-10 score increased in the groups with the worse WHO functional status (I, 5.0; II, 17.0±2.4; III, 24.1±6.1; and IV, 39.5±2.5) as hypothesized (Figure). A linear increasing trend was observed in the score across the 4 WHO functional classes (Jonckheere-Terpstra test, 1-sided, P<0.001).

Reliability
For the analysis of the test-retest reliability, 66 participants whose PH symptoms between the first and second questionnaire remained stable and who completed the emPHasis-10 were included. The ICC was 0.86, indicating a sufficient reproducibility. The internal consistency in responses obtained from 76 participants who completed the emPHasis-10 in the first questionnaire was 0.89, demonstrating a good consistency.

Discussion
The present study assessed the psychometric properties of the linguistically validated Japanese emPHasis-10 using data collected from patients with PH in hospitals across Japan, and found that the Japanese emPHasis-10 has good validity and reliability.

Overall, the present results were consistent with those of the original and other language versions. The internal consistency and test-retest reliability were slightly lower but were consistent with that of the original and 2 other versions (≥0.9 for all).7,10,11 The Japanese emPHasis-10 also had a strong correlation with the MLHFQ-PH, consistent with the original and Turkish versions (0.61 and 0.85, respectively).7,10 and had a moderate association with 6MWT, consistent with the original version (−0.40).7 Furthermore, the Japanese emPHasis-10 was equally capable of discriminating the levels of exertional intolerance, similar to the English and Turkish versions.7,10

Meanwhile, the correlations between the Japanese emPHasis-10 and HADS and D-12 varied from the original version. The Japanese version had weaker correlations with those measurements than the English version (HADS, 0.77; D-12, 0.74). The correlation was particularly weak in the affective aspects of D-12. The present mean (±SD) HADS and D-12 scores were lower (HADS: total, 8.8±7.0; anxiety, 4.6±3.8; depression, 4.2±3.7; D-12: total, 2.3±4.1; physical, 1.9±2.8; affective, 0.4±1.7) than the original version (HADS: total, 13.3±7.5; anxiety, 6.9±4.4; depression, 6.3±3.9; D-12: total, 12.8±9.8; physical, 8.5±5.8; affective, 4.4±4.6).7 These results are probably attributable to the fact that this study involved mainly patients with mild and stable symptoms (i.e., the proportion of patients with WHO functional class II was larger than that with III), and to the present inclusion criteria, which limited patient selection to those whose symptoms had remained stable after pharmacological therapy for a certain time period. For these reasons, the present patients probably had lower levels of anxiety and depression and had lower physical and mental impacts of dyspnea, resulting in the weaker correlations between the Japanese emPHasis-10 and HADS and D-12.

Regardless of these correlations with the external criteria, the Japanese emPHasis-10 overall has sound validity and reliability for assessing disease-specific QOL in Japanese patients with PH. The emPHasis-10, compared with the Cambridge Pulmonary Hypertension Outcome Review (CMAPHOR)10 and Pulmonary Arterial Hypertension Symptoms and Impact (PAH-SYMPECT®) PRO often used in research, is a shorter and easier to administer questionnaire in clinical settings, for which it was developed.7 This questionnaire has been translated into various languages including Dutch, Spanish, French, German, Italian, and Turkish.8–11 Due to its simplicity, a wide use in routine clinical practice and in clinical research can be expected. Furthermore, this simple questionnaire can also achieve comparable assessment results to the widely used disease-specific PRO.

Study Limitations
This study had some limitations. The study involved patients with stable symptoms after pharmacological therapy, and a few had WHO functional class I or IV. However, the distribution of PH classifications was consistent with that in a previous multicenter registry study conducted in Japan.6 Further research is need to reinforce the present known-group validity results. Given the exclusion of patient groups who were not targeted in this study due to their comorbid conditions, the Japanese emPHasis-10 is a valid tool for patients with PH after pharmacological interventions. Another limitation is that the emPHasis-10 was administered at 2 time points in this study. For the sensitivity assessments for change over time, further study is required.

Conclusions
The linguistically validated Japanese version of the emPHasis-10 has sound psychometric properties in terms of validity and reliability. The Japanese emPHasis-10 is a valid questionnaire that evaluates QOL in Japanese patients with PH in a clinical setting.

Acknowledgments
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Data Availability
Individual de-identified participant data will not be shared.
Disclosures

Y.T. received lecture fees from Actelion Pharmaceuticals Japan and Nippon Shinyaku, and received research funding from Actelion Pharmaceuticals Japan and Nippon Shinyaku. K.A. received lecture fees from Actelion Pharmaceuticals Japan and Bayer, and received research funding from Actelion Pharmaceuticals Japan. N.T. received lecture fees from Actelion Pharmaceutical Japan, Bayer, Nippon Shinyaku, and Daiichi Sankyo. I.T. received research funding and scholarship funds/donations from Actelion Pharmaceuticals Japan. The authors declare no conflicts of interest.

IRB Information

Ethics approval was obtained from International University of Health and Welfare Mita Hospital (5-17-24), Kyorin University Hospital (H30-078), Hokkaido University Hospital (018-0169), Kyushu University Hospital (30-470), and Chiba University Hospital (3305).

References


28. Terpstra TJ. The asymptotic normality and consistency of kendall’s test against trend, when ties are present in one ranking. *Indagationes Mathematicae* 1952; 55: 327 – 333.


