

Article

Reliability and validity of the Thai Drug Hypersensitivity Quality of Life Questionnaire: a multi-center study

YUDA CHONGPISON¹, PAWINEE RERKNIMITR^{2,3}, CAMERON HURST⁴,
PUNGJAI MONGKOLPATHUMRAT^{3,5}, SIRINOOT PALAPINYO⁶,
LEENA CHULAROJANAMONTRI⁷, YUTTANA SRINOULPRASERT⁸,
TICHA RERKPATTANAPIPAT⁹, KUMUTNART CHANPRAPAPH¹⁰,
WAREEPORN DISPHANURAT¹¹, PANLOP CHAKKAVITTUMRONG¹²,
NAPATRA TOVANABUTRA¹³, CHUTIKA SRISUTTIYAKORN¹³,
CHONLAPHAT SUKASEM¹⁴, PAPAPIT TUCHINDA⁷, ILARIA BAIARDINI¹⁵,
and JETTANONG KLAEWSONGKRAM^{3,5}

¹Center for Excellence in Biostatistics, Faculty of Medicine, The Skin and Allergy Research Unit, Chulalongkorn University, 1873 Rama IV Rd, Pathum Wan, Bangkok, Thailand, ²Division of Dermatology, Department of Medicine, Faculty of Medicine, The Skin and Allergy Research Unit, Chulalongkorn University, 1873 Rama IV Rd, Pathum Wan, Bangkok, Thailand, ³King Chulalongkorn Memorial Hospital, Thai Red Cross Society, 1873 Rama IV Rd, Pathum Wan, Bangkok, Thailand, ⁴Center for Excellence in Biostatistics, Faculty of Medicine, Chulalongkorn University, 1873 Rama IV Rd, Pathum Wan, Bangkok, Thailand, ⁵Division of Allergy and Clinical Immunology, Department of Medicine, Faculty of Medicine, The Skin and Allergy Research Unit, Chulalongkorn University, 1873 Rama IV Rd, Pathum Wan, Bangkok, Thailand, ⁶Department of Pharmacy Practice, Faculty of Pharmaceutical Sciences, Chulalongkorn University, 254 Phayathai Rd, Pathum Wan, Bangkok, Thailand, ⁷Department of Dermatology, Faculty of Medicine Siriraj Hospital, Mahidol University, 2 Wang Lang Rd., Bangkok Noi, Bangkok, Thailand, ⁸Department of Immunology, Faculty of Medicine Siriraj Hospital, Mahidol University, 2 Wang Lang Rd., Bangkok Noi, Bangkok, Thailand, ⁹Division of Allergy, Immunology and Rheumatology, Department of Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, 270 Rama VI Road, Ratchathewi, Bangkok, Thailand, ¹⁰Division of Dermatology, Department of Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, 270 Rama VI Road, Ratchathewi, Bangkok, Thailand, ¹¹Division of Dermatology, Department of Medicine, Faculty of Medicine, Thammasat University, 95 Moo 8 Phahonyothin Rd, Khlong Luang, Pathumthani, Thailand, ¹²Dermatological Division, Department of Internal Medicine, Chiang Mai University, 110 Intha-Warorot Rd Mueang Chiang Mai District, Chiang Mai, Thailand, ¹³Division of Dermatology, Department of Medicine, Phramongkutklao Hospital, Phramongkutklao College of Medicine, 315 Ratchawithi Rd, Ratchathewi, Bangkok, Thailand, ¹⁴Division of Pharmacogenomics and Personalized Medicine, Department of Pathology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, 270 Rama VI Road, Ratchathewi, Bangkok, Thailand, and ¹⁵Department of Biomedical Science, Personalized Medicine Clinic Asthma & Allergy, Humanitas Clinical and Research Center, Humanitas University, Via Rita Levi Montalcini, 4, 20090 Pieve Emanuele Milan, Italy

Address reprint requests to: Jettanong Klaewsongkram, Division of Allergy and Clinical Immunology, Department of Medicine, Faculty of Medicine, The Skin and Allergy Research Unit, Chulalongkorn University, Bangkok 10330, Thailand.
Tel: +66-22-56-4000x80601; Fax: +66-22-54-2323; Email: jettanong.k@chula.ac.th

Editorial Decision 10 August 2018; Accepted 18 September 2018

Abstract

Objective: To adapt the Drug Hypersensitivity Quality of Life (DrHy-Q) Questionnaire from Italian into Thai and assess its validity and reliability.

Design: Prospectively recruited during January 2012–May 2017.

Setting: Multicenter; six Thai tertiary university hospitals.

Study Participants: Total of 306 patients with physician-diagnosed drug hypersensitivity.

Interventions: Internal consistency and test–retest reliability were evaluated among 68 participants using Cronbach's α and intra-class correlation coefficient (ICC). The validity of Thai DrHy-Q was assessed among 306 participants who completed World Health Organization Quality of Life-BREF (WHOQOL-BREF-THAI). Construct and divergent validities were assessed for Thai DrHy-Q. Known-groups validity assessing discriminating ability was conducted in Thai DrHy-Q and WHOQOL-BREF-THAI.

Main outcome measures: Validity; reliability; single vs. multiple drug allergy; non-severe cutaneous adverse reactions (SCAR) vs. SCAR.

Results: Thai DrHy-Q showed good reliability (Cronbach's $\alpha = 0.94$ and ICC = 0.8). Unidimensional factor structure was established by confirmatory factor analysis (CFI&TLI = 0.999, RMSEA = 0.02). Divergent validity was confirmed by weak correlation between Thai DrHy-Q and WHOQOL-BREF-THAI domains (Pearson's $r = -0.41$ to -0.19). Known-groups validity of Thai DrHy-Q was confirmed with significant difference between patients with and without life-threatening SCAR ($P = 0.02$) and patients with multiple implicated drug classes vs. those with one class ($P < 0.01$); while WHOQOL-BREF-THAI could differentiate presence of life-threatening SCAR ($P < 0.01$) but not multiple-drug allergy.

Conclusions: Thai DrHy-Q was reliable and valid in evaluating quality of life among patients with drug hypersensitivity. Thai DrHy-Q was able to discriminate serious drug allergy phenotypes from non-serious manifestations in clinical practice and capture more specific drug-hypersensitivity aspects than WHOQOL-BREF-THAI.

Key words: drug hypersensitivity, quality of life, validity and reliability, adverse drug reaction

Introduction

Drug hypersensitivity in Thailand has been a prominent problem among Thai population [1–3]. Drug hypersensitivity, by its nature, is dynamic with some symptoms subsiding quickly, and patients recovering in a short time without any sequelae; whereas, other patients have life-threatening symptoms with long-term sequelae (e.g. developing new diseases and ocular or pulmonary sequelae [4, 5]). An encounter with drug hypersensitivity reaction may leave patients with vivid memories that could trigger anxiety, fear and concerns about the future, and, consequently, may influence patient's quality of life (QOL).

Issues related to quality of care and health-related QOL among patients with drug hypersensitivity are scarcely addressed. Tools eliciting health-related QOL have been translated and validated among non-English speaking countries, and associations between quality of care and health-related QOL among patients with various conditions have been evaluated [6–8]. However, the lack of a valid and reliable questionnaire makes it difficult for addressing the correlation between quality of care and drug-hypersensitivity related QOL. To our knowledge, despite questionnaires addressing QOL among patients with allergy diseases being available [9–11], to date no validated questionnaire for assessing QOL among patients with drug hypersensitivity exists in the Thai language.

Baiardini *et al.* [12] developed Drug Hypersensitivity Quality of Life Questionnaire (DrHy-Q), which was shown to be suitable for evaluating QOL related to having drug hypersensitivity. Subsequently, cross-cultural validation studies of DrHy-Q questionnaire were

conducted in Spain, Turkey and the Netherlands [13–16]. This tool could potentially be used among Thai population.

The aims of study were to translate the original Italian version of the DrHy-Q into Thai, assess its validity and reliability for use in Thai patients, and compare known-groups validity of Thai version of DrHy-Q (Thai DrHy-Q) to that of the Thai version of the World Health Organization Quality of Life-BREF (WHOQOL-BREF-THAI). Hypotheses were that the translated questionnaire would be valid and reliable to use in Thai patients with drug hypersensitivity and that patients with severe drug-hypersensitivity symptoms would have poorer QOL than those with mild allergic symptoms.

Methods

Study population

Patients with suspected drug hypersensitivities referred to allergy and clinical immunology clinics at six tertiary university teaching hospitals in Bangkok and Chiang Mai, Thailand were recruited during January 2012 to May 2017. Hospital centers included King Chulalongkorn Memorial Hospital, Ramathibodi Hospital, Siriraj Hospital, Pramongkutklao Hospital, Thammasart University Hospital and Maharaj Nakorn Chiang Mai Hospital. Inclusion criteria were patients with at least 15 years of age, having history of suspected drug allergy or symptoms related to drug hypersensitivity, and had been reviewed by allergists and/or dermatologists. Informed consent was obtained from all patients by completion of the

questionnaire. Clinical presentations (e.g. life-threatening severe-cutaneous adverse reaction (SCAR)), and drug-hypersensitivity characteristics including onset of drug hypersensitivity reaction were obtained.

Measures

The original 15-item DrHy-Q was in Italian, and contained five-point Likert response scale [12]. The items address any burden, such as physical and psychological aspects, of having drug hypersensitivity. Higher scores signify worse QOL.

The Thai version of the WHOQOL-BREF-THAI consists of 26 items, two generic items and 24 domain-specific items, with a 5-point Likert scale response [17, 18]. The two generic items address overall QOL and general health status. Four domains assessed are physical health (7 items), psychological health (6 items), social relationships (3 items) and environmental health (8 items). Each domain scores range from four to 20 points, and scores from two global items range from one to five. Higher WHOQOL-BREF-THAI scores indicate better QOL.

Translation

To ensure the meaning of original questionnaire has not been lost, the forward- and back-translations method proposed by World Health Organization [19] was conducted on the original Italian version of the DrHy-Q.

The Italian version was translated into Thai by two independent translators who were proficient in both languages. The draft of Thai version of the DrHy-Q (Thai DrHy-Q) was back-translated by a bilingual native Italian. The back-translated version was then reviewed by the developer group and tested for comprehension of the questions. An additional question about comprehensibility of the items with a 10-point Likert scale (ranging from 1—most difficult to 10—very easy) was added to assess face validity.

Reliability

Internal consistency was evaluated using Cronbach's α . We noted that, for group comparison, values of 0.7–0.8 was adequate. Cronbach's α of 0.9–0.95 was needed for clinical application [20].

Test-retest reliability was conducted among 68 subjects who were asked to complete the Thai DrHy-Q twice. To minimize patients' ability to recall the questions and answers, the second administration of the Thai DrHy-Q occurred at least 1 week apart after the initial administration. Prior to completing to the questionnaire second time, participants were asked if there was any significant change in life including their health. Participants with any substantial change during the 1 week period were excluded. The intra-class correlation coefficient (ICC 3,1: two-way mixed effect model) were used to assess the test-retest reliability [21, 22]. Criteria for ICC values were <0.4 suggesting poor correlation, 0.4–0.59 as fair, 0.6–0.74 as good and >0.75 as excellent reliability [23].

The *Bland-Altman plot* was also generated to visualize the agreement between the questionnaire responses at the two time points [24].

Validity

Construct validity, divergent validity and known-groups validity were performed to assess the validity of the Thai DrHy-Q.

Confirmatory factor analysis to evaluate the fit of the unidimensional model acquired from the original Italian version to our data. As the items were measured using ordinal scales, we employed using diagonally weighted least squares robust estimation to fit the DrHy-Q

measurement model. Goodness-of-fit indices indicating how well the model fits the sample were Comparative Fit Index (CFI), Tucker-Lewis Index (TLI) and root mean square error of approximation (RMSEA). The CFI and TLI of >0.90 and >0.95 suggested acceptable and excellent fit, respectively, and RMSEA of <0.08 suggested reasonable fit [25]. Chi-square statistics, a conventional index for measurement of model fit, was also included. Any item with factor loading below 0.40 would be excluded.

In absence of a 'gold standard' for assessing health-related QOL in drug hypersensitivity, divergent validity was evaluated with Pearson's correlation coefficients to measure the association between the Thai DrHy-Q and the WHOQOL-BREF-THAI. Divergent validity was considered to be confirmed if the absolute value of correlations are <0.40 [26, 27].

Known-groups validity establishes the instrument ability to distinguish between different subgroups based on clinical outcomes or characteristics [28]. Known-groups validity of both Thai DrHy-Q and WHOQOL-BREF-THAI was evaluated. The WHOQOL-BREF-THAI has been used in assessing QOL among various clinical populations [29–31]; however, its ability to differentiate between subgroups of patients with drug hypersensitivity is unknown. Subgroups were determined based on clinical presentations and drug-hypersensitivity characteristics. Clinical presentations included present or absence of anaphylaxis or life-threatening SCAR. Drug-hypersensitivity characteristics were onset of drug-hypersensitivity reaction (immediate: <2 h after the exposure to an implicated drug and non-immediate: >2 h), number of implicated pharmaceutical classes (one vs. multiple classes), non-steroidal anti-inflammatory drugs (NSAIDs) allergy and/or beta-lactam antibiotics allergy. The analyses were performed using Student's t test (for the two group case) or analysis of variance (ANOVA) with Tukey's post-hoc multiple comparison (for the multiple group case), with the significance level of $P < 0.05$. Where a statistical difference was established, receiving operating characteristic (ROC) curves were generated to assess the discriminating ability on criteria such as present or absence of life-threatening SCAR.

We determined sample size for all analyses. We aimed to recruit 300 subjects which were suitable for confirmatory factor analysis [32]. With this number of subjects, we would have sufficient power to conduct all other analyses for validation and reliability. For comparison between clinical groups, 40 subjects for each group was needed such that we would have 80% power to detect a clinical significant difference of 8 points on the DrHy-Q scale at significance level of 0.05. All validity and reliability analyses were conducted on subjects with complete values of Thai DrHy-Q and The R version 3.4.1 for Windows was used [33]. R libraries used in the study were sem, lavaan, nFactors, BlandAltmanLeh, psych, stats, Epi and dplyr. The COSMIN checklist was followed to ensure a good methodological quality of validation procedure [34]. This study was registered in [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT01666470).

Results

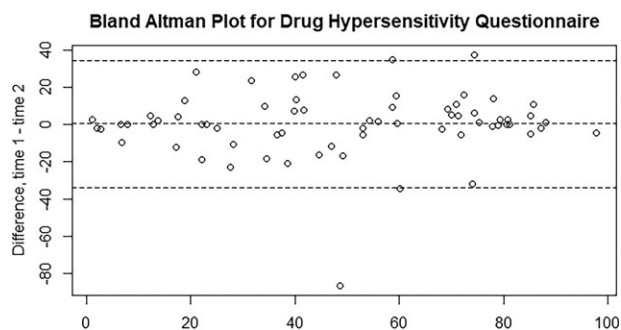
Pre-test and study population: The Thai DrHy-Q was initially tested among a group of physicians and patients with drug-hypersensitivity experience at King Chulalongkorn Memorial Hospital. The questions were considered by these participants to be acceptable, but a minor amendment was suggested on one item. A phrase was added to help ensure an item carrying the meaning of the original item. The item was then back-translated to Italian and was shown to have the same meaning. No further modifications were suggested. The final version was used in this study (Appendix 1).

Table 1 Characteristics of 306 participants with drug hypersensitivity experience

Characteristics	Mean (SD)
Age (years)	46.3 (15.9)
Time to complete questionnaire (min)	7.44 (5.90)
Self-reported comprehensibility of questionnaire	7.57 (2.47)
Sex	N (%)
Females	225 (76.0)
Males	71 (24.0)
Pharmaceutical classes ^a	
Non-steroidal anti-inflammatory drugs and other pain reliefs	149 (34.9)
Beta-lactam antibiotics	129 (30.2)
Sulfonamide antibiotics	13 (3.0)
Other antibiotics ^b	71 (16.6)
Anti-epileptic drugs	11 (2.6)
Other drugs	54 (12.6)

^aEach participant can be hypersensitive to more than one drug classes.

^bIncluding antituberculosis drugs.

**Figure 1** Bland Altman plot between responses of Thai DrHy-Q Questionnaire at time 1 and time 2.

A total of 306 participants with average age of 46.3 years (SD = 15.9) were included in this study. The average time to complete the Thai DrHy-Q was ~7.4 min and the average self-reported ease of comprehensibility was 7.57 points. Table 1 also shows the number of implicated drug classes where NSAIDs and beta-lactam antibiotics classes are the two largest groups.

Reliability

Internal consistency among 306 participants was shown to be quite strong with a Cronbach's α of 0.94 (95% confidence interval (95% CI): 0.93, 0.95). Test-retest reliability was performed on 68 participants with average age of 45.7 (SD = 16.1) and proportion of males was 25%. Average duration between first and subsequent tests was 22 days (SD = 16.4 days). The single measure of ICC was 0.80 (95% CI: 0.7, 0.87) indicating excellent test-retest reliability.

The Bland-Altman plot indicated no systematic bias (Figure 1). Test and retest scores were close to each other with mean difference of 0.35. Only one participant fell outside of the expected 95% limits of agreement (LOA: -33.87, 34.57).

Validity

Percentages of missing values for each Thai DrHy-Q items were quite low with values ranging from 0 to 1.2%. The confirmatory

Table 2 Factor loading of each item in the Thai DrHy-Q questionnaire

Items	Standardized factor loading ^a
Since I am unable to take drugs every illness limits me more than other	0.683
I am afraid of being administered a drug during an emergency to which I am allergic	0.652
I feel frightened due to my problem of allergy reaction	0.817
The problem of adverse reaction to drugs affects my life	0.751
I would like the allergist's opinion before taking drugs prescribed by other specialists	0.635
Even a little discomfort for me is a problem	0.775
The fact that I cannot use medication safely made me feel different from others	0.784
I feel anxious due to my problem of allergy reaction	0.866
For each disease I would be confident that there is a drug that I can safely take	0.501
I am afraid I could not deal with the pain	0.698
I feel anguished due to my problem of allergy reaction	0.829
I worry every time I take a drug different from ones that cause my allergic reactions	0.809
I give up leisure activities (sport, vacations, trips) because of my problem	0.517
I'm in a bad mood due to my problem of allergy reaction	0.667
The idea of taking a medicine makes me feel anxious	0.803

Thai DrHy-Q = Thai version of Drug Hypersensitivity Quality of Life Questionnaire.

^aAll coefficients were significantly different from zero ($P < 0.05$).

Table 3 Pearson's correlation coefficients between WHOQOL-BREF-THAI domains and global items and Thai DrHy-Q scores

WHOQOL-BREF domains and global items	Pearson's correlation (95% CI, P -value)
Physical health	-0.41 (-0.50, -0.31, $P < 0.001$)
Psychological health	-0.39 (-0.48, -0.29, $P < 0.001$)
Social relationship	-0.19 (-0.30, -0.08, $P < 0.01$)
Environmental	-0.27 (-0.37, -0.16, $P < 0.001$)
General health	-0.29 (-0.39, -0.18, $P < 0.001$)
Overall quality of life	-0.26 (-0.36, -0.15, $P < 0.001$)

factor analysis showed that the unidimensional structure was confirmed for Thai DrHy-Q version with χ^2 of 101.25 (df = 90, $P = 0.196$). The CFI and TLI were both 0.999. RMSEA was 0.02 (95% CI: 0.00, 0.038, $P = 0.999$). Table 2 provides items' standardized factor loading for Thai DrHy-Q. None of the items had factor loading < 0.40 , and all were statistically different from zero ($P < 0.05$).

Divergent validity of Thai DrHy-Q was established by low levels of negative correlations with all WHOQOL-BREF-THAI domain scores, general health scores, and overall QOL scores (r ranging from -0.41 to -0.19, Table 3). The lowest level of correlation was between Thai DrHy-Q scores and WHOQOL-BREF-THAI social relationship domain scores.

Known-groups validity analysis for the Thai DrHy-Q confirmed its ability to distinguish patients with multiple implicated pharmaceutical classes from those with one drug class ($P < 0.01$), and patients with life-threatening SCAR from those without the condition ($P = 0.02$, Table 4). The ANOVA showed significant differences in means of the Thai DrHy-Q scores among subgroups of

Table 4 Comparison of Thai DrHy-Q scores between clinical presentations and drug-hypersensitivity characteristics

	N (%)	Thai DrHy-Q scores mean (95% CI)
Reaction time		
Immediate	124 (42.8)	46.03 (41.58, 50.49)
Non-immediate	149 (51.4)	43.14 (39.07, 47.20)
Unknown	17 (5.9)	48.43 (36.40, 60.45)
Number of suspected pharmaceuticals		
Single	189 (64.9)	41.48 (37.92, 45.05)
Multiple	102 (35.1)	50.67 (45.65, 55.69) ^a
NSAIDs vs. beta-lactam ABX allergy [*]		
NSAIDs	113 (46.7)	38.75 (34.14, 43.36) ^a
Beta-lactam ABX	93 (39.7)	46.12 (41.04, 51.21) ^a
Allergic to both groups	36 (13.6)	58.11 (49.94, 66.28)
Life threatening SCAR		
Yes	44 (15.4)	52.61 (45.63, 59.58) ^{**}
No	242 (84.6)	42.94 (39.73, 46.16)
Anaphylaxis		
Yes	13 (4.5)	43.11 (28.10, 58.12)
No	273 (95.5)	44.49 (41.47, 47.50)

95% CI = 95% confidence interval; ABX = antibiotics; NSAIDs = non-steroidal anti-inflammatory drugs.

^{*} $P < 0.01$, ^{**} $P = 0.02$.

^aThose groups sharing a letter did not differ significantly.

patients allergic to NSAIDs and/or beta-lactam antibiotics ($F = 8.51$, $df = 2$, $P < 0.001$). The Tukey's post hoc test showed patients allergic to NSAIDs only had lower DrHy-Q scores (i.e. better QOL) than either those with beta-lactam antibiotic allergy only or those who were allergic to both (Table 4).

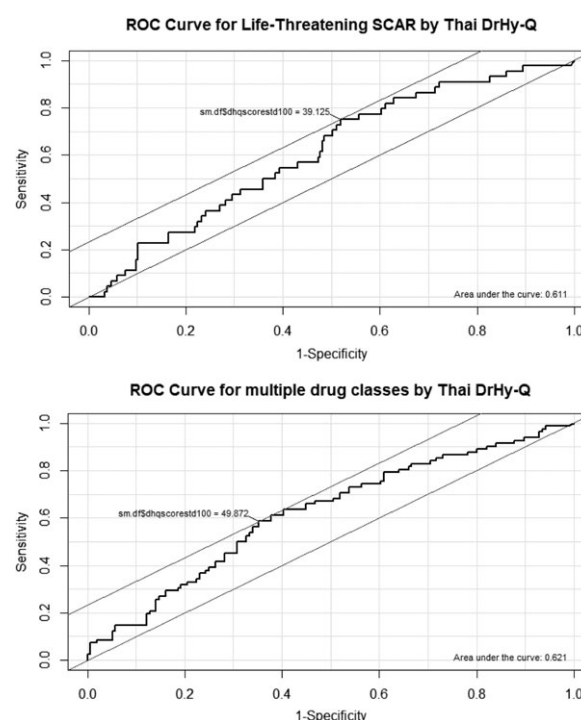
The known-groups validity of WHOQOL-BREF-THAI was not confirmed for all domains and facets. Only physical health, psychological health and overall QOL showed ability to differentiate between patients with life-threatening SCAR and those without. Patients with life-threatening scar had poorer physical health (mean, $\bar{X} = 12.62$; 95% CI: 11.77, 13.53, $P < 0.001$), psychological health ($\bar{X} = 14.04$, 95% CI: 13.12, 14.96, $P = 0.002$), and overall QOL ($\bar{X} = 3.68$, 95% CI: 3.47, 3.90, $P = 0.007$) than those without the life-threatening condition (physical health: $\bar{X} = 14.44$, 95% CI: 14.11, 14.77; psychological health: $\bar{X} = 15.33$, 95% CI: 15.02, 15.64; overall QOL: $\bar{X} = 3.97$; 95% CI: 3.89, 4.05).

Areas under the ROC curves (AUCs) for predicting clinical criteria—multiple implicated drug classes and a life-threatening SCAR by Thai version of DrHy-Q, were 0.621 and 0.611, respectively (Figure 2). The physical health, psychological health, and overall QOL of WHOQOL-BREF-THAI poorly discriminated the life-threatening SCAR condition with AUCs ranging between 0.334 and 0.390.

Discussion

In this study, we describe the translation process and evaluate the psychometric properties for the Thai DrHy-Q. We found that the Thai version of DrHy-Q to be both reliable and valid for assessing health-related QOL among patients with drug hypersensitivity.

The finding shows that the internal consistency and test-retest reliability were good. To reduce recall of the questions and patient's answers, we had a wider time interval (22 days) between test and

**Figure 2** The receiving operating characteristic curves for life-threatening severe cutaneous adverse reaction and multiple numbers of implicated pharmaceutical classes by Thai DrHy-Q.

retest than other studies [12–14, 16]. This potentially suggested that an impact of drug-hypersensitivity experience on QOL may not change rapidly over time. The Bland–Altman plot suggested no systematic bias between the two time points, and slightly wide variation.

The correlation between DrHy-Q and WHOQOL-BREF was negative as expected. Higher WHOQOL-BREF domain scores referred to better QOL; whereas higher scores of Thai DrHy-Q suggested poorer QOL. The observed poor-to-fair correlations support the notion of adequate divergent validity. These results suggest that the Thai DrHy-Q not only measures specific drug-hypersensitivity burden, but also partially captures general QOL. Our findings differed from Italian DrHy-Q where very weak correlations were reported [12]. However, the magnitudes of reported correlations were similar to that of the Turkish and Dutch versions of DrHy-Q [13, 14]. Interestingly, the higher levels of correlations were observed between Thai DrHy-Q scores and two domains of WHOQOL-BREF-THAI (physical health and psychological health). This seems to reflect the wordings in the Thai DrHy-Q which were mainly emotional- and physical-related concerns.

Although, this is not the first study to validate DrHy-Q for another population, we employed a comparatively large and multi-center sample ($N = 306$). Four studies have sample size ranging from 30 to 736 subjects [12–14, 16]. However, only one study reported 6% (41/657) of patients with delayed cutaneous reaction, which includes mild cutaneous conditions and found no significant difference between two groups [14]. Our study not only have relatively large group of participants with life-threatening SCAR (15%), but also found significantly a poorer QOL in patients with life-threatening SCAR. In addition, our study evaluated different factors, specifically comparison between two specific drug classes (NSAIDs

vs. beta-lactam antibiotics) and number of implicated drug classes instead of a specific drug. This reflected current practice where patients are advised to avoid an entire pharmaceutical class.

The Thai DrHy-Q was able to distinguish patients with or without life-threatening SCAR, patients with allergy to either NSAIDs or beta-lactam antibiotics, or both, and participants with one or multiple implicated drug classes. We could not demonstrate that the DrHy-Q can discriminate between patients with and without anaphylaxis, a result similar to the Turkish and Dutch studies [13, 14]. However, the original Italian validation study and its subsequent study showed that significant difference in the DrHy-Q scores between participants with or without anaphylaxis reaction [12, 35]. Culturally different impression of anaphylaxis reaction could explain this departure. For Thais, the anaphylaxis reaction may not leave permanent physical and psychological damages such that a recall of anaphylaxis experience was not so tormenting to have a substantial impact on the QOL.

The Thai DrHy-Q with ability to discriminate three subgroups was superior to the WHOQOL-BREF-THAI which was able to only detect the difference between patients with or without life-threatening SCAR. The areas under the ROC curves supported this finding. The AUCs of Thai DrHy-Q for differentiating multiple drug classes and life-threatening SCAR condition were close to 0.70; while the AUCs of WHOQOL-BREF-THAI physical health, psychological health and overall QOL for discriminating life-threatening SCAR were substantially lower, and none exceeded 0.50.

The strengths of the study include having multi-center sample with large proportion of life-threatening SCAR and the use of drug classes as clinical subgroups, which provide us an adequate generalizability of our finding to other Thai patients with drug hypersensitivity. In addition to conventional approach in assessing known-groups validity, ROC analysis was performed and shown evidence supporting that the Thai DrHy-Q was suitable as a disease-specific instrument. However, our study did not investigate the responsiveness of the Thai DrHy-Q to interventions (e.g. oral provocation test or drug desensitization), the different underlying diseases, and the difference between patients experiencing drug hypersensitivity once and patients with recurrent events.

We demonstrate that the Thai version of DrHy-Q is both reliable and valid for evaluating patients with drug hypersensitivity among Thai population, and capture more specific drug-hypersensitivity aspects than the WHOQOL-BREF-THAI does. The instrument was non-invasive and low cost. The Thai DrHy-Q is suitable for use in the future studies in assessing QoL among patients with drug hypersensitivity. In this study, we observed poorer QoL among patients with allergic reactions to multiple drug classes or life-threatening SCAR. Future studies should include other factors, such as underlying diseases and number of drug-hypersensitivity reactions, investigate long-term impact of the drug hypersensitivity experience, and design a care approach such that patient's QoL is maintained.

Acknowledgements

Authors thank the WHO for the permission to use WHOQOL-BREF-Thai Questionnaire. This study has been supported by (i) Rachadapisek Sompote Fund for Postdoctoral Fellowship, Chulalongkorn University; (ii) the Skin and Allergy Research Unit, Chulalongkorn University and the National Research University Project, Office of Higher Education Commission (WCU-002-HR-57); and (iii) the Thailand Research Fund (RSA5880041). Study data were collected and managed using Research Electronic Data Capture (REDCap) hosted at HIV Netherlands Australia Thailand Research Collaboration.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional Review Boards of Faculty of Medicine Chulalongkorn University and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all patients included in the study.

References

1. Sukasem C, Jantararoungtong T, Kuntawong P *et al.* HLA-B(*)58:01 for allopurinol-induced cutaneous adverse drug reactions: implication for clinical interpretation in Thailand. *Front Pharmacol* 2016;7:186.
2. Puangpetch A, Koomdee N, Chamnanphol M *et al.* HLA-B allele and haplotype diversity among Thai patients identified by PCR-SSOP: evidence for high risk of drug-induced hypersensitivity. *Front Genetics* 2014;5:478.
3. Health Product Vigilance Center. *Reports of Adverse Drug Reaction 2015. Nontaburi, Thailand: Health Product Vigilance Center, Food and Drug Administration, Ministry of Public Health, Thailand* 2016. http://thaihpvc.fda.moph.go.th/thaihpvc/Public/News/uploads/hpvc_1_3_4_100626.pdf.
4. Kano Y, Tohyama M, Aihara M *et al.* Sequelae in 145 patients with drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms: survey conducted by the Asian Research Committee on Severe Cutaneous Adverse Reactions (ASCAR). *J Dermatol* 2015;42:276–82.
5. Verma R, Vasudevan B, Pragasaam V. Severe cutaneous adverse drug reactions. *Med J Armed Forces India* 2013;69:375–83.
6. Wang HF, Bradley C, Chang TJ *et al.* Assessing the impact of diabetes on quality of life: validation of the Chinese version of the 19-item Audit of Diabetes-Dependent Quality of Life for Taiwan. *Int J Qual Health Care* 2017;29:335–42.
7. Xu RH, Cheung AWL, Wong ELY. The relationship between shared decision-making and health-related quality of life among patients in Hong Kong SAR, China. *Int J Qual Health Care* 2017;29:534–40.
8. Aung E, Donald M, Williams GM *et al.* Influence of patient-assessed quality of chronic illness care and patient activation on health-related quality of life. *Int J Qual Health Care* 2016;28:306–10.
9. Kulthanan K, Chularojanamontri L, Tuchinda P *et al.* Minimal clinical important difference (MCID) of the Thai Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL). *Asian Pac J Allergy Immunol* 2016;34:137–45.
10. Poachanukoon O, Visitsunthorn N, Leurmankul W *et al.* Pediatric Asthma Quality of Life Questionnaire (PAQLQ): validation among asthmatic children in Thailand. *Pediatr Allergy Immunol* 2006;17:207–12.
11. Bunnag C, Leurmankul W, Jareoncharisri P *et al.* Development of a health-related quality of life questionnaire for Thai patients with rhinoconjunctivitis. *Asian Pac J Allergy Immunol* 2004;22:69–79.
12. Baiardini I, Braidò F, Fassio O *et al.* Development and validation of the Drug Hypersensitivity Quality of Life Questionnaire. *Ann Allergy Asthma Immunol* 2011;106:330–5.
13. Moayeri M, Van Os-Medendorp H, Baiardini I *et al.* Assessment of validity and reliability of Drug Hypersensitivity Quality of Life Questionnaire: The Dutch experience. *Eur Ann Allergy Clin Immunol* 2017;49:129–34.
14. Baybek S, Kepil Ozdemir S, Doganay Erdogan B *et al.* Turkish version of the Drug Hypersensitivity Quality of Life Questionnaire: assessment of reliability and validity. *Qual Life Res* 2016;25:101–9.
15. Gastaminza G, Herdman M, Baiardini I *et al.* Cross-cultural adaptation and linguistic validation of the Spanish version of the drug hypersensitivity quality of life questionnaire. *J Invest Allergol Clin Immunol* 2013;23:508–10.
16. Gastaminza G, Ruiz-Canela M, Baiardini I *et al.* Psychometric validation of the Spanish Version of the DHRQoL Questionnaire. *J Invest Allergol Clin Immunol* 2016;26:322–3.
17. Mahatnirundkul S, Tantipiwattanasasul W, Poompaislachai W *et al.* Comparison of the WHOQOL-100 and the WHOQOL-BREF (26 item). *J Mental Health Thai* 1998;5:4–15.

18. Skevington SM, Lotfy M, O'Connell KA *et al.* The World Health Organization's WHOQOL-BREF quality of life assessment: psychometric properties and results of the international field trial. A report from the WHOQOL group. *Qual Life Res* 2004;**13**:299–310.
19. World Health Organization. *Process of Translation and Adaptation of Instruments*, 2012. http://www.who.int/substance_abuse/research_tools/translation/en/.
20. Bland JM, Altman DG. Statistics notes: Cronbach's alpha. *Br Med J* 1997;**314**:572.
21. Koo TK, Li MY. A guideline of selecting and reporting intraclass correlation coefficients for reliability research. *J Chiropr Med* 2016;**15**: 155–63.
22. Shrout PE, Fleiss JL. Intraclass correlations: uses in assessing rater reliability. *Psychol Bull* 1979;**86**:420–8.
23. Fleiss JL, Levin B, Paik MC. *Statistical Methods for Rates and Proportions*. Hoboken, NJ: Wiley, 2003.
24. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986;**1**:307–10.
25. Hu LT, Bentler PM. Cutoff criteria for fit indexes in covariance structure analysis: conventional criteria versus new alternatives. *Struct Equ Modeling* 1999;**6**:1–55.
26. Costantini M, Rabitti E, Beccaro M *et al.* Validity, reliability and responsiveness to change of the Italian palliative care outcome scale: a multicenter study of advanced cancer patients. *BMC Palliat Care* 2016;**15**:23.
27. Baiardini I, Braido F, Molinengo G *et al.* Chronic urticaria patient perspective (CUPP): the first validated tool for assessing quality of life in clinical practice. *J Allergy Clin Immunol Pract* 2018;**6**:208–18.
28. Davidson M. Known-Groups Validity. In: Michalos AC (ed). *Encyclopedia of Quality of Life and Well-Being Research*. Dordrecht: Springer Netherlands, 2014, 3481–2.
29. Apidechkul T. Comparison of quality of life and mental health among elderly people in rural and suburban areas, Thailand. *Southeast Asian J Trop Med Public Health* 2011;**42**:1282–92.
30. Dajpratham P, Kuptniratsaikul V, Kovindha A *et al.* Prevalence and management of poststroke spasticity in Thai stroke patients: a multicenter study. *J Med Assoc Thai* 2009;**92**:1354–60.
31. Sakthong P, Schommer JC, Gross CR *et al.* Psychometric properties of WHOQOL-BREF-THAI in patients with HIV/AIDS. *J Med Assoc Thai* 2007;**90**:2449–60.
32. MacCallum RC, Widaman KF, Zhang S *et al.* Sample size in factor analysis. *Psychol Methods* 1999;**4**:84–99.
33. Team RC. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing, 2017.
34. Mokkink LB, Terwee CB, Patrick DL *et al.* The COSMIN checklist for assessing the methodological quality of studies on measurement properties of health status measurement instruments: an international Delphi study. *Qual Life Res* 2010;**19**:539–49.
35. Baiardini I, Gaeta F, Molinengo G *et al.* Quality-of-life issues in survivors to anaphylactic reactions to drugs. *Allergy* 2015;**70**:877–9.

Appendix

Thai version of Drug Hypersensitivity Questionnaire.

เลขที่ผู้ป่วย _____ ผู้มีประวัติแพ้ยาเป็นผู้ให้ข้อมูล
 อักษรย่อชื่อผู้ป่วย (Initial) ☐ ☐ วันที่เก็บข้อมูล (วัน/เดือน/ปี) ____/____/____

ปฏิกิริยาข้างเคียงจากการใช้ยาสามารถส่งผลกระทบต่อสุขภาพจิตของแต่ละบุคคล
 กรุณาระบุความยากลำบากที่ท่านได้รับเนื่องจากปัญหานี้
 (โปรดทำเครื่องหมาย ☒ ลงในช่องเพียงช่องเดียวที่ตรงกับคำอธิบายของคุณมากที่สุด)

	ไม่เลย	เล็กน้อย	ปานกลาง	มาก	มากยิ่งขึ้น
	▼	▼	▼	▼	▼
1. เนื่องจากไม่สามารถใช้ยาได้ ฉันจึงมีข้อจำกัดเมื่อเป็นโรคต่างๆ มากกว่าผู้อื่น	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2. ฉันกลัวว่าในกรณีฉุกเฉิน ฉันอาจจะถูกจ่ายยาตัวที่ฉันแพ้	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
3. ปัญหาเรื่องยารองฉันทำให้ฉันรู้สึกหวาดกลัว	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
4. ปัญหาเรื่องปฏิกิริยาที่เกิดจากยาที่มีผลกระทบต่อชีวิตฉัน	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
5. ฉันต้องการความเห็นของแพทย์ผู้เชี่ยวชาญด้านโรคภูมิแพ้ก่อนที่จะใช้ยาที่สั่งจ่ายโดยผู้เชี่ยวชาญด้านอื่นๆ	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
6. แม้ความรู้สึกไม่สบายเพียงเล็กน้อยก็กลายเป็นปัญหาสำหรับฉันได้	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
7. ความจริงที่ว่าไม่สามารถใช้ยาได้อย่างปลอดภัย ทำให้ฉันรู้สึกแตกต่างจากผู้อื่น	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
8. ปัญหาเรื่องปฏิกิริยาที่เกิดจากยาของฉันทำให้ฉันรู้สึกวิตกกังวล	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
9. ฉันอยากมั่นใจว่า ในแต่ละโรคมียาที่ฉันสามารถใช้ได้อย่างปลอดภัย	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
10. ฉันกลัวว่าจะไม่สามารถได้รับการรักษาเมื่อมีอาการเจ็บปวด	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
11. ปัญหาการแพ้ยาทำให้ฉันรู้สึกกลัดกลุ้ม	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
12. ฉันรู้สึกวิตกกังวลทุกครั้งที่ต้องใช้ยา ถึงแม้จะเป็นยาคนละชนิดกับที่ฉันแพ้	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
13. ฉันทิ้งโอกาสทำกิจกรรมพักผ่อนหย่อนใจต่างๆ (เช่น กีฬา, พักผ่อน, ท่องเที่ยว, ฯลฯ) เนื่องจากปัญหานี้ของฉัน	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
14. เพราะปัญหาแพ้ยาของฉัน ทำให้ฉันรู้สึกหดหู่	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
15. เพื่อมีความคิดที่จะใช้ยา ก็ทำให้ฉันรู้สึกกังวลใจ	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

ท่านคิดว่า ภาษาที่ใช้ในแบบสอบถาม เข้าใจง่ายมากน้อยเพียงใด (เข้าใจยากที่สุด = 1, เข้าใจง่ายที่สุด = 10)

☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

เวลาที่ใช้ในการตอบแบบสอบถาม _____ นาที