Development and validation of a set of patient reported outcome measures to assess effectiveness of asthma prophylaxis

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Abstract

Background: Several asthma patient reported outcome measures (PROMs) have been developed in developed countries. Since social and cultural differences may indirectly influence the PROM, therefore, this study has been carried out in Northern Sri Lanka to develop an Asthma Control PROM (AC-PROM) Tamil in the local context.

Methods: The AC-PROM Tamil was developed in 3 steps: item generation, item reduction and psychometric evaluation as guided by the USA Food and Drug Administration. Items were generated through thematic analysis from six focus group discussions among patients with asthma. Items were generated in Tamil and English Languages. A clinician and a clinical pharmacologist refined the items to suit the cultural context. Items were converted to an interviewer administered questionnaire in Tamil in the format of 5–point Likert scale. Item reduction was done by two rounds of online Delphi surveys among 10 experts and an exploratory factor analysis among 200 patients with asthma. Thus developed AC-PROM Tamil was assessed by experts for face and content validity. Criterion validity was evaluated against the forced expiratory volume in one second of 187 patients with asthma. Cut-off value for PROM to assess the asthma control was determined by receiver operating characteristic curve. Reliability was verified by Cronbach’s alpha coefficient.
**Results:** From thematic analysis of FGD 10 items were generated and these items were refined and subjected to item reduction. During Delphi survey out of 10 items, one was removed. In exploratory factor analysis another one item was removed and remaining 8 items were categorised under 2 factors. Cronbach’s alpha coefficient for AC-PROM Tamil was 0.904, which indicated good reliability. Clarity and relevance of the content of the items were confirmed by the experts. Criterion validity was demonstrated significant correlation between AC-PROM Tamil and forced expiratory volume in one second \((r = 0.66, p = 0.001)\). Cut-off value of AC-PROM Tamil to detect asthma control was 28.5 with sensitivity (79%) and specificity (71%). The AC-PROM Tamil has moderate accuracy \((\text{AUC} = 0.796; 95\% \text{ CI: 0.73-0.86})\). Response rate of the AC-PROM Tamil was 100% with no missing data and time taken to complete the PROM was 3-4 minutes.

**Conclusion:** The AC-PROM Tamil is a simple, reasonably accurate, reliable, objective and valid tool to assess effectiveness of asthma control in Tamil speaking patients during clinical practice and researches.

**Keywords:** Patient reported outcome measure, Effectiveness, Asthma control, Inhaled medications, Development, Validation

**Background**

Asthma is one of the common chronic respiratory diseases, affecting 339 million people worldwide, and Global Asthma Network has marked Sri Lanka as one of the high prevalence countries (1). In Sri Lanka, asthma accounts for 13.8% of the non-communicable diseases (2). Although asthma cannot be cured, appropriate management can control the disease and enable people to enjoy good quality of life (1). The aim of asthma treatment is to achieve asthma control.
which includes minimising the risk of exacerbations, reducing the adverse effects and minimising asthma-related mortality (3). Inhaled medications, which are being used for more than 40 years, are the mainstay in asthma control (4).

Effectiveness of inhaled medications in control of asthma is assessed by improvement in the symptoms, lung function measurements and measuring biomarkers in blood, broncho alveolar lavage and bronchial biopsy (5). However, improvements in the symptoms, peak expiratory flow rate and forced expiratory volume in one second (FEV1) are generally used in clinical practice. The current trend in assessing effectiveness of treatment options for chronic diseases in routine clinical care is by using patient reported outcome measures (PROMs) which capture the patients’ subjective perceptions of their health status, effects of health care interventions, functional status and their health related quality of life that occur as a result of treatment (6,7,8). Patient reported outcome measure is defined as “any report of the status of the patient’s health condition that comes directly from the patient, without interpretation of the patient’s response by a clinician or anyone else” (9). Incorporating the patients’ perspective into clinical management could provide more holistic interpretation and comprehensive assessment of benefits of the treatment because patient can be an invaluable source of information for monitoring disease control (7, 10).

Since social and cultural factors can influence the patients’ perception of well-being and disease which indirectly influence the PROMs (11), there is a need for developing specific PROM for different social and cultural settings. Although, many PROMs had been in use in developed countries, suitability of such tools for patients from developing countries is largely unknown and to our best of knowledge, there is no published PROMs for developing countries in the literature. Therefore, this study has been conducted in Northern Sri Lanka with the aim of developing Asthma Control PROM (AC-PROM) Tamil which can be used to assess effectiveness of asthma control.
Methods

This study was conducted in the Northern Province of Sri Lanka. We followed the three steps namely, item generation, item reduction and psychometric evaluation, recommended by the USA Food and Drug Administration to develop and validate the PROM (9). Approval was obtained from the Ethics Review Committee, Faculty of Medicine, University of Colombo, Sri Lanka (EC-18-108) and administrative approvals were obtained from relevant authorities. Written informed consent was obtained from all participants.

Asthma was defined as symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and intensity together with variable airflow limitation (3). This definition was used wherever the patients were involved in this procedure.

Item generation

Six focus group discussions (FGD) were conducted with 51 adult asthmatic patients who were on inhaled medications at least for 3 months to generate the items. They were recruited from the medical clinics of Teaching Hospital, Jaffna. Patients with chronic obstructive pulmonary disease, tuberculosis and congestive cardiac failure were excluded. Purposive sampling was used to recruit participants with the aim of achieving maximum variation and sampling frame confirmed patients with a range of age, sex and disease duration were recruited. Moderator guide was developed and FGDs were moderated by researcher. The FGDs were held separately for three distinct groups based on the educational level of participants: (1) Grade 1-5, (2) Grade 6-11 and (3) advanced level and above. For each category 2 FGDs were conducted (12). Number of participants per group was 6-10 (13). All FGDs were audio recorded.

Item reduction
Both qualitative (Delphi survey) and quantitative (exploratory factor analysis) methods were used in item reduction. Two rounds of online Delphi survey were conducted with a panel of 10 experts comprising respiratory physicians, general physicians, clinical pharmacologists, general practitioners and senior medical officers working in medical units. Ten items generated from the FGDs with patients were submitted to the expert panel inviting each member to rate the item in a 5-point Likert scale from 1 ‘not at all important’ to 5 ‘very important’. Items which were selected having scores above the cut-off value in the round 1 were subjected for round 2.

Exploratory factor analysis (EFA) is recommended to reduce the number of items and group the similar items under different categories (14). Data for EFA were obtained from 200 asthmatic patients who were on inhaled medications at least for 3 months recruited at Base Hospital, Tellipalai, Jaffna. Patients with chronic obstructive pulmonary disease, tuberculosis and congestive cardiac failure were excluded. Sample size for EFA was calculated based on subject to item ratio of 5:1 (15) and minimum sample size should be 200 (16). Considering these numbers, facts, sample size for EFA was determined as 200. Systematic random sampling was used to select participants and every other participant was selected starting from either first or second patient. Nine items selected for EFA were rated with 5-point Likert scale and used for data collection.

**Psychometric evaluation**

Reliability, face, content and criterion validity and acceptability were assessed. Reliability was assessed during the EFA phase whereas face and content validity were assessed by the experts subjectively during the Delphi survey.

Criterion validity of AC-PROM Tamil was evaluated with percent predicted FEV1 which is the gold standard measurement for asthma control (17). Sample size of 187 was determined using
Buderer’s formula (sensitivity 95%, specificity 85%) (18). Participants who were on inhaled medications at least for 3 months were consecutively recruited till reaching 187. Patients who have not participated in FGD/EFA were recruited from the medical clinics of Teaching Hospital Jaffna. Same exclusion criteria were used. Lung function tests were done in these patients using spirometer according to American Thoracic society and European Respiratory society guidelines (19, 20).

Acceptability of AC-PROM Tamil was assessed by examining the response rate, completion rate and response time for completion among 20 patients with asthma receiving treatment at medical clinics of Teaching Hospital Jaffna who were not included in FGD/EFA or criterion validation process.

**Data analysis**

Data were computerized and analysed as per the objectives. Recordings of FGD were transcribed into verbatim and items were generated through thematic analysis. A clinician and a clinical pharmacologist refined the items.

For item reduction by Delphi survey, scores assigned by the ten experts for each item was compiled and the mean score was calculated. Items scored more than 3 (21) were subjected to round 2. Items which had a mean score above 4 with 80% consensus among participants (22) were selected for EFA.

In EFA, principal component analysis was carried out for the retained items (n=9) from Delphi survey. Kaiser’s criteria (eigenvalues >1) was used for identifying number of factors and varimax rotation was used to categorize the related items under different factors (23).

Cronbach’s alpha coefficient was used to assess internal consistency (reliability). Cronbach’s alpha coefficient 0.7 or above suggests that items have acceptable internal consistency (24).
Criterion validity was determined using Pearson correlation coefficient between FEV1 and AC-PROM Tamil of the patients. A Receiver operating characteristics (ROC) curve plotted on sensitivity against (1-specificity) was used to determine the cut-off value of AC-PROM Tamil for asthma control. The optimal cut-off value for asthma control was determined by closest distance from ROC curve to the upper left corner of graph which was determined by the following formula; 
\[ d^2 = [(1-S_{N})^2 + (1-S_p)^2] \] in which \( S_{N} \) – sensitivity, \( S_p \) – specificity (23, 25). Accuracy of AC-PROM Tamil was measured by area under the curve (AUC).

**Results**

**Item generation**

Fifty one patients with asthma were participated across six FGDs and mean age of the participants was 51 years (SD ± 15.47) with male: female ratio of 1:2.5. Each FGD lasting for 90 minutes. Number of participants who have been educated between grades 1 and 5, grades 6 and 11 and advanced level and above were 14, 18 and 19 respectively. Number of participants per FGD varied from 6 to 10. Ten items were generated through thematic analysis which are shown in Table 1.

**Table 1** List of generated items

| Item                                                                 | Page |
|----------------------------------------------------------------------|------|
| 1. My cough is reducing after using inhaler                         | 18   |
| 2. I am able to breathe without difficulties                        | 19   |
| 3. After using inhaler heaviness of chest symptoms reduced          | 20   |
| 4. I feel less tiredness                                            | 21   |
| 5. I am able to sleep well                                          | 22   |
| 6. Inhaler controls my wheeze                                       | 23   |
| 7. After using inhaler, I need less frequency of nebulization       |      |
Item reduction

Delphi survey

In round 1, scores of all 10 items were above the cut-off value. In round 2, all except one item (while on treatment, I feel less tiredness) scored above the cut-off value and these 9 items were taken for EFA.

Exploratory factor analysis

Mean age of the 200 participants was 57 years (SD ± 13.56) with male: female ratio of 1:4. Out 9 items, 8 had the correlation coefficient was > 0.3. The item (While on treatment, I can go to work regularly) scored <0.3, was removed. From principal component analysis 2 factors with eigenvalues >1 were identified and similar items under these 2 factors were categorised (Table 2). Factor 1 items were related to activity/exacerbation and factor 2 items were related to asthma symptoms.

Table 2 Items selected for asthma control patient reported outcome measures

| Factor 1 (Activity/ Exacerbation) | Factor 2 (Asthma symptoms) |
|----------------------------------|-----------------------------|
| When I am on treatment I can do my household activities | When I am on treatment, my cough becomes less |
| When I am on treatment I can sleep well | When I am on treatment, I can breathe without difficulties |
When I am on treatment frequency of nebulization becomes less
When I am on treatment, heaviness of my chest becomes less
While on treatment need for hospitalization is reduced
While on treatment, I feel less wheezing

The retained 8 items were converted to a 5-point Likert scale with 1 indicating ‘never’ and 5 indicating ‘all the time’.

**Psychometric evaluation**

Cronbach’s alpha coefficient for AC-PROM Tamil was 0.904 indicating good reliability. Observations made by the experts to improve the clarity and relevance of the items were incorporated.

**Criterion validity**: Mean age of the 187 participants was 54.1 years (SD ± 12.4) with ranging from 18 to 75 years and majority (72.2%, n=135) were female. The AC-PROM Tamil scores of the patients ranged from 8 to 40. Significant correlation was observed between AC-PROM Tamil and FEV1 ($r = 0.66$, $p = 0.001$). Figure 1 shows the ROC curve for AC-PROM Tamil. Cut-off value of AC-PROM Tamil for asthma control was 28.5 which corresponded with closest distance (0.11) of the ROC curve to the left hand corner of the graph with the sensitivity (79%) and specificity (71%) which is shown in (Table 3). The AUC of the ROC curve was 0.796 (95% CI: 0.73-0.86; $p = 0.01$), indicating moderate accuracy in differentiating between controlled and uncontrolled asthma.
Figure 1 Receiver operating characteristic curve for asthma control patient reported outcome measure

Table 3 Validity of the asthma control patient reported outcome measure

| Cut-off value | Sensitivity | Specificity | PPV  | NPV   | LR+  | LR-  |
|---------------|-------------|-------------|------|-------|------|------|
| >28.5         | 79.1%       | 70.8%       | 72.4%| 78.6% | 2.71 | 0.29 |

PPV – Positive predictive value, NPV – Negative predictive value, LR+ - Likelihood ratio positive, LR- - Likelihood ratio negative

Acceptability of the AC-PROM Tamil: Response rate of the AC-PROM Tamil was 100% with no missing data. Time taken to complete AC-PROM Tamil was 3-4 minutes.

Discussion

There is no PROM for asthma that is validated involving patients in Sri Lanka. Currently, in Sri Lanka clinicians assess the asthma control using GINA symptom control tool. Purpose of this
study was to develop and validate PROM to assess the control of asthma involving patients with asthma in Sri Lanka. The AC-PROM Tamil was developed through recommended multistep methodology (9) including FGD, Delphi survey, EFA and criterion validity. As inhaled medications are the mainstay of treatment for asthma, AC-PROM Tamil was designed to specifically assess the effectiveness of asthma prophylaxis with inhaled medications. This is the first asthma control PROM developed in Sri Lanka.

We chose FGD for item generation as it incorporates the subjective views of patients with asthma from diverse social and educational background. Item reduction was done with the aim of removing the unsuitable items and developing a simple and applicable tool. Purpose of the Delphi survey was to get the reliable consensus of the experts on the generated items and to assess the face and content validity, while EFA was carried out to reduce the items by statistical method and to assess reliability of the tool. During Delphi Survey an item was removed which was a vague symptom (while on treatment, I feel less tiredness). During EFA another item was removed (while on treatment, I can go to work regularly) which was not suitable for unemployed patients. At the end of this extensive process eight items were retained and taken for AC-PROM Tamil. Reliability of AC-PROM Tamil was good (Cronbach’s alpha coefficient > 0.7).

When comparing the AC-PROM Tamil with already existing PROMs for asthma, there were similarities and dissimilarities. Number of items in AC-PROM Tamil was 8. Number of items in the other PROMs varied from 5 to 17: Asthma Control Test (ACT) - 5 items; Asthma Control Questionnaire (ACQ) - 7 items Lara Asthma Symptom Scale (LASS) - 8 items and Asthma Therapy Assessment Questionnaire (ATAQ) - 17 items (26, 27, 28, 29). In AC-PROM Tamil items were categorised under 2 factors (activity/ exacerbation and symptoms). There were no grouping of items in ACT, ACQ and LASS while items of ATAQ were categorised under 5 domains (control, communication, behaviour, self-efficacy and knowledge). In ACQ, in addition to the symptoms, measurement of FEV1 was also included. Like ACT, LASS and ATAQ the AC-PROM
Tamil does not require measurement of FEV1. Further, the AC-PROM Tamil had moderate correlation with FEV1 while ACT and LASS had mild correlation with FEV1 (28, 29). Criterion validity of ACT was assessed against specialist assessment of asthma control and FEV1 while other three PROMs were assessed for construct validity. We have assessed the criterion validity of AC-PROM Tamil using FEV1. Sensitivity and specificity of the cut-off value of the AC-PROM Tamil score (28.5) for asthma control were 79.1% and 70.8% respectively with the positive predictive value of 72.4% and negative predictive value of 78.6%. Whereas, sensitivity and specificity of ACT to identify uncontrolled asthma were 71.3% and 70.8% respectively with the positive predictive and negative predictive values of 72.6% and 63.3% respectively (28). The AC-PROM Tamil has similar specificity and positive predictive values as ACT and better sensitivity and negative predicted value. The AC-PROM Tamil specifically assesses the asthma control with inhaled medications while ACT, ACQ, LASS and ATAQ assess asthma control in general.

The latest GINA symptom control tool comprises of 4 indicators: daytime symptoms, night-time waking, short acting beta2-agonist use and activity limitation. The AC-PROM Tamil assess the asthma symptoms wheeze, chest tightness, shortness of breath and cough (3) specifically, while the GINA tool assesses vaguely as daytime symptoms. The AC-PROM Tamil is a numerical tool validated with FEV1 while the GINA is a categorical tool. Therefore, AC-PROM Tamil can assess the asthma control more accurately than GINA criteria (3). As it is a numerical tool the AC-PROM Tamil is more sensitive to change in symptom control and can be used to assess the patient progress.

Further, the AC-PROM Tamil is a feasible tool as the response rate was 100% with no missing data and takes less than 5 minutes to complete. However, the actual usefulness of the AC-PROM Tamil need to be confirmed by applying the tool in a larger population.
Conclusions

We conclude that the AC-PROM Tamil is a simple, reasonably accurate, reliable and valid tool that specifically assesses the effectiveness of asthma prophylaxis in patients with asthma by assessing the asthma control. Asthma control is detected by the PROM score of 28.5 or more. As it takes only few minutes to complete it can be used even in busy clinic settings. Further it has the advantage of not requiring measurement of FEV1, which makes a suitable tool for resource limited settings where spirometer is not available. The above-mentioned properties make the AC-PROM Tamil as a suitable tool for the use in routine clinical practice and researchers to assess the asthma control and progress particularly in developing countries.

Abbreviations

PROM: patient reported outcome measure, FGDs: focus group discussions, EFA: exploratory factor analysis, FEV1: forced expiratory volume in one second, ROC curve: receiver operating characteristic curve, ACT: asthma control test, ACQ: asthma control questionnaire, ATAQ: asthma therapy assessment questionnaire

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Availability of data and materials
This is a part of a larger study. The dataset generated and analysed during the current study are not publicly available but available from the corresponding author on a reasonable request.

Author’s contribution
SSR, TSN, NG, GS and YG were involved in the research conception. Study was conceptualized by all 5 authors. YG was the principal investigator and responsible for the data collection, entry and analysis with TSN and SSR for manuscript preparation. All authors approved the manuscript.

Ethics approval and consent to participants
This study was conducted in accordance with the Declaration of Helsinki. Ethical permission was granted by the Ethics Review Committee, Faculty of Medicine, University of Colombo, Sri Lanka (EC-18-108). Permission was obtained from the hospital authorities to collect the data. Written informed consent was obtained from all participants.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.
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