Circulation Reports
Circ Rep 2020; 2: 255–259
doi:10.1253/circrep.CR-20-0014

ORIGINAL ARTICLE
Pulmonary Circulation

Psychometric Validation of a Japanese Version of the emPHasis-10 Questionnaire, a Patient-Reported Outcome Measure for Pulmonary Hypertension

— Multicenter Study in Japan —

Rika Takeyasu, BSc; Yuichi Tamura, MD, PhD; Kohtaro Abe, MD, PhD; Ayumi Goda, MD, PhD; Toru Satoh, MD, PhD; Rika Suda, MD, PhD; Nobuhiro Tanabe, MD, PhD; Ichizo Tsujino, MD, PhD; Tsutomu Yamazaki, MD, PhD; Koichiro Tatsumi, MD, PhD

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 [MLHFQ-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 MLHFQ-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.[1] 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.[2,3] Advancement in medical therapy for pulmonary arterial hypertension (PAH),[4] which improves the long-term prognosis of PH,[5,6] 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.[7] It consists of 10 questions on the important compo-

Received February 11, 2020; accepted February 11, 2020; J-STAGE Advance Publication released online March 20, 2020 Time for primary review: 1 day

Graduate School of Public Health (R.T.), Innovation and Research Support Center (T.Y.), International University of Health and Welfare, Tokyo; Pulmonary Hypertension Center, International University of Health and Welfare Mita Hospital, Tokyo (R.T., Y.T.); Department of Cardiology, International University of Health and Welfare School of Medicine, Narita (Y.T.); Department of Cardiovascular Medicine, Graduate School of Medical Sciences, Kyushu University, Fukuoka (K.A.); Department of Cardiovascular Medicine, Kyorin University School of Medicine, Tokyo (A.G., T.S.); Department of Respirology, Graduate School of Medicine, Chiba University, Chiba (R.S., N.T., K.T.); Department of Respirology, Pulmonary Hypertension Center, Saiseikai Narashino Hospital, Narashino (N.T.); and Internal Medicine I, Hokkaido University Hospital, Sapporo (I.T.), Japan
Mailing address: Yuichi Tamura, MD, PhD, Pulmonary Hypertension Center, International University of Health and Welfare Mita Hospital, 1-4-3 Mita, Minato-ku, Tokyo 108-8329, Japan. E-mail: tamura.u1@gmail.com

ISSN-2434-0790

Table 1. PH Patient Clinical Characteristics

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

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; PH, pulmonary hypertension; PVOD, pulmonary veno-occlusive disease; WHO, World Health Organization.

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

External criteria	Spearman rank correlation coefficient
MLHFQ-PH	0.77
HADS	
Total	0.52
Anxiety	0.42
Depression	0.53
D-12	
Total	0.35
Physical	0.31
Affective	0.24
EQ-5D	−0.64
6-min walk test	−0.38

D-12, Dyspnea-12 questionnaire; EQ-5D, European Quality of Life-5 Dimensions questionnaire; HADS, Hospital Anxiety and Depression Scale; MLHFQ-PH, Minnesota Living with Heart Failure modified for pulmonary hypertension.

nents of PH, such as breathlessness, fatigue, lack of energy, and social restrictions, and concerns about the effects of the disease on the patient's family and friends. Each item is evaluated on a scale from 0 to 5. The total score is the sum of the 10 item scores, and ranges from 0 to 50 points. The questionnaire is suitable for use in the clinical setting, and is a brief and comprehensive evaluation of the effects of PH on the patient's life. Validation of an extended version has been confirmed in a follow-up study by the developers, who also examined its use in patients with chronic thromboembolic PH.[8]

Although emPHasis-10 is a relatively new questionnaire, it has already been translated into several languages such as Dutch, Spanish, French, German, Italian, and Turkish,[9,10] and its psychometric properties have been assessed in some languages.[10,11] The expanded use of the emPHasis-10 is expected worldwide because it is easy to use, and can be used for non-profit research/medical purposes after a simple application process. In Japan, we conducted a linguistic validation of a Japanese-translated version of the emPHasis-10.[12] Therefore, the aim of this study was to psychometrically validate the Japanese emPHasis-10.

Methods

Participants

We recruited native Japanese speaking patients with PH aged ≥18 years, with no change in World Health Organization (WHO) functional class[13] 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 Mita 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,[14] WHO functional class,[13] 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);[15] Dyspnea-12 (D-12) questionnaire;[16,17] Hospital Anxiety and Depression Scale (HADS);[18] and the European Quality of Life-5 Dimensions (EQ-5D) questionnaire.[19]

MLHFQ-PH The MLHFQ-PH is a 21-item questionnaire originally developed as the MLHFQ.[20] 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.[21] 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.[15] Each item is

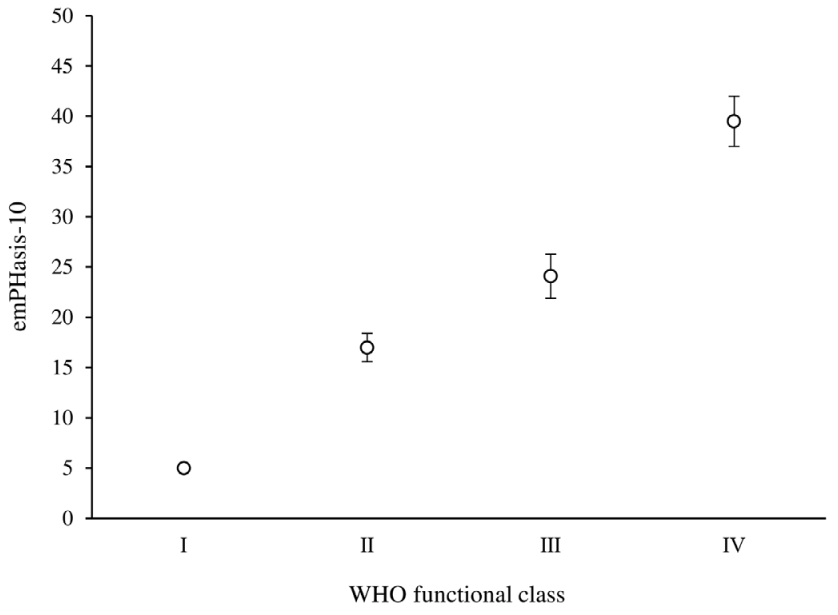

Figure. Mean emPHasis-10 score vs. World Health Organization (WHO) functional class. Differences in emPHasis-10 score between the WHO functional classes was tested using Jonckheere–Terpstra test (1-sided, P<0.001). (○) Mean; error bar, standard error.

rated between 0 and 5, based on the impact of the disease on physical, socioeconomic, and psychological aspects of daily life. The total score of the MLHFQ-PH is the summed score of all of the items and ranges from 0 to 105, with higher scores reflecting a worse perceived QOL.

D-12 The D-12 questionnaire is a 12-item instrument measuring the severity of dyspnea based on physical and affective aspects (7 and 5 items, respectively) that require no reference to activity.[16,17] Each item is rated at 0–3, and the total score ranges from 0 to 36, with higher scores indicating worse dyspnea. A validated Japanese version of the D-12 questionnaire was used in this study after approval to use this questionnaire was obtained.

HADS The HADS is a 14-item tool measuring the state of anxiety and depression.[18] Seven items assess the anxiety and depression subscales, respectively. The total score is the summed score of each item (ranging between 0 and 3), and has a range of 0–42. Higher scores indicate greater emotional distress. A validated Japanese version of the HADS[22,23] was used in this study.

EQ-5D The EQ-5D is a 5-item questionnaire measuring general health status.[19] The index score produced by conversion of the assessed health status ranges from −0.025 to 1.00. A score of 1 indicates "perfect health" and a score of 0 indicates "death". The Japanese version of a 5-level version of the EQ-5D[24] was included in the first questionnaire.

The second questionnaire was administered only to participants whose symptom severity had remained stable since the first questionnaire. The second questionnaire consisted solely of the Japanese emPHasis-10.

Statistical Analysis

Participant demographic and clinical characteristics were analyzed descriptively. For item analyses of the Japanese emPHasis-10, the total score was calculated, and missing data and floor and ceiling effects were examined. Flooring and ceiling effects were determined when ≥15% of the data fell into the worst or best status.[25]

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.[26] 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,[27,28] 1-sided at a 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.[29] 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 consistency.[30]

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 56.5±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.

Item Analysis

The mean (±SD) Japanese emPHasis-10 total score was 19.4±10.6. There was no ceiling (0.0%) or flooring effect (1.3%) identified. Only 1 missing data point was noted.

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±1.4; III, 24.1±2.2; 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)[31] and Pulmonary Arterial Hypertension Symptoms and Impact (PAH-SYMPACT®)[32] 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.[9–11] 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

This research was supported by Health and Labor Sciences Research Grant and by AMED under Grant Number JP19lk1601003h0002.

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 other 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).

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