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Original Article

Development and validation of the self-report symptom inventory of immune-related adverse events in patients with lung cancer

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ABSTRACT

Objective: This study aims to develop and validate the Self-Report Symptom Inventory of immune-related Adverse Events in Patients with Lung Cancer (SRSI-irAEs-LC) to allow for systematic assessment of symptomatic irAEs in patients with lung cancer treated with programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) immune checkpoint inhibitors (ICIs).

Methods: A sequential two-phase mixed-methods study was conducted. In phase I, a draft version of the SRSI-irAEs-LC was constructed through item generation and draft inventory construction. Delphi expert consultation, cognitive interviews and a pilot study were conducted to evaluate the content validity and refine the scale. In phase II, psychometric testing was performed on 512 patients with lung cancer treated with PD-1/PD-L1 ICIs using item analysis, exploratory factor analysis (EFA), confirmatory factor analysis (CFA), criterion validity, discriminant validity, and reliability evaluations.

Results: Through 5 sequential steps in phase I, the preliminary version of the SRSI-irAEs-LC comprised 10 dimensions with 41 items. Through EFA, the final version of the SRSI-irAEs-LC included 8 dimensions and 26 items that explained 62.33% of the variance. The CFA model showed that the 8-factor model fitted the data well. Good criteria validity and known-groups discriminant validity were demonstrated. Cronbach's *alpha*, split-half reliability, and test-retest reliability of the scale were 0.824, 0.725, and 0.851, respectively.

Conclusions: Preliminarily, the SRSI-irAEs-LC is a valid and reliable instrument for assessing symptomatic irAEs in patients with lung cancer treated with PD-1/PD-L1 ICIs. Further research is needed to confirm its generalizability to a broader population as well as its validity and reliability.

Introduction

Globally, lung cancer has the highest incidence and mortality rates, causing serious disease burdens.[1,2] The traditional treatments for lung cancer include surgery, chemotherapy, and radiotherapy, but the overall prognosis remains unchanged, probably because of tumor heterogeneity and mutations.[3] In recent years, immune checkpoint inhibitors (ICIs) therapy has emerged as a promising option for lung cancer treatment, even as a first-line therapy.[4,5] Through monoclonal antibodies, ICIs inhibit the expression of proteins such as programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), thereby boosting T cell activation against cancer.[4] Given the limited efficacy of CTLA-4 ICIs in lung cancer treatment, along with its serious adverse events (AEs), clinical use of CTLA-4 ICIs remains limited,[6] whereas PD-1 and PD-L1 ICIs are widely used.[5] While ICI-therapy has improved lung cancer patients' survival,[7,8] it can also cause immune-related adverse events (irAEs).[9] It has been reported that approximately 33.1%–78.5% of lung cancer

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patients treated with ICI-therapy experienced irAEs.[10,11] Compared to AEs resulting from traditional cancer treatments, irAEs are more unpredictable since they can occur in any organ system exhibiting pleomorphic clinical manifestations at any time.[12] In addition, most irAEs are low grade, treatable and reversible, whereas some toxicities can result in hospitalization, increased treatment costs, treatment discontinuation, permanent conditions, or even death.[13–15] As it has been pointed out that, if irAEs can be identified and treated at an earlier stage, most of them can be avoided or relieved.[16] Therefore, early detection and monitoring of irAEs in lung cancer patients treated with ICIs play a crucial role in improving their safety and health-related quality of life (HRQOL).[17]

Currently, AEs are mainly collected and reported using the Common Terminology Criteria for Adverse Events (CTCAE).[18] The CTCAE version 5.0 consists of 790 items, each representing a discrete event identified, graded and reported by health professionals. However, approximately 10% of the AEs in the CTCAE are symptomatic toxicities which are dependent on patients' subjective experiences, but are currently evaluated by clinicians.[19] There is empirical evidence that in comparison to patient self-reports, clinician-based assessments of symptomatic AEs can be unreliable, as clinicians may underestimate and/or delay reporting symptoms as well as misinterpret their frequency, severity, and associated distress.[20,21] Furthermore, substantial evidence shows that direct patient self-reporting of symptomatic toxicities improves the precision and comprehensiveness in the identification of symptomatic AEs caused by anti-cancer therapies.[22–25] Hence, integrating patient-reported outcome (PRO) into clinicians' reports is highly recommended, and is increasingly being used in both clinical practice and research contexts for cancer.[26]

There are several PRO-based symptom inventories and HRQOL questionnaires available for lung cancer patients, which include commonly occurring symptomatic toxicities associated with chemotherapy, radiotherapy and target therapy.[27–29] However, due to the unique nature of irAEs,[12] the anticipated symptomatic toxicities resulting from ICIs, such as dry eyes, rash, dry skin etc, can't be fully covered by current PRO measures (PROMs).[30] In consequence, the existing PROMs are unable to capture 55% of common symptomatic irAEs and even 29% of specific symptomatic irAEs.[30] Besides, the existing measurements of symptoms or HRQOL are commonly applied for evaluating treatment efficacy or overall clinical outcomes in cancer research and clinical care, but PRO-based inventories of symptomatic AEs are primarily used as a means of detecting and monitoring treatment-related side effects.[19] In recent years, several tools have been developed to monitor symptomatic irAEs, such as the M.D. Anderson Symptom Inventory for Early-Phase Trials module (MDASI-Immunotherapy EPT),[31] the PRO-CTCAE-based subset for lung cancer patients receiving immunotherapy developed by Peng,[32] and the symptom assessment scale for non-small cell lung cancer (NSCLC) patients treated with ICIs developed by Wu.[33] However, Wu[34] found that the MDASI-Immunotherapy EPT failed to adequately capture some common symptomatic irAEs of patients, like coughing and palpitations. Additionally, Peng[32] constructed the item pool using PRO-CTCAE, which has been shown to have limitations in covering symptomatic irAEs,[35] and the clinical feasibility of this subset needs to be further tested. Moreover, the scale constructed by Wu[33] was only applicable to NSCLC patients, and has not been applied within clinical practice and its reliability and validity have yet to be tested.

In light of this, there is still a lack of appropriate instruments to assess symptomatic irAEs among lung cancer patients. This study aimed to develop and initially validate the Self-Reported Symptom Inventory of immune-related Adverse Events in Patients with Lung Cancer (SRSI-irAEs-LC) treated with PD-1/PD-L1 ICIs. The Theory of Unpleasant Symptoms (TUS), a widely used theory related to cancer symptom management,[36] which consists of three core components: symptoms, influencing factors and performance outcomes,[37] provided the conceptual framework for the study.

Methods

Study design

A sequential two-phase mixed-methods design was used in this study (Fig. 1). The Phase I involved the development of the preliminary version of the SRSI-irAEs-LC. The Phase II involved two separate studies. In study 1, exploratory factor analysis (EFA) was carried out to estimate the factorial structure of the scale. In study 2, confirmatory factor analysis (CFA) was conducted to confirm its factorial structure, and criteria validity, discriminant validity, and reliability of the scale were also examined.

Participants and procedures

Between September 2021 and March 2023, a sample of patients with lung cancer was recruited from one cancer center and two general hospitals in Guangzhou, China. The inclusion criteria were: (a) had a histological diagnosis of lung cancer,[38] (b) over 18 years old, (c) had been receiving at least one cycle of PD-1/PD-L1 therapy,[39] either alone or in combination with chemotherapy/bevacizumab, or both chemotherapy and bevacizumab,[38] (d) were capable of listening, communicating, reading and writing, (e) agreed to provide written informed consent. Patients were deemed ineligible if they were receiving targeted therapy (except for bevacizumab) and/or radiation therapy at the same time.[38] A multidisciplinary panel of oncologists, oncology nurse specialists, oncology pharmacists, and psychologists from three medical institutions were invited to participate in the Delphi expert consultation in this study. Experts needed to have: (a) an intermediate professional title or higher, (b) a master's degree or higher (nurse specialists need a bachelor's degree or higher), (c) a minimum of 5 years of professional experience, (d) had been engaging in lung cancer immunotherapy for at least 3 years (except for psychologists).

Phase I: Development of the preliminary version of the SRSI-irAEs-LC

In the phase I of this study, the typical five steps for developing scale were followed:[40] item generation, draft inventory construction, Delphi expert consultation, cognitive interview and pilot study.

Step 1. Item generation. The methodology used in item generation was inspired by Nissen et al.,[41] who developed the prostate cancer patient's symptom assessment scale. In order to construct a complete graph of symptomatic irAEs of lung cancer patients treated with PD-1/PD-L1 ICIs, documentation on symptomatic irAEs was collected from the following six sources.

(1) FDA, EMA and NMPA

The ICIs have been approved by the Food and Drug Administration (FDA) or the European Medicines Agency (EMA) or the National Medical Products Administration (NMPA) in China. The documentation from these agencies contained information on the symptomatic irAEs discovered in clinical trials.

(2) Randomized controlled trials

All the symptomatic irAEs reported in the phase II and phase III Randomized Controlled Trials (RCTs) derived from the 2021 edition of the Chinese Society of Clinical Oncology (CSCO) guidelines for clinical application of ICIs in lung cancer[42] were included into this study.

(3) Audit of patients' medical records

A retrospective audit of medical records of lung cancer patients treated with PD-1/PD-L1 ICIs between October 2020 and October 2021 was conducted. Only symptomatic irAEs reported by oncologists or nurses during each cycle of the ICI-therapy were included. The audit of

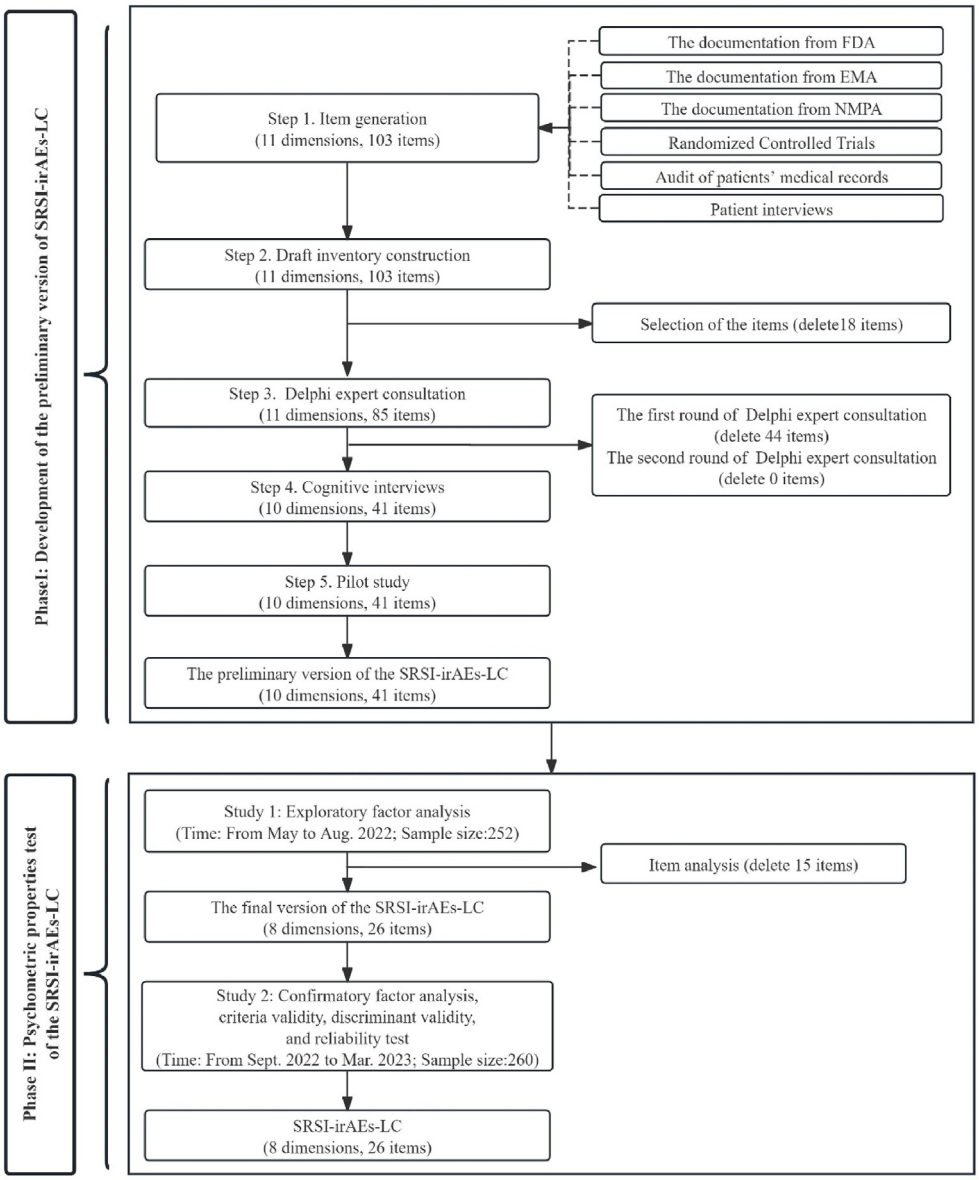

Fig. 1. The steps of the development of the SRSI-irAEs-LC. SRSI-irAEs-LC, Self-Report Symptom Inventory of immune-related Adverse Events in Patients with Lung Cancer. FDA, Food and Drug Administration; EMA, European Medicines Agency; NMPA, National Medical Products Administration.

medical records was stopped if the symptomatic irAEs were similar to those reported in previous studies (FDA, EMA, NMPA, RCTs).[41]

(4) Patient interviews on symptomatic irAEs

The interview outline was developed based on four dimensions of symptoms (intensity, distress, timing and quality) in the TUS[37] to supplement symptomatic irAEs collected from the five sources. Two research nurses interviewed 20 patients face-to-face about their perceptions and experiences with symptomatic irAEs during ICI-therapy. All symptomatic irAEs mentioned by the patients were noted and included. The recruitment ceased when concepts were repeated without any new information being provided.[43]

Step 2. Draft inventory construction. A draft version of the SRSI-irAEs-LC was developed by performing the following three stages.

(1) Classification of the items

All symptomatic irAEs collected from step 1 were classified using the Medical Dictionary for Regulatory Activities system organ classes (MedDRA SOC).[41] Afterwards, a consensus-based synonym classification of the same symptoms expressed in different wording (e.g., 'appetite loss/decreased appetite' = 'anorexia') was conducted by two research nurses and an oncologist.

(2) Selection of the items

There must be at least one of the following criteria met for the item to be retained:[41] (a) two of the six sources must include the symptoms, with at least one being the FDA, EMA, or NMPA product summary listing symptoms, (b) the symptoms were reported in patients' medical records and in patient interviews.

(3) Design of the item descriptions and response options

According to the four dimensions of symptoms mentioned in the TUS,[37] and the purpose of the SRSI-irAEs-LC being developed, the item descriptions and response options of scale items were designed. The intensity and distress of each symptom were assessed using a 5-Likert score ranging from 1 to 5, with higher score indicating more severe

or higher distress. Only intensity scoring data were used for statistical analysis, since it was the most commonly measured parameter among the quantitative symptom assessment studies.[44] Based on the treatment cycle of ICI-therapy and the specificity of irAEs, 21-day recall period was utilized. In addition, quality was not used, as it is primarily used in qualitative studies.

Step 3. Delphi expert consultation. The experts were asked to rate the correlation of each item on a four-point rating scale ranging from one (extremely uncorrelated) to four (extremely correlated). Additionally, they could comment on the wording and item allocation of the consultation drafts, and present reasons and suggestions for revising, removing or adding items. They were required to return the consultation questionnaire within one week of receiving it. The item with a Content Validity Index (I-CVI) < 0.70 would be deleted.[45,46]

Step 4. Cognitive interviews. To ensure the draft version of the SRSI-irAEs-LC was comprehensive and clear to the target study population, cognitive interviews were applied.[47]

Step 5. Pilot study. To test the readability, comprehensibility, acceptability, and ease of completing the instrument, a pilot study was conducted among a new group of 30 eligible patients.

Phase II: Psychometric properties test of the SRSI-irAEs-LC

Sample. Participants in study 1 were recruited between May 2022 and August 2022. The preliminary version of the SRSI-irAEs-LC included 41 items, based on 5 to 10 subjects for each variable,[48] a minimum sample size of 205 was estimated, and taking into account the 10.0% loss rate, at least 226 participants were required. In study 2, participants were recruited from September 2022 to March 2023, and the sample size for CFA should be at least 200.[49] Similarly, considering the 10.0% loss rate, at least 220 participants were needed.

Measures. In addition to the preliminary version of the SRSI-irAEs-LC, a structured self-report sociodemographic information sheet and a clinical characteristics information sheet were designed according to the situational and physiologic factors influencing symptoms as defined by the TUS.[37]

The Chinese version of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and the Lung Cancer Module (QLQ-LC13)[27] questionnaires were used to examine the criterion validity, as both questionnaires have been confirmed to be valid and reliable, and are widely used in cancer ICI-therapy studies, with 58.64% utilizing them to evaluate PROs.[30] The 30-item EORTC QLQ-C30 consists of a global health status (GHS)/HRQOL subscale, five functional subscales (physical functioning, role functioning, emotional functioning, cognitive functioning and social functioning), three symptomatic subscales (fatigue, nausea and vomiting, and pain), five single symptomatic items (dyspnoea, insomnia, appetite loss, constipation and diarrhoea), and a financial difficulty subscale. The linearly transformed score of each subscale/item ranges between 0 and 100, with a higher score representing better HRQOL for GHS/functioning, but poor HRQOL for severe symptoms. For the QLQ-LC13, it contains a symptomatic subscale (dyspnoea) and 9 single symptomatic items (coughing, haemoptysis, sore mouth, dysphagia, peripheral neuropathy, alopecia, chest pain, arm or shoulder pain, and pain in other parts) that assess lung cancer symptoms and treatment-related adverse effects, with higher scores indicating more severe symptoms. In this study, Cronbach's *alpha* for the EORTC QLQ-C30 and the QLQ-LC13 were 0.893 and 0.729, respectively.

Data analysis. The statistical analyses were performed using IBM SPSS Statistics (Version 25.0) and IBM AMOS Statistics (Version 24.0).

(1) Item analysis

The items of the preliminary version of the SRSI-irAEs-LC were screened by using the following methods: coefficient variation (CV), critical ration (CR), correlation coefficient, Cronbach's *alpha* coefficient, and factor analysis.[50] The screening criteria were as follows: (a) items with CV values $< 25\%$ were deleted, (b) by putting the scale's score in order, the top 27.00% were the upper group, and the bottom 27.00% were the lower group. The two independent samples *t* test was used to compare the mean score of each item between the two groups. Items with CR value < 3 or $P > 0.05$ were deleted, (c) correlation between the item score and the scale score was calculated. Items with a correlation coefficient < 0.3 or $P > 0.05$ were deleted, (d) if Cronbach's *alpha* coefficient increased after an item was deleted, it was considered for deletion, (e) in the EFA, items with factor loading value < 0.4, aggregated into a single dimension, with cross-loaded on multiple dimensions, or inconsistent with theoretical dimensions were considered for deletion. If four or more screening results suggest that an item should be retained, it was retained; otherwise, it was deleted.[51]

(2) Validity

The content validity of the SRSI-irAEs-LC was evaluated using the results of the second round of expert consultation (I-CVI) > 0.78, Scale Content Validity Index (S-CVI) > 0.90).[49] The EFA and CFA were performed to determine the construct validity of the scale.[52] The EFA was conducted using Maximum Likelihood analysis (maximum variance orthogonal rotation). To confirm that data were suitable for factor analysis, Kaiser–Meyer–Olkin test (KMO) > 0.50 and Bartlett's test of sphericity were used. In the item analysis, the factor loading should be > 0.40. The number of common factors was determined by the scree plot and the eigenvalues > 1.0. The CFA was conducted using structural equation modelling. The degree of fit between the data and the model was evaluated by the following criteria: Chi-square and degrees of freedom ratio (χ^2/df) < 3.00, Root Mean Square Error of Approximation (RMSEA) < 0.05, Normed Fit Index (NFI) > 0.90, Relative fit index (RFI) > 0.90, Incremental fit index (IFI) > 0.90, Tucker Lewis Index (TLI) > 0.90, Comparative Fit Index (CFI) > 0.90, Parsimonious normed Fit Index (PNFI) > 0.50, and Parsimonious comparative Fit Index (PCFI) > 0.50. Based on literature analysis,[53] gender, age, smoking status, type of ICIs, and Eastern Cooperative Oncology Group (ECOG) score showed significant associations with risk of irAEs among cancer patients, so they were selected as the discriminant factors in this study, and the discriminant validity of the SRSI-irAEs-LC was tested using two independent samples nonparametric tests.

(3) Reliability

The internal consistency reliability of the SRSI-irAEs-LC was assessed using Cronbach's *alpha*, and split-half reliability coefficient. It is generally considered acceptable when Cronbach's *alpha* and split-half reliability coefficient are > 0.7, and 0.80 or more is recommended.[54] In addition, to determine test-retest reliability, 44 lung cancer patients treated with PD-1/PD-L1 ICIs were surveyed twice with an interval of one week during the same treatment cycle, and Pearson correlation coefficient was used to calculate the correlation between the two surveys.

Ethical considerations

This study was approved by the Ethics committee of Guangzhou Medical University (IRB No. 202201002). Each participant volunteered to participate in the study after receiving sufficient explanation of the purpose of this study. All participants provided written informed consent. Furthermore, participants had the option of withdrawing from the study at any time.

Results

Phase I

Item generation for symptomatic irAEs

Documents from FDA, EMA, NMPA, RCTs were reviewed separately by two researchers, and their findings for each document were agreed upon by a consensus. The medical records of 162 lung cancer patients treated with PD-1/PD-L1 ICIs from October 2020 to October 2021 were reviewed, and a total of 725 medical records were audited. A total of 20 eligible patients participated in the patient reviews. Their ages ranged from 41 to 71 years old (58.20 ± 8.54), and 14 of them had a junior high school education or less. As for clinical characteristics, 18 patients were diagnosed with NSCLC, and 16 had clinical stages III to IV. Most of them (n = 17) were treated with PD-1 ICIs. Symptomatic irAEs reported by them were generally consistent with those from the above five sources. In total, a pool of 103 symptomatic irAEs items in 11 dimensions was constructed in this step (Appendix A).

Draft inventory construction for symptomatic irAEs

In the item selection stage, 18 items were removed (gray bottom part of Appendix A), leaving 85 items in 11 dimensions.

Delphi expert consultation for content validity verification and item revision

A total of 15 experts including 8 oncologists, 3 oncology nurse specialists, 3 oncology pharmacists, and 1 psychologist, were invited. Their ages ranged from 33 to 53 years old, and they had worked for 9–32 years, with most holding deputy senior professional titles or higher (n = 11). The overall authority coefficient of the two rounds of expert consultation were 0.89 and 0.90, and the positive coefficients were 100% and 93.33%, respectively, indicating that the experts had authority and high interest in the study.

In the first round of expert consultation, all experts returned the expert letter questionnaires. The mean scores of the correlation of each item ranged from 2.20 to 3.87, and I-CVI of the SRSI-irAEs-LC ranged from 0.27 to 1.00, with 44 items having the I-CVI < 0.7. Based on expert advice, the scale was revised. Specifically, the item "appetite loss" was reclassified from "nutritional and metabolic symptoms" dimension to "digestive system symptoms", and the "circulatory system symptoms" dimension was revised into the "cardiac symptoms". Consequently, 44 items were deleted, 1 item was modified, and 41 items were retained.

In the second round of expert consultation, 14 expert letter questionnaires were returned. The mean correlation scores of each item ranged from 3.21 to 3.93, and the I-CVI ranged from 0.86 to 1.00, indicating high content validity. Finally, no items were revised or deleted in this round, and the revised scale consisted of 41 items in 10 dimensions.

Cognitive interviews for improving the quality of the scale

A total of 10 eligible patients participated in the cognitive interviews. The participants were aged 41–76 years old (63.60 ± 10.06), and most had junior high school education or less (n = 9). Their clinical stages were III or IV, most of them were diagnosed with NSCLC (n = 8), and all treated with PD-1 ICIs. They generally agreed on the whole draft version of the SRSI-irAEs-LC, except for 2 recommendations to clarify some wording of items. six patients were unclear about the meaning of "reactive cutaneous capillary endothelial proliferation (R-CCEP)", prompting a revision to "strawberry-like nodules or plaques on the skin surface". In addition, three patients were confused about "fatigue (feeling tired)" and "asthenia (feeling weak of limbs)", so the statements were revised into "fatigue (feeling tired, do not want to move)" and "asthenia (feeling weak, unable to move)".

Pilot study to verify the feasibility of the scale

Thirty lung cancer patients treated with ICIs participated in the pilot study. They were 40–79 years old (62.86 ± 9.09), most of them had junior high school education or less (n = 26), clinical stages III or IV (n = 29), and diagnosed with NSCLC (n = 26). All participants found the scale to be relatively easy to understand, taking approximately 11–19 minutes to complete.

Phase II

Sociodemographic and clinical characteristics

In total, 528 lung cancer patients were recruited for the study, of whom 260 were in study 1 and 252 (96.92%) completed the questionnaires, while 268 were in study 2 and 260 (97.01%) completed the questionnaires. The sociodemographic and clinical characteristics of the participants in the two studies are shown in Table 1.

Item analysis

All items had the CV values > 25% in coefficient variation, and 4 items had the CR values < 3.0. As the correlation coefficients between item scores and the scale score ranged from 0.045 to 0.620, 18 items failed to meet the standard. Moreover, when the items "skin

Table 1
Sociodemographic and clinical characteristics of participants.

Characteristics	Study 1, n (%) (n = 252)	Study 2, n (%) (n = 260)	Total, n (%) (n = 512)
Age (years, Mean ± SD)	61.97 ± 9.38	61.55 ± 9.74	61.73 ± 9.56
Sex			
Male	209 (82.94)	206 (79.23)	415 (81.05)
Female	43 (17.06)	54 (20.77)	97 (18.95)
Educational level			
Primary school or less	98 (38.89)	83 (31.92)	181 (35.35)
Junior high school	84 (33.33)	92 (35.39)	176 (34.38)
High school	52 (20.63)	65 (25.00)	117 (22.85)
College or higher	18 (7.15)	20 (7.69)	38 (7.42)
Marital status			
Married/Cohabited	238 (94.44)	255 (98.08)	493 (96.29)
Divorce/Separated/ Widowed/Single	14 (5.56)	5 (1.92)	19 (3.71)
Residency			
Rural	142 (56.35)	132 (50.77)	274 (53.52)
Urban	110 (43.65)	128 (49.23)	238 (46.48)
Employment			
Employed	219 (86.9)	232 (89.23)	451 (88.09)
Unemployed	33 (13.10)	28 (10.77)	61 (11.91)
Average monthly income per capital (RMB)			
≤ 5000	178 (70.63)	215 (82.69)	393 (76.76)
> 5000	74 (29.37)	45 (17.31)	119 (23.24)
Smoking			
Yes	182 (72.22)	183 (70.38)	365 (71.29)
No	70 (27.78)	77 (29.62)	147 (28.71)
Drinking alcohol			
Yes	149 (59.13)	167 (64.23)	316 (61.72)
No	103 (40.87)	93 (35.77)	196 (38.28)
Type of pathology			
NSCLC	220 (87.30)	211 (81.15)	431 (84.18)
SCLC	26 (10.32)	38 (14.62)	64 (12.50)
Other	6 (2.38)	11 (4.23)	17 (3.32)
Stage of cancer			
I	12 (4.76)	4 (1.54)	16 (3.13)
II	5 (1.99)	11 (4.23)	16 (3.13)
III	78 (30.95)	81 (31.15)	159 (31.05)
IV	157 (62.30)	164 (63.08)	321 (62.69)
ECOG score			
0	101 (40.08)	110 (42.31)	211 (41.21)
1	100 (39.68)	94 (36.15)	194 (37.89)
2	45 (17.86)	41 (15.77)	86 (16.80)
3	6 (2.38)	14 (5.39)	20 (3.91)
4	0 (0.00)	1 (0.38)	1 (0.19)
Type of ICIs			
PD-1	239 (94.84)	235 (90.38)	474 (92.58)
PD-L1	13 (5.16)	25 (9.62)	38 (7.42)

NSCLC, Non-small cell lung cancer; SCLC, Small cell lung cancer; ECOG, Eastern Cooperative Oncology Group; ICIs, Immune checkpoint inhibitors; PD-1, Programmed cell death protein 1; PD-L1, Programmed death-ligand 1.

depigmentation" and "diarrhea" were deleted, the Cronbach's *alpha* increased. Furthermore, 11 items were not consistent with the theory, 3 items with factor loading value < 0.4, 2 item aggregated into a single dimension, and 1 item cross-loaded on two dimensions, all of 17 items were excluded in the EFA. Therefore, combining the results of the 5 methods, a total of 15 items were deleted, and the final version of the SRSI-irAEs-LC contained 26 items across 8 dimensions (Table 2).

Validity

Content validity. The I-CVI of the SRSI-irAEs-LC ranged from 0.86 to 1.00, and the S-CVI for the overall scale was 0.98.

Construct validity. After item analysis, the EFA was performed on the 26 items of the final version of the SRSI-irAEs-LC. The KMO value was 0.696 and the Bartlett's test of Sphericity reached statistical significance ($\chi^2 = 3461.946$, $P < 0.001$). Without limiting the number of factors, 8 factors with eigenvalues greater than 1.0 were generated, which explained 65.53% of the total variance.

In study 2, after several CFA revisions based on the modified index (MI > 4) provided by AMOS, combined with the item analysis results in this study, the fixed parameters among some error variables were released as free parameters, an optimal pattern was eventually fitted and confirmed (Fig. 2). The value of χ^2/df was 1.632, indicating the fitness of the model. The RMSEA of the model was 0.049. The IFI, TLI, CFI were all

Table 2
Items analysis results of SRSI-irAEs-LC (N = 252).

Dimension/Items	Coefficient Variation (CV)	Critical Ration (CR)	Correlation Coefficient (*r*)	Cronbach's *alpha*	Factor Loading	Result
1.Skin symptoms						
Rash	59.90%	6.926***	0.381***	0.828	0.775	retain
Erythema	52.13%	4.867***	0.371***	0.828	0.665	retain
Pruritus	59.03%	13.984***	0.374***	0.829	0.537	retain
Photosensitivity reaction	36.66%	3.305***	0.202***	0.831	0.838[a]	delete
Skin exfoliation	49.43%	6.773***	0.418***	0.826	0.800	retain
Dry skin	51.63%	9.270***	0.477***	0.825	0.750	retain
Skin depigmentation	29.16%	2.344***	0.045	0.833	0.697[a]	delete
Skin pigmentation	44.37%	7.387***	0.243***	0.830	0.749[a]	delete
Reactive cutaneous capillary endothelial proliferation	38.76%	4.083***	0.265***	0.830	0.397	delete
2.Digestive system symptoms						
Dry mouth	50.94%	2.968***	0.265***	0.830	0.696	delete
Anorexia	46.80%	15.650***	0.470***	0.825	0.456[a]	retain
Diarrhoea	45.06%	4.746***	0.104	0.833	0.757[c]	delete
Abdominal pain	48.87%	6.205***	0.327***	0.829	0.510/0.512[b]	retain
Gingival bleeding	43.29%	2.871***	0.289***	0.829	0.794	delete
Mouth ulceration	36.11%	3.962***	0.123	0.832	0.763[a]	delete
3.Respiratory system symptoms						
Cough	45.71%	11.882***	0.454***	0.825	0.746	retain
Productive cough	45.33%	12.118***	0.427***	0.826	0.716	retain
Dyspnoea	58.20%	7.224***	0.412***	0.827	0.654	retain
Chest pain	53.68%	6.980***	0.408***	0.827	0.622	retain
Chest discomfort	51.25%	7.777***	0.515***	0.824	0.518	retain
4.Bone and muscle symptoms						
Myalgia	61.13%	14.459***	0.509***	0.824	0.698	retain
Arthralgia	59.99%	11.413***	0.413***	0.827	0.755	retain
Joint swelling	31.95%	3.453***	0.228***	0.829	0.641[a]	delete
Musculoskeletal stiffness	38.76%	3.930***	0.208***	0.829	0.471[a]	delete
Pain in extremity	61.15%	9.703***	0.456***	0.825	0.726	retain
5.Neurological system symptoms						
Dizziness	54.41%	7.304***	0.278***	0.831	0.548	retain
Hypoaesthesia	53.78%	17.746***	0.340***	0.831	0.751	retain
6.Eyes symptoms						
Dry eye	32.46%	5.155***	0.208***	0.831	0.648	retain
Lacrimation increased	34.00%	5.308***	0.126***	0.832	0.752[c]	delete
Vision blurred	49.43%	15.795***	0.373***	0.828	0.374	retain
Conjunctival hyperaemia	29.28%	5.045***	0.271***	0.830	0.697	retain
7. Cardiac symptoms						
Palpitations	45.48%	28.024***	0.391***	0.827	0.875	retain
Heart rate irregular	40.69%	10.484***	0.279***	0.830	0.872	retain
8.Urinary system symptoms						
Pollakiuria	48.34%	30.773***	0.236***	0.829	0.649[a]	delete
9.Nutritional and metabolic symptoms						
Oedema	37.65%	6.904***	0.210***	0.831	0.732[a]	delete
Weight decreased	56.78%	17.224***	0.284***	0.828	0.383	delete
10.General symptoms						
Fatigue	48.62%	33.704***	0.620***	0.819	0.937	retain
Asthenia	48.50%	33.191***	0.610***	0.819	0.935	retain
Lethargy	53.85%	19.308***	0.526***	0.823	0.836	retain
Somnolence	41.76%	4.094***	0.305***	0.829	0.518[a]	retain
Pyrexia	52.18%	2.964***	0.305***	0.829	0.688[a]	delete

***$P < 0.001$. SRSI-irAEs-LC, Self-Report Symptom Inventory of immune-related Adverse Events in Patients with Lung Cancer.
Note:
[a] The dimension was not consistent with the theory.
[b] The symptom was cross-loaded on two dimensions.
[c] The dimensions only included one symptom.

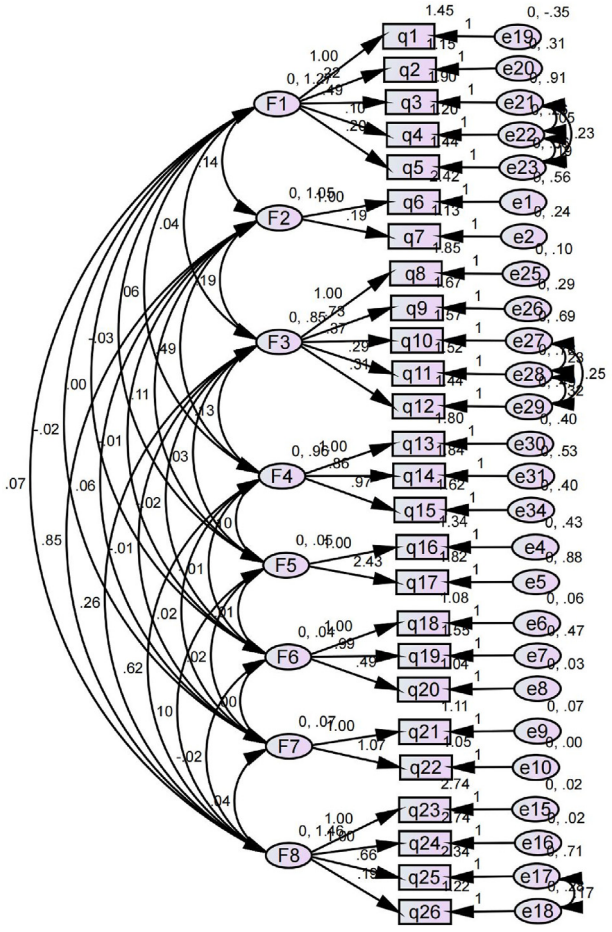

Fig. 2. The CFA standardized item factor loadings and factor correlations for the SRSI-irAEs-LC (n = 260; $P < 0.001$). F1 = skin symptoms; F2 = digestive system symptoms; F3 = respiratory system symptoms; F4 = bone and muscle symptoms; F5 = neurological system symptoms; F6 = eyes symptoms; F7 = cardiac symptoms; F8 = general symptoms. SRSI-irAEs-LC, Self-Report Symptom Inventory of immune-related Adverse Events in Patients with Lung Cancer; CFA, confirmatory factor analysis.

greater than 0.90, while the NFI, RFI were less than 0.90, but still within acceptable limits.[52] And the PNFI, PCFI were greater than 0.50. Accordingly, the 8-factor model fitted the data well in most cases (Table 3).

Criteria validity. The results showed that the scores of digestive system symptoms, respiratory system symptoms, bone and muscle symptoms, general symptoms, and the entire scale of the SRSI-irAEs-LC were generally negatively correlated with most functional subscales and the HRQOL subscale scores of the EORTC QLQ-C30 ($|r| > 0.3$), whereas they were mostly positively correlated with the symptom subscales of the EORTC QLQ-C30 ($|r| > 0.3$) (Table 4). In addition, the scores of digestive system symptoms, respiratory system symptoms, bone and muscle symptoms, general symptoms, and the entire scale of the SRSI-irAEs-LC were positively related to the total symptom scores of QLQ-LC13 ($|r| > 0.3$). Besides, when the dimensions of the SRSI-irAEs-LC included the symptoms of the QLQ-LC13 including cough, hemoptysis, dyspnoea, and pain in the body, there was almost a positive correlation between the corresponding symptoms of QLQ-LC13 and the corresponding dimensions of SRSI-irAEs-LC ($|r| > 0.3$). (Table 5).

Discriminate validity. There was no significant difference in the SRSI-irAEs-LC scores between the two groups for gender ($t = -0.453$, $P = 0.651$), age ($t = -1.250$, $P = 0.211$), smoking ($t = -0.160$, $P = 0.873$) and type of ICIs ($t = -1.821$, $P = 0.069$), but there was a significant difference between the two groups of ECOG score < 2 and ECOG score ≥ 2 ($t = -8.407$, $P < 0.001$).

Reliability

The Cronbach's *alpha* and the split-half reliability of the SRSI-irAEs-LC were 0.824, and 0.725, respectively. The test-retest reliability showed that there was a large positive correlation between the double measurement results (r = 0.622–0.973, $P < 0.05$) (Table 6).

Discussion

This study describes the development and initial validation of the SRSI-irAEs-LC, proving initial evidence of its validity and reliability. As the unique characteristics of symptomatic irAEs and the inadequacy instruments for self-reporting symptomatic irAEs in lung cancer patients, the SRSI-irAEs-LC has the potential to be particularly useful for detecting and monitoring symptomatic irAEs in lung cancer clinical and research settings.

A scale is usually developed by constructing it according to a theoretical model or by revising an existing scale.[40,55] Considering the lack of mature symptom assessment instruments for irAEs in lung cancer, we developed the SRSI-irAEs-LC under the guidance of the TUS, ensuring its scientific validity and rationality.[55,56] This study also further enriched the application of the TUS in the field of PRO scale development. Furthermore, this study completely presented the process of item generation and scale construction. Inspired by symptom assessment scale developed by Nissen et al.,[41] we collected the symptomatic irAEs from six different sources to provide a comprehensive picture of potential symptomatic irAEs in lung cancer patients. Despite patients' medical records and patient interviews add few to the symptomatic irAEs obtained from FDA, EMA, NMPA product summaries information and RCTs, our study demonstrates a good match between the symptomatic irAEs reported in public documentations and the information provided by doctors, nurses and patients. As has been found in previous study,[41] there was good harmony between the profile of identified adverse events found in official document and information from oncologists and

Table 3
Appropriate indices of model for confirmatory factor analysis of the SRSI-irAEs-LC (N = 260).

Absolute Fit Indexes	Result	Criteria	Incremental Fit Indexes	Result	Criteria	Simplicial Fit Indexes	Result	Criteria
χ^2/df	1.632	< 3.000	NFI	0.866	> 0.900	PNFI	0.703	> 0.500
RMSEA	0.049	< 0.050	RFI	0.835	> 0.900	PCFI	0.765	> 0.500
			IFI	0.943	> 0.900			
			TLI	0.929	> 0.900			
			CFI	0.942	> 0.900			

χ^2, Chi-square goodness of fit statistic; *df*, Degrees of freedom; RMSEA, Root-mean-square Error of Approximation; NFI, Normed Fit Index; RFI, Relative Fit Index; IFI, Incremental Fit Index; TLI, Tucker Lewis Index; CFI, Comparative Fit Index; PNFI, Parsimonious Normed Fit Index; PCFI, Parsimonious Comparative Fit Index; SRSI-irAEs-LC, Self-Report Symptom Inventory of immune-related Adverse Events in Patients with Lung Cancer.

Table 4
Correlation of the SRSI-irAEs-LC scores with the EORTC QLQ-C30 scores ($N = 260$).

SRSI-irAEs-LC scores	EORTC QLQ-C30 scores															
	Physical functioning	Role functioning	Emotional functioning	Cognitive functioning	Social functioning	Global Health Status/ HRQOL	Fatigue	Nausea and vomiting	Pain	Dyspnoea	Insomnia	Appetite loss	Constipation	Diarrhoea	Financial difficulty	Total symptom scores
Skin symptoms	−0.102	−0.185**	−0.220**	−0.019	−0.176**	−0.219**	0.148*	−0.018	0.067	−0.014	0.106	0.205**	0.067	−0.04	−0.074	0.109
Digestive system symptoms	**−0.519****	**−0.583****	**−0.475****	**−0.346****	**−0.484****	**−0.607****	**0.619****	**0.460****	**0.387****	0.308**	**0.417****	**0.823****	**0.329****	0.105	0.008	**0.710****
Respiratory system symptoms	**−0.389****	**−0.323****	−0.267**	−0.282**	−0.275**	**−0.429****	**0.343****	0.121	**0.334***	**0.573****	**0.337****	0.212**	0.163**	−0.011	0.149*	**0.454****
Bone and muscle symptoms	**−0.343****	**−0.454****	**−0.309****	**−0.308****	**−0.431****	**−0.470****	**0.517****	**0.331****	**0.733****	0.196**	**0.321****	**0.341****	0.087	−0.063	0.046	**0.525****
Neurological system symptoms	−0.118	−0.212**	−0.15**	−0.222**	−0.189**	−0.276**	0.206**	0.151*	0.202**	0.056	0.172**	0.217**	0.059	0.069	0.175**	0.262**
Cardiac symptoms	−0.137*	−0.143*	−0.155*	−0.122*	−0.078	−0.134*	0.143*	0.025	0.118	0.248**	0.159*	0.124*	−0.018	0.018	−0.044	0.165**
Eyes symptoms	−0.135**	−0.173**	−0.115	−0.205**	−0.155*	−0.139*	0.133*	0.075	0.140*	0.071	0.073	0.119	0.039	0.032	0.129*	0.162**
General symptoms scores	**−0.683****	**−0.701****	**−0.482****	**−0.418****	**−0.583****	**−0.685****	**0.808****	**0.307****	**0.474****	**0.423****	**0.407****	**0.598****	**0.343****	0.117	−0.013	**0.712****
Entire scale scores	**−0.626****	**−0.696****	**−0.533****	**−0.453****	**−0.603****	**−0.747****	**0.751****	**0.347****	**0.631****	**0.471****	**0.489****	**0.625****	0.285**	0.038	0.071	**0.768****

*$P < 0.05$, **$P < 0.01$.

Bold font means the $|r| > 0.3$. SRSI-irAEs-LC, Self-Report Symptom Inventory of immune-related Adverse Events in Patients with Lung Cancer; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; HRQOL, health-related quality of life.

Table 5
Correlation of the SRSI-irAEs-LC scores with the QLQ-LC13 scores ($N = 260$).

SRSI-irAEs-LC scores	QLQ-LC13 scores										
	Cough	Hemoptysis	Dyspnoea	Sore mouth	Dysphagia	Peripheral neuropathy	Alopecia	Chest pain	Arm or shoulder pain	Pain in other parts of the body	Total symptom scores
Skin symptoms	0.117	0.088	0.032	0.239**	0.154**	−0.032	−0.004	−0.054	0.121*	0.122*	0.130*
Digestive system symptoms	0.094	0.173**	**0.355****	0.185**	**0.306****	0.121	0.207**	0.287**	**0.386****	**0.377****	**0.508****
Respiratory system symptoms	**0.708****	**0.422****	**0.550****	−0.092	−0.003	0.051	0.226**	**0.564****	**0.314****	0.272**	**0.632****
Bone and muscle symptoms	0.096	0.079	0.191**	0.169**	0.221**	0.419**	0.171**	**0.373****	**0.594****	**0.586****	**0.626****
Neurological system symptoms	0.077	0.066	−0.01	0.011	0.064	0.297**	0.118	0.058	0.055	0.201**	0.199**
Cardiac symptoms	0.015	−0.032	0.193**	0.035	−0.022	0.02	0.018	0.105	0.138*	0.099	0.132*
Eyes symptoms	0.022	0.055	0.038	0.273**	0.209**	0.145**	−0.059	0.054	0.108	0.169**	0.168**
General symptoms scores	0.202**	0.173**	**0.473****	0.053	0.187**	0.187**	0.296**	**0.302****	**0.310****	**0.321****	**0.531****
Entire scale scores	**0.391****	0.286**	**0.486****	0.167**	0.253**	0.278**	0.276**	**0.453****	**0.515****	**0.525****	**0.754****

*$P < 0.05$, **$P < 0.01$.
Bold font means the $|r| > 0.3$. SRSI-irAEs-LC, Self-Report Symptom Inventory of immune-related Adverse Events in Patients with Lung Cancer; QLQ-LC13, Quality of Life Questionnaire-Lung Cancer 13.

Table 6
Reliability of the SRSI-irAEs-LC.

SRSI-irAEs-LC	Study 2 ($n = 260$)	Study 2 ($n = 260$)	Test-retest reliability ($n = 44$)
	Cronbach's *alpha*	Spearman–Brown coefficient (SB)	*r*
Skin symptoms	0.710	0.511	0.973**
Digestive system symptoms	0.346	0.346	0.819**
Respiratory system symptoms	0.759	0.602	0.816**
Bone and muscle symptoms	0.853	0.772	0.750**
Neurological system symptoms	0.242	0.242	0.794**
Cardiac symptoms	0.811	0.811	0.792**
Eyes symptoms	0.292	0.183	0.879**
General symptoms	0.811	0.748	0.622**
Entire scale	0.824	0.725	0.851**

**$P < 0.05$. SRSI-irAEs-LC, Self-Report Symptom Inventory of immune-related Adverse Events in Patients with Lung Cancer.

patients. Hence, our study further confirms the reliability and practicality of collecting symptomatic irAEs from publicly available documentation when constructing the item pool of PRO-based symptom assessment tool.

The I-CVI and the S-CVI of the SRSI-irAEs-LC were greater than the criteria,[49] suggesting good content validity for the SRSI-irAEs-LC. The 8 factors explained 62.33% of the total variance, which was higher than 50%,[57] and the CFA showed the model fit the data well in most cases, indicating good construct validity for the SRSI-irAEs-LC. Besides, the SRSI-irAEs-LC had significant correlations with the EORTC QLQ-C30 and the QLQ-LC13, suggesting it has good criteria validity. As indicated in other studies,[58] the existing PROs questionnaires developed several decades ago may not be able to capture most of symptomatic irAEs due to their unique characteristics. It is noteworthy that the SRSI-irAEs-LC could be used to capture some common symptomatic irAEs not covered by the EORTC QLQ-C30 and the QLQ-LC13, such as skin symptoms, neurological system symptoms, cardiac symptoms, and eyes symptoms. The SRSI-irAEs-LC also showed good discrimination between patients with higher ECOG scores and those with lower ECOG scores. The possible reason was that patients with ECOG score ≥ 2, who had high levels of inflammatory cytokines, may be more prone to be involved in the pathophysiology of irAEs.[59]

For the reliability of the SRSI-irAEs-LC, the Cronbach's *alpha* coefficient, split-half reliability and test-retest of the whole scale reliability were > 0.70,[50] indicating high reliability. However, the Cronbach's *alpha* coefficients for the dimensions of "digestive system symptoms", "neurological system symptoms", and "eyes symptoms" were < 0.70, which were related to the large differences in the incidence of symptoms within the dimensions. Similarly, the split-half reliabilities for the dimensions of "skin symptoms", "digestive system symptoms", "respiratory system symptoms", "neurological system symptoms", "eyes symptoms" were < 0.7, which were attributed to the large variation in the incidence of symptoms or the odd number of items in the dimension.

Implications for nursing practice and research

To develop the SRSI-irAEs-LC, symptomatic irAEs were collected from six multiple sources, and the terminology of symptoms were standardized according to MedDRA SOC. Thus, this scale may be helpful to medical professionals across the country and abroad in better understanding the incidence and severity of symptomatic irAEs in lung cancer patients, so that these symptoms can be identified and managed earlier. In addition, it may be used to evaluate the effectiveness of interventions targeting irAEs-related symptoms or symptom clusters. Finally, with regard to the development of telemedicine, the SRSI-irAEs-LC lays the foundation for the development of a digital acquisition system for symptomatic irAEs to realize remote monitoring of irAEs among lung cancer patients.

Limitations

There were also a few limitations to this study. Firstly, we recruited participants from three hospitals in Guangzhou, one of the largest cities

in south China, which may have affected the representation of lung cancer patients in the sample, thus limiting generalizability. Hence, future studies should investigate whether the present findings can be replicated in a broader group of lung cancer patients. Secondly, 94.84% of the patients included in this study were treated with PD-1 ICIs, and although there was no significant difference in irAEs caused by PD-1 and PD-L1 ICIs,[60] it would be beneficial to expand the number of patients treated with PD-L1 ICIs to verify that the SRSI-irAEs-LC is applicable to these patients in the future. Finally, the psychometric testing of the scale was conducted on only 512 lung cancer patients receiving ICIs, and further large-scale studies are needed to verify its validity and reliability.

Conclusions

In conclusion, the SRSI-irAEs-LC comprises 8 dimensions with 26 items and is preliminarily valid and reliable. It is a newly developed PROs symptom measurement scale for lung cancer patients treated with PD-1/PD-L1 ICIs, which may assist health professionals in identifying and managing patients' symptomatic irAEs earlier and effectively. However, it is necessary to conduct further large-scale research to verify the generalizability, reliability and validity of this scale.

CRediT authorship contribution statement

Tiantian Fan: Conceptualization, Investigation, Data curation, Formal analysis, Writing – Original draft, and Writing – Review & editing. **Siying Zhu:** Conceptualization, Investigation, Data curation, and Writing – Review & editing. **Hong Wang:** Conceptualization, Investigation, Data curation, Formal analysis, Writing – Original draft. **Yan Dong:** Conceptualization, Investigation, and Data curation. **Ying Zhou:** Supervision, Writing – Review & editing. **Yalan Song:** Investigation. **Shan Pan:** Investigation. **Qiujuan Wu:** Investigation. **Graeme Drummond Smith:** Writing – Review & editing. **Yumei Li:** Conceptualization, Formal analysis, Project administration, Validation, Data curation, Writing – Review & editing, and Supervision. **Yuan Han:** Conceptualization, Formal analysis, Project administration, Validation, Data curation, Writing – Review & editing, and Supervision. All authors had access to the study data, and the corresponding author had final responsibility for submitting the manuscript for publication. The corresponding author confirms that all listed authors meet authorship criteria and that no individuals who qualify for authorship have been omitted.

Ethics statement

The study was approved by the Ethics Committee of Guangzhou Medical University (IRB No. 202201002). All participants provided written informed consent.

Declaration of generative AI and AI-assisted technologies in the writing process

No AI tools/services were used during the preparation of this work.

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Declaration of competing interest

The authors declare no conflict of interest.

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Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to their containing information that could compromise the privacy of research participants.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.apjon.2024.100603.

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