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Comprehensive validation of the functional assessment of anorexia/cachexia therapy (FAACT) anorexia/cachexia subscale (A/CS) in lung cancer patients with involuntary weight loss

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Abstract

Purpose Comprehensive (qualitative and quantitative) assessments of the 12-item functional assessment of anorexia/cachexia therapy (FAACT) anorexia/cachexia subscale (A/CS) and relevant subscales were undertaken for use in constructing potential endpoints in clinical trials of non-small cell lung cancer (NSCLC) with involuntary weight loss.

Methods Eleven participants (≥ 18 years) from six clinical sites with a diagnosis of stage III unresectable or stage IV NSCLC and involuntary weight loss (either ≥ 5% body weight loss within six months prior to screening or screening BMI < 20 kg/m^2) were interviewed to evaluate the content validity of the A/CS domain. A psychometric evaluation was conducted on the A/CS domain, and symptoms and concerns subscales, using data from previously completed phase III clinical trials (ROMANA1 [N = 474] and ROMANA2 [N = 488]).

Results Anorexia-related symptoms were highly relevant to participants and had important impacts on their lives including energy levels, and physical, social, and psychological functioning. The majority of participants endorsed the A/CS domain items and found them to be easily understood, relevant, and comprehensive. Confirmatory factor analyses established that the A/CS symptoms and concerns subscales provided an acceptable fit as single factor models in ROMANA1 and ROMANA2. Reliability, validity, and responsiveness were established for the 12item A/CS domain, 5item anorexia symptoms subscale, and 4-item anorexia concerns subscale.

Conclusions These scales have good content validity, favorable psychometric properties, and can be used for characterizing the effect of treatment on anorexia symptoms and/or anorexia-related concerns in patients with NSCLC.

Keywords Anorexia · Cachexia · Non-small cell lung cancer · FAACT A/CS · Content validity · Psychometric validation

Introduction

Cancer cachexia is a syndrome typically characterized by anorexia, weight loss, systemic inflammation, and loss of muscle mass, which leads to poor functional state and is often associated with disease progression and shortened survival [1–5]. It is estimated to affect approximately 50–80% of patients with advanced cancer [6], with the highest prevalence observed in patients with lung and gastrointestinal cancers [7, 8]. However, despite the high prevalence and significant clinical impact, there is no current standard of care to manage cancer cachexia or to address the key associated symptoms including weight loss and anorexia.

In patients with advanced cancer, anorexia is a major contributor to weight loss and is characterized as a general loss of appetite, early satiety, altered food preferences, or

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a combination of these symptoms [9]. Cancerrelated anorexia also adversely influences nutritional status in advanced cancer [10] and has been associated with poorer survival [11–17]. In a study by Sundstrom and colleagues, appetite loss emerged as the most significant independent indicator for survival in patients with advanced non-small cell lung cancer (NSCLC), suggesting that an assessment of anorexia, including appetite loss, may be a valuable tool in determining treatment strategy [12]. Moreover, in a recent survey of patients with advanced NSCLC, considerable weight loss was found to negatively impact health-related quality of life (HRQL) and functional status, and was associated with more severe symptoms. It has been found that the most commonly experienced weight loss-related symptoms, which had the most significant impact on patients' lives, were anorexia-related symptoms (including decreased appetite, altered food taste, and early satiety) and fatigue [18]. Collectively, these data highlight the clinical burden and importance of cancer anorexia.

The functional assessment of anorexia/cachexia therapy (FAACT) instrument is a patient-reported outcome (PRO) measure that was originally designed to assess specific anorexia/cachexia-related symptoms and concerns among patients with cancer and HIV/AID-related anorexia/cachexia. The FAACT instrument contains 39 items, including a 12-item additional concerns anorexia/cachexia scale (A/CS), which specifically measures the symptoms and concerns of patients with anorexia/cachexia [19, 20], and the 27-item functional assessment of cancer therapy-general (FACT-G) instrument, which assesses general aspects of HRQL within four primary domains (physical well-being, social/family wellbeing, emotional well-being, and functional well-being) [21, 22]. The 12 items of the A/CS can be scored alone to yield a domain score or in conjunction with the 27 items of the FACT-G to yield the FAACT total score.

The A/CS was initially developed based on qualitative data from ten cancer and six HIV-infected patients with anorexia-cachexia and five expert providers [19]. The 18 candidate items were then tested in a randomized controlled trial that compared 2 doses of megestrol acetate oral suspension (200 mg vs. 800 mg) in 213 patients ($n = 155$ with advanced cancer, including $n = 41$ with lung cancer, and $n = 48$ with HIV). A combined empirical and conceptual approach was used to reduce the 18 candidate items to the current 12-item format [20]. Subsequently, the performance of the FAACT and the A/CS domain alone were evaluated within a dataset of patients with advanced NSCLC, where both measures demonstrated good internal consistency, and convergent and divergent validity [23].

Because the A/CS was initially developed in the early 1990s, prior to the Food and Drug Administration's PRO guidance [24] and recognition of the minimum measurement standards for PROs [25], the current study was aimed at exploring the A/CS domain, with a focus on understanding the content validity of patient-reported anorexia symptoms and concerns overall and by construct Specifically, as concepts used in support of product labeling claims refer to a patient's symptoms, signs, or functioning, it was of interest to investigate the possibility of evaluating and scoring anorexia-related symptoms and concerns separately [24]. This type of modification requires supporting evidence of content validity (i.e., qualitative data showing that the items reflect the full range of patient symptoms and concerns related to anorexia/appetite loss, and quantitative evidence of item-level and scale-level performance) [25]. Therefore, a qualitative concept elicitation and cognitive debriefing study, and an assessment of the factor structure and a quantitative evaluation of the psychometric properties of the full 12-item A/CS scale and relevant subscales were undertaken.

Methods

Qualitative study

Qualitative interviews were conducted to support the content validity of the anorexiarelated symptoms component of the A/CS. This included demonstrating that the items reflect the full range of patient symptoms and concerns related to anorexia/appetite loss, ascertaining the impact of anorexia-related symptoms on patients' lives, and assess the clarity and interpretability of the anorexia-related symptoms component of the A/CS, including the items, response scale, and recall period. This cross-sectional, qualitative study used semi-structured telephone interviews of 11 participants who were recruited from six clinical sites in the US (Connecticut, Louisiana, New York, and Ohio). Key inclusion criteria: participants were 18 years of age or older, had a diagnosis of stage III (unresectable) or IV NSCLC, and involuntary weight loss (defined as either 5% or more of body weight loss within the six months prior to screening or body mass index [BMI] less than 20 kg/m^2). Participants were also required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or better, and ongoing problems with appetite/eating for more than a few days over the past six months not due to reasons other than lung cancer.

The first part of the interview included open-ended questions and was focused on eliciting participants' experiences with appetite/eatingrelated symptoms, appetite/eating-related concerns, and impact on HRQL. In the second part of the interview, each participant completed the A/CS instrument, and then was asked questions to evaluate comprehension and interpretation of the items, the appropriateness and ease of use of the response scale and recall period in relation to their experience with appetite/eating-related symptoms,

and the comprehensiveness or content coverage of the instrument. Participants also completed a sociodemographic form and the FACT-G. Interviews were audio-recorded and transcribed. A content analysis approach was used to analyze data from the qualitative interviews using ATLAS.ti version 7.0 (or later). Data were entered into saturation grids to organize the concepts that emerged in each interview; saturation was said to occur when no novel information was obtained in two consecutive interviews [26, 27].

Psychometric validation

Quantitative validation was conducted to evaluate the psychometric properties of the 12-item A/CS domain and the symptoms and concerns subscales in the population of interest. A secondary data analysis was conducted using data from two randomized, double-blind, placebocontrolled clinical trials (ROMANA1 and ROMANA2) that assessed the safety and efficacy of anamorelin in patients with advanced NSCLC and cachexia (ClinicalTrials.gov identifiers: NCT01387269 and NCT01387282) [28]. In these trials, eligible patients were at least 18 years of age, had Stage III or IV NSCLC, involuntary weight loss of $\geq 5\%$ body weight within 6 months prior to screening or a screening body mass index < 20 kg/m^2, body mass index ≤ 30 kg/m^2, ECOG performance status ≤ 2, estimated life expectancy of > 4 months at the time of screening, and adequate hepatic and renal function. Patients were ineligible if they had other forms of lung cancer, were pregnant or breast feeding, had known HIV, hepatitis, or active tuberculosis, had major surgery within 4 weeks prior to randomization, were currently taking prescription medications intended to increase appetite or treat weight loss, were unable to readily swallow oral tablets, had severe gastrointestinal disease or intractable or frequent vomiting, had an active, uncontrolled infection, uncontrolled diabetes mellitus, untreated hypothyroidism, or known or symptomatic brain metastases, or were receiving strong CYP3A4 inhibitors within 14 days of randomization.

Key measures

The PRO measures used in the ROMANA1 and ROMANA2 studies were the FAACT A/CS scale, the Hunger Assessment Scale (HAS), and the Functional Assessment of Chronic Illness Therapy–Fatigue scale (FACIT-Fatigue), which were administered at baseline and every three weeks during the 12-week treatment period. These scales were formatted for self-administration and used a 5point Likert-type scale where patients rated each item from 0 to 4 (0 = not at all; 1 = a little bit; 2 = somewhat; 3 = quite a bit; and 4 = very much). The recall period for each question is "during the past 7 days." Possible scores for the 12-item A/CS range from 0 to 48, with 0 being the worst possible score and 48 the best. The HAS was developed specifically for the ROMANA1 and ROMANA2 clinical trials and consists of two items: "I have felt hungry" and "My family and friends are pleased with my appetite." The range of possible scores for the sum of the two items of the HAS is 0 to 8, with 0 being the worst possible score and 8 the best. The 13-item FACIT-Fatigue scale assesses fatigue and its impact upon daily activities and function. The range of possible scores for the 13 items of the FACIT-Fatigue is 0–52, with 0 being the worst possible score and 52 the best.

Statistical analyses

Analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC) and Mplus software [29]. Descriptive statistics were used to describe the study population and PRO measures.

Means and standard deviations were reported for continuous variables, and the numbers and percent distributions were provided for categorical variables. Confirmatory factor analysis (CFA) was conducted using baseline A/CS data to determine whether the A/CS items showed adequate fit to several hypothesized factor models that were informed by the qualitative study results. Model fit was assessed with the comparative fit index (CFI) and root mean square error of approximation (RMSEA).

Internal consistency reliability of relevant A/CS scales was assessed by Cronbach's alpha coefficient using baseline data. Alpha coefficients range from 0 to 1.0, with higher scores indicating a more reliable (homogeneous) instrument (0.7–0.9 = good; 0.4 to < 0.7 = moderate; < 0.4 = low). Test–retest reliability was examined to assess the stability of each A/CS scale and subscale over time within a stable population. Stable patients were defined as those with no change on the HAS total score and no change in body weight (-0.2 to 0.2 kg change). Testretest reliability was conducted by comparing the stable patients' scores at baseline to week 3 using paired *t*-tests and intraclass correlations coefficients (ICC) using formulas from Deyo and colleagues [31]. ICCs range from 0 to 1.0, with higher scores indicating a more stable instrument (≥ 0.7 = good; 0.4 to 0.7 = moderate; $<$ 0.4 = low).

The relevant A/CS scales were assessed for construct validity and known-groups validity. The relationship between the A/CS scale scores and clinical measures (lean body mass, weight, fat mass, and BMI) were examined using Pearson's product-moment correlation coefficients at baseline. The relationship between the A/CS scale scores and the FACIT-Fatigue and HAS were examined using baseline data. A correlation coefficient greater than 0.3 for measures that assess the same construct indicates acceptable convergent validity [30]. To evaluate known-groups validity, the

relevant A/CS scales were analyzed by HAS, body weight, ECOG status, and BMI. For each scale, analysis of covariance models included the A/CS scales as the dependent variables, and each known group criterion variable as the independent variable; the models included age and gender as covariates.

To measure responsiveness, analysis of covariance models were used to estimate least squares mean change in the relevant A/CS scales from baseline to 6 weeks, and also from baseline to 12 weeks. The responsiveness analyses were based on changes for HAS (decrease ≤ 0; no change $= 0$; small increase $= 1$; large increase ≥ 1). Responsiveness analyses were also conducted using changes in body weight (decrease $\leq -1\%$; stable $= -1$–1%; small increase $= 1$–5%; large increase $\geq 5\%$) as a criterion variable.

Anchor- and distribution-based [0.2 standard deviations (SD), 0.5 SD and one standard error of measurement] methods for determining responder definitions were used to estimate meaningful individual level change and suggest a responder definition (important difference) for each of the relevant A/CS scales. The anchor-based analyses for the A/CS were conducted using the HAS item 1, "I have felt hungry," and HAS item 2, "My family and friends are pleased with my appetite." A 1point improvement on each HAS item was used as the criterion for a responder. Analysis of covariance (ANCOVA) was performed, adjusting for age, gender, and race, and using Scheffe's test adjusting for multiple comparisons. The results of the anchor- and distribution-based methods were plotted together for comparison and triangulation, which is an iterative process examining results of the described anchor- and distribution-based methods to determine a single estimate of a responder definition threshold [31–33].

The available sample for the analyses (ROMANA1, $N = 474$; ROMANA2, $N = 488$) provide more than sufficient power to conduct the proposed analyses, the factor analyses being the most power intensive [34]. Written informed consent was obtained from each patient in the qualitative study and each of the clinical trials. The qualitative study was approved by Chesapeake IRB (Pro00012740). The study protocols for ROMANA1 and ROMANA2 were approved by the institutional review board or independent ethics committee at each participating center.

Results

Qualitative study

Saturation of concepts was achieved with the inclusion of 11 participants. These participants were 54.5% male, White (100%), had a mean age of 72.1 (SD, 10.2) years, and were mostly retired (63.6%) (Table 1). Most participants had NSCLC stage IV (63.6%) followed by stage IIIB (27.3%), and stage IIIA (9.1%). The mean time since diagnosis was 15.6 (SD, 18.2) months.

By virtue of the study inclusion criteria, all study participants were currently experiencing issues with their appetite, and most described their prior appetite as "good" or "normal" and reported previously eating typically three meals a day. The initial anorexia-related symptom experienced by patients included *"lack of hunger/appetite"* ($n = 6$; 55%), *"no interest in eating"* ($n = 2$; 18%), *"trouble swallowing"* ($n = 1$; 9%), *"nausea"* ($n = 1$; 9%), and *"getting full quickly"* ($n = 1$; 9%).

Anorexia-related symptoms were highly relevant to the participants and had important impacts on their lives including energy levels, and physical, social, and psychological functioning. Some relevant participant quotes are included in Table 2. A primary concern among study participants was their weight, specifically their "weight loss." All but one of the study participants ($n = 10$; 91%) described the relevance of their weight loss to their life or how it related to their appetite, with impacts on strength, their overall health, and nutrition.

The majority of study participants (i.e., six or more) endorsed five of the seven items from the A/CS symptoms domain ("good appetite," "interest in food drops," "food tastes unpleasant," "get full quickly," and "difficulty eating rich/heavy foods") (Fig. 1). No study participants reported experiencing anorexia-related "pain in stomach," and only two reported "vomiting". The rank order frequency of endorsement for the seven respective symptom items was as follows: "good appetite" ($n = 11$; 100%), "interest in food drops" ($n = 8$; 73%), "get full quickly" ($n = 8$; 73%), "food tastes unpleasant" ($n = 7$; 64%), "difficulty eating rich/heavy foods" ($n = 6$; 55%), "vomiting" ($n = 2$; 18%), and "pain in stomach" ($n = 0$; 0%). Nearly all ($n = 9$) participants stated that there were no relevant concepts missing from the A/CS symptom items. One participant suggested nausea be added, another suggested smell and swallowing be included.

With the exception of the "general health improving" item, the concern items ("amount I eat is sufficient to meet my needs," "worried about weight," "concerned about thinness," and "pressured to eat") were also found to be relevant to the study participants. The rank order frequency of endorsement of the five concern items was as follows: "worried about weight" ($n = 10$; 91%), "amount I eat sufficient" ($n = 7$; 64%), "concerned about thinness" ($n = 5$; 45%), "pressured to eat" ($n = 4$; 36%), "general health improving" ($n = 0$; 0%). There were no suggestions from study participants for additional A/CS items addressing concerns.

The cognitive interview portion revealed that study participants found all but one of the A/CS items were easily understood, had appropriate response options, were relevant, and were comprehensive of their experiences. The

Table 1 Key sociodemographic and clinical characteristics of the clinical trial samples

Key characteristic	Qualitative study ($N=11$)	Psychometric validation studies	
		ROMANA1 ($N=474$)	ROMANA2 ($N=488$)
Age, mean (SD), years	72.1 (10.2)	61.87 (9.28)	63.21 (8.50)
Male, *n* (%)	6 (54.5%)	360 (75.95%)	358 (73.36%)
Race, *n* (%)[a,b]			
White	11 (100%)	469 (98.95%)	483 (98.98%)
Black or African American	0 (0.00%)	1 (0.21%)	3 (0.61%)
Asian/other	0 (0.00%)	1 (0.21%)	2 (0.40%)
Geographic region, *n* (%)			
North America	11 (100%)	49 (10.34%)	14 (2.87%)
Western Europe	0 (0.00%)	178 (37.55%)	216 (44.26%)
Eastern Europe and Russia	0 (0.00%)	247 (52.11%)	239 (48.98%)
Australia	0 (0.00%)	0 (0.00%)	19 (3.89%)
Body mass index, mean (SD), kg/m^2	21.25 (3.84)	23.21 (3.60)	22.41 (3.69)
ECOG performance status, *n* (%)[c]			
0	10 (90.9%)	55 (11.60%)	36 (7.38%)
1	1 (9.1%)	329 (69.41%)	326 (66.80%)
2	0 (0.00%)	89 (18.78%)	126 (25.82%)
Current cancer treatment status, *n* (%)[d]			
Chemotherapy/radiation therapy/targeted therapy	7 (63.63%)	426 (89.87%)	385 (78.89%)
Not receiving treatment	4 (36.36%)	48 (10.13%)	103 (21.11%)
FAACT A/CS domain, mean (SD), range (min, max)	28.5 (8.0), (14.00–41.00)	29.83 (8.52) (0.00–46.00)	28.08 (8.71) (2.00–48.00)

ECOG Eastern Cooperative Oncology Group; *NSCLC* non-small cell lung cancer; *SD* standard deviation

[a]Categories are not mutually exclusive

[b]Missing: $n=3$ (0.63%)

[c]Missing: $n=1$ (0.21%)

[d]For ROMANA1 and ROMANA2 studies, patients were categorized by (1) initiating therapy within ±14 days of randomization or receiving maintenance chemotherapy at randomization and (2) No plan to initiate therapy within 12 weeks from randomization

majority ($n=7$) of participants interpreted the "general health improving" concern item to be too broad, and not specific to appetite.

Psychometric evaluation

Data analysis was conducted separately for the ROMANA1 and ROMANA2 clinical trial populations. For the purposes of this psychometric evaluation, the study population included all randomized patients who had a baseline visit FAACT A/CS domain score (ROMANA1, $N=474$; ROMANA2, $N=488$). The sociodemographic and clinical characteristics of the study population are shown in Table 1.

A/CS factor analyses

The factor structure of the 12-item A/CS was examined in several ways: (1) as a full 12-item single factor model, (2) as an 11-item single factor model (with the general health item removed), (3) as a 2-factor 12-item model (7 symptom items forming the first factor, 4 concern items and the general health item forming the second factor), and (4) as a 2-factor 11-item conceptual model (7 symptom items forming the first factor, 4 concern items forming the second factor). The above models showed poor fit to the data with comparative fit index ranging from 0.783 to 0.791 in ROMANA1 and 0.754–0.787 in ROMANA2, and root mean square error of approximation (RMSEA) values above 0.2 for all models. Based on these results, bifactor models were also explored that allowed for variance to be explained by both a common factor across all items, and specific factors for the symptoms and concerns items, respectively. Bifactor models evaluate essential unidimensionality and are interpreted as supported if factor loadings for all the items on the general factor are greater than 0.3, and higher on the general factor than they are on the subdomains [35]. These bifactor models also showed less than adequate fit, with items 9 (vomiting) and 11 (pain in stomach), which were identified as less relevant

Table 2 Participant responses to anorexia-related items

Anorexia-related items	Participant quotes
Anorexia-related concerns	
"Amount I eat sufficient"	003–001: "I probably didn't have this much energy or strength, but I knew the reason for it, that I wasn't eating and taking in enough liquid at the time, but I still couldn't seem to make myself do it"
	003–006: "Well, I lost 50 lbs. I'm weak as a baby. I used to really enjoy eating. Now I can barely choke down enough to survive"
"Worried about weight"	001–002: "Well, I lost a lot of muscle. I lost a lot of weight, and muscle mass which I'm trying to get back now. I'm on, I'm going through therapy, two or three times a week right now trying to build my muscle back–and you know, keep—keep my appetite to a certain level where I can do all the exercises"
	004–008: "Um, it was scary just for the fact that I wasn't sure how much I would lose, you know, how long it would go on before, you know, it had some severe affects"
"Concerned about thinness"	006–042: "…when I get on the scale I just—I mean, And I'm size four and, um, I just look thin. And I think when you have a few pounds on you, you just feel better, you can–I think you have a little more energy"
"Pressured to eat"	003–006: "Basically, when I sit down to eat, uh, it's a major deal. My wife hounds me incessantly about eating. And I feel so bad because I—I just can't eat"
Importance of weight loss	
	003–006: It's a real, real serious issue. That's my main concern probably as much as my cancer. **What about your weight loss concerns you in particular?** I don't know if it's killing me. It—you know–that's just—that's all I can say. I cannot continue to lose weight or eventually, you know, I'll weigh 150. Last time I weighed 196 lbs. When all this started I weighed 250 something—but I felt good, you know. At 59 I was healthy, wealthy and wise; whatever. Today, I have, you know, I have no strength. I have no anything… I'm concerned about it health wise because I can't continue to just lose weight, lose weight, lose weight. I get weaker, and weaker, and weaker
	006–001: "Well, I don't want to lose weight. I'm 5, 5 ½ and I weigh 105 pounds, so I don't want to lose weight and I'm educated, so I know the value of nutrition, so it -- it bothers me when I know that I haven't consumed enough nutrients or calories during the day"
Anorexia-related symptoms	
"Good appetite"	003–006: "I have absolutely no appetite whatsoever and the food that I do eat, I won't—have no want for it. I have no appetite. The food I do eat tastes terrible"
"Interest in food drops"	003−001: "When I did try to eat or want to eat, you know, I would take a portion, and I couldn't finish it, that was quite frequent"
"Food tastes unpleasant"	004–008: "For an example, something that we were eating for breakfast, scrambled eggs, every day, suddenly I just didn't like the taste of them, I didn't like the smell of them, you know, I didn't know whether to associate it with the, you know, butter used in the pan or whether, you know, the eggs themselves were, you know, unpleasant to me anymore, but that's something that I experienced—I just could no longer do, you know, eggs for breakfast, so we kept trying different things"
"Get full quickly"	004–008: "I do not eat as much as I did previously. Just as an example, normally the only red meat that I eat is either, you know, ground chuck as burgers or cooked in a food or filet mignon, which my husband typically butterflies for me. I would typically eat the whole filet, both sides and now I'm only—first I would only eat half the one side, now I can eat half of—I mean I can eat one side, but I still don't—I can't make myself—I still don't eat, you know—and I think it's just probably because I've gone so long without eating that much that I just fill up faster"
"Difficulty eating rich/heavy foods"	004–008: "I guess an example for me would be, like I said, you know, we kept trying several different things to come up with some good that I could, you know, and would eat, and we ordered just a plain cheese and pepperoni pizza one night, you know, um, and we were tired from visits and treatment and stuff, so let's just order a pizza and have it delivered. So, we did—I took one bite and almost threw up, and I associated that with the cheese"
General Health Item	
"My general health is improving"	006−001: "I don't think it's pertinent because I don't think anybody knows what that means…I don't think I'd use that -- that phrase because nobody knows what their general health is like. They know if they feel better, but, you know, they don't know whether it, you know, if someone told me that, um, I don't know, some blood count was up over the level, I'd think oh my God, my general health is not improving. But unless you have someone telling you that every day if you live with a doctor, which I don't, you -- you -- you don't know that"
	006–042: "General health is improving. It seems like it's a separate, subject–than, appetite"

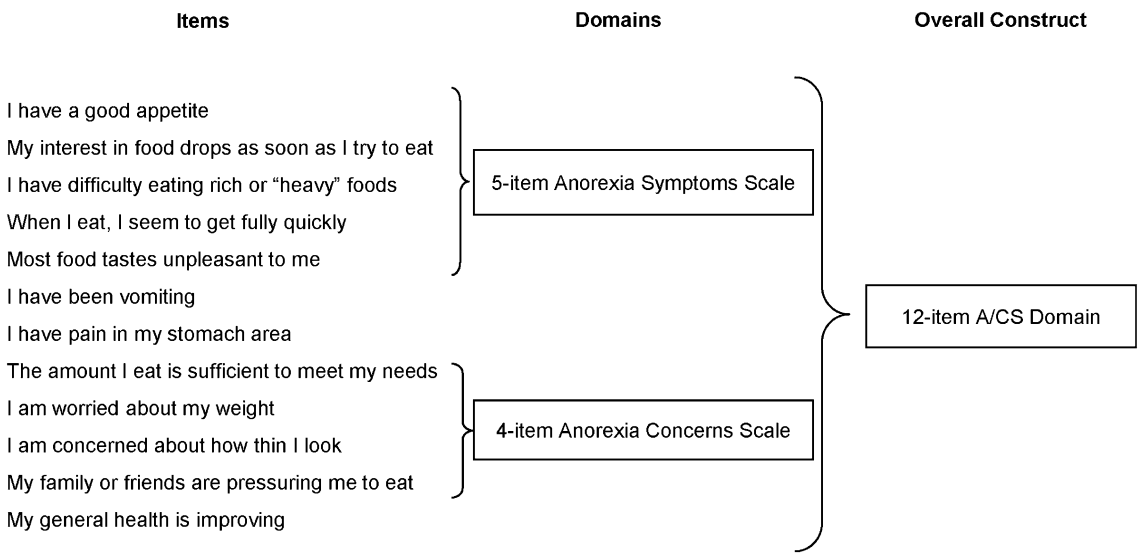

Fig. 1 FAACT A/CS conceptual framework

in the qualitative work, displaying higher loadings on the symptoms factor than on the common factor in all model iterations.

Based on the CFA results for the full 12-item A/CS domain, and the results of the qualitative study, the factor structure of the symptoms and concerns subscales were further evaluated as independent single factor models. Both 7-item symptoms and 5-item symptoms scales (vomiting and stomach pain removed), and the 4-item concerns scale were evaluated (Table 3). These anorexia symptoms and concerns subscales derived from the A/CS domain showed improved fit as separate single factor models in ROMANA1 (7-item symptoms: CFI, 0.970 and RMSEA, 0.101; 5-items symptoms: CFI, 0.993 and RMSEA, 0.077; 4-item concerns: CFI, 0.995 and RMSEA, 0.082) and ROMANA2 (7-item symptoms: CFI, 0.972 and RMSEA, 0.095; 5-items symptoms:

Table 3 Confirmatory factor analysis

FAACT A/CS item	CFA factor loadings					
	7-item anorexia symptoms scale		5-item anorexia symptoms scale		4-item anorexia concerns scale	
	ROMANA1	ROMANA2	ROMANA1	ROMANA2	ROMANA1	ROMANA2
F1. I have a good appetite	0.556	0.533	0.583	0.559	–	–
F6. My interest in food drops as soon as I try to eat	0.915	0.883	0.939	0.891	–	–
F7. I have difficulty eating rich or "heavy" foods	0.705	0.684	0.698	0.673	–	–
F10. When I eat, I seem to get full quickly	0.729	0.641	0.711	0.639	–	–
F4. Most food tastes unpleasant to me	0.737	0.778	0.723	0.776	–	–
F9. I have been vomiting	0.618	0.606	–	–	–	–
F11. I have pain in my stomach area	0.439	0.495	–	–	–	–
F2. The amount I eat is sufficient to meet my needs	–	–	–	–	0.295	0.166
F3. I am worried about my weight	–	–	–	–	0.829	0.812
F5. I am concerned about how thin I look	–	–	–	–	0.908	1.014
F8. My family or friends are pressuring me to eat	–	–	–	–	0.546	0.493
F12. My general health is improving	–	–	–	–	–	–
Factor model statistics						
Chi-Square (df)	14	14	5	5	2	2
CFI	0.970	0.972	0.993	0.977	0.995	0.994
RMSEA	0.101	0.095	0.077	0.128	0.082	0.122
90% CI for RMSEA	0.080, 0.123	0.075, 0.117	0.042, 0.115	0.095, 0.163	0.030, 0.143	0.072, 0.180

CFI, 0.977 and RMSEA, 0.128; 4-item concerns: CFI, 0.994 and RMSEA, 0.122).

Given that (1) no qualitative study participants reported experiencing anorexia-related "pain in stomach," and only two reported "vomiting," and that most found the "general health improving" concern item to be too broad, and not specific to appetite, and (2) adequate factor analysis results, the psychometric analyses were conducted on the original 12-item A/CS, and also the newly identified 5-item anorexia symptoms scale and 4-item anorexia concerns scale (Fig. 1).

Reliability

Tests of the internal consistency reliability using the ROMANA1 data yielded Cronbach's alphas of 0.85 for the 12item A/CS domain, 0.82 for the 5-item anorexia symptoms scale, and 0.69 for the 4-item anorexia concerns scale. Item total correlations ranged from 0.15 ("my general health is improving") to 0.76 ("my interest in food drops as soon as I try to eat") for the 12-item A/CS domain, from 0.46 ("I have a good appetite") to 0.77 ("my interest in food drops as soon as I try to eat") for the 5-item anorexia symptoms scale, and from 0.24 ("the amount I eat is sufficient to meet my needs") to 0.63 ("I am concerned about how thin I look"). For the ROMANA2 study, Cronbach's alphas were 0.83 for the 12-item A/CS domain, 0.79 for the 5-item anorexia symptoms scale, and 0.67 for the 4-item anorexia concerns scale. Item total correlations were similar in the ROMANA2 study, ranging from 0.16 to 0.72, 0.44–0.72, and 0.16–0.66, for the same items in the 12item A/CS domain, 5-item anorexia symptoms scale, and 4-item anorexia concerns scale, respectively.

In the ROMANA1 study, the test–retest reliability ICCs were 0.71 for the 12-item A/CS domain, 0.71 for the 5-item anorexia symptoms scale, and 0.65 for the 4-item anorexia concerns scale. In the ROMANA2 study, the ICCs were 0.80 for the 12-item A/CS domain, 0.78 for the 5-item anorexia symptoms scale, and 0.77 for the 4-item anorexia concerns scale.

Construct and known-groups validity

Correlations between the A/CS domain and associated subscales and other PRO measures at baseline are shown in Table 4. Correlations between the 12-item A/CS domain, the 5-item anorexia symptoms scale, and the 4-item anorexia concerns scale, and the FACIT Fatigue and HAS appetite and total scores were positive and generally in the moderate range, as expected (r range: ROMANA1, 0.31–0.57; ROMANA2, 0.26–0.64). Correlations of the A/CS scales with clinical measures such as lean body mass, fat mass, body weight and BMI were all in the expected direction and significant, but tended to be low to moderate: 12-item A/CS (r range: ROMANA1, 0.22–0.33; ROMANA2, 0.27–0.37), 5-item anorexia symptoms scale (r range: ROMANA 1, 0.14–0.20; ROMANA2, 0.14–0.23), 4-item anorexia concerns scale (r range: ROMANA1, 0.24–0.45; ROMANA2, 0.31–0.47).

Known-groups validity was calculated using the HAS total score. All patientreported scores in these scales were significantly different among patients with a HAS total score < 2, 2–4, and > 4 in both ROMANA1 and ROMANA2 (Fig. 2). Significant results were also observed for known-groups validity when using body weight, BMI, and ECOG performance status as criterion variables (see supplemental material).

Table 4 Correlations between the FAACT A/CS scales and other PRO measures at baseline

	FACIT-fatigue domain score	HAS: hunger item	HAS: appetite item	HAS: total score	5-Item anorexia symptoms scale	4-Item anorexia concerns scale
ROMANA1						
FAACT A/CS 12-item domain score	0.57***	0.21***	0.50***	0.43***	0.91***	0.87***
5-item anorexia symptoms scale	0.52***	0.24***	0.49***	0.45***	1.00	0.64***
4-item anorexia concerns scale	0.46***	0.13*	0.38***	0.31***	0.64***	1.00
ROMANA2						
FAACT A/CS 12-item domain score	0.64***	0.10*	0.55***	0.40***	0.91***	0.85***
5-item anorexia symptoms scale	0.60***	0.16**	0.53***	0.42***	1.00	0.62***
4-item anorexia concerns scale	0.49***	0.00	0.41***	0.26***	0.62***	1.00

A/CS anorexia/cachexia scale; *FAACT* functional assessment of anorexia/cachexia therapy; *PRO* patient-reported outcome

*$p < 0.05$; ** $p < 0.001$; *** $p < 0.0001$

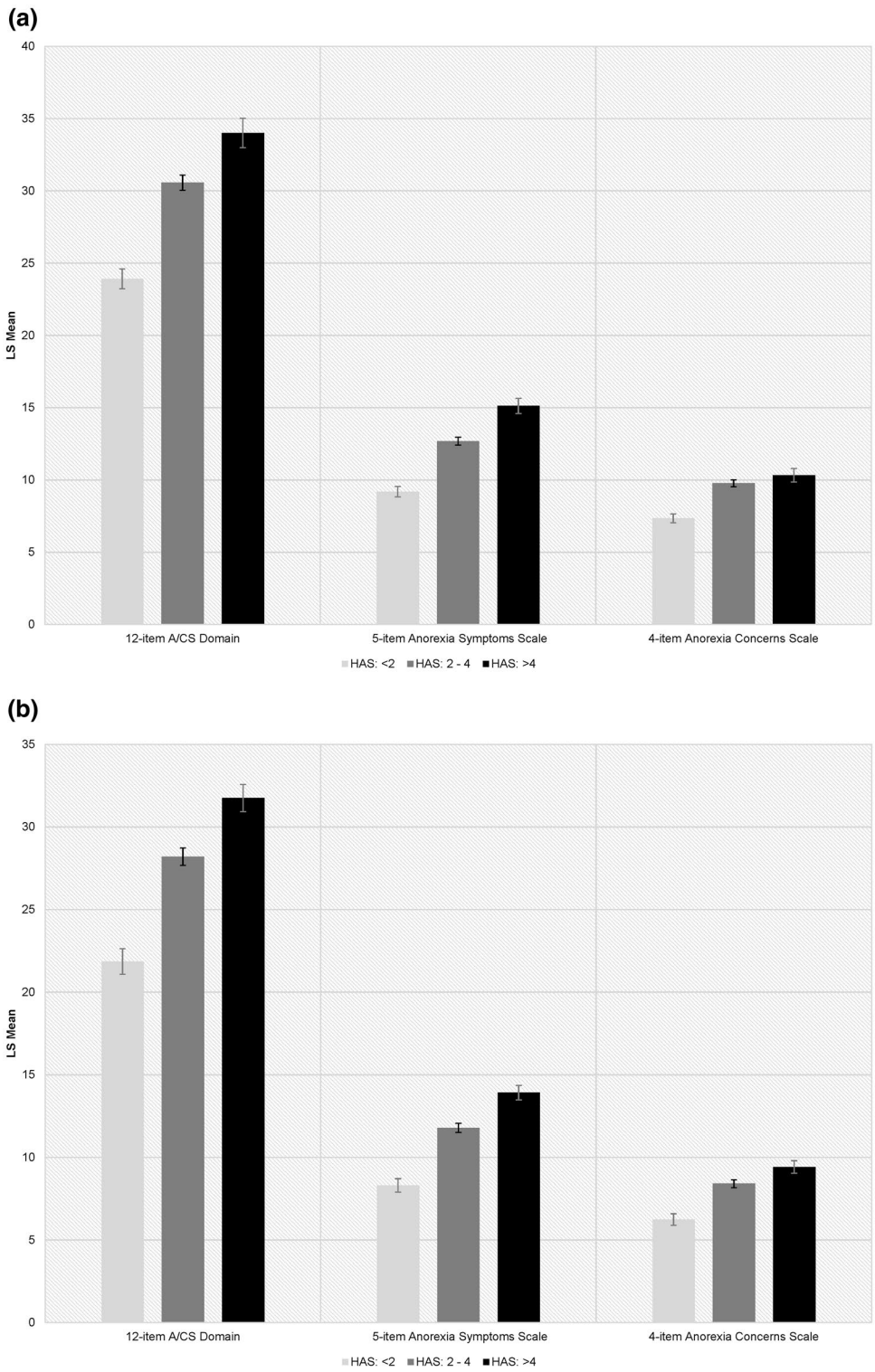

Fig. 2 Known-groups validity using Hunger Assessment Scale total score groups: ROMANA1 study population (**a**) and ROMANA2 study population (**b**)

Responsiveness

The HAS total score criterion measure supported the responsiveness of the 5item anorexia symptoms scale, the 4-item anorexia concerns scale, and the 12item A/CS domain from baseline to week 12 (all $p < 0.0001$) (Fig. 3). Pairwise comparisons were statistically significant between change groups in both the ROMANA1 and ROMANA2 clinical trials. Similar results were observed for responsiveness when using the 4-item anorexia concerns scale as the criterion measure for the 12-item A/CS domain and the 5-item anorexia symptoms scale. Similar results were also observed for

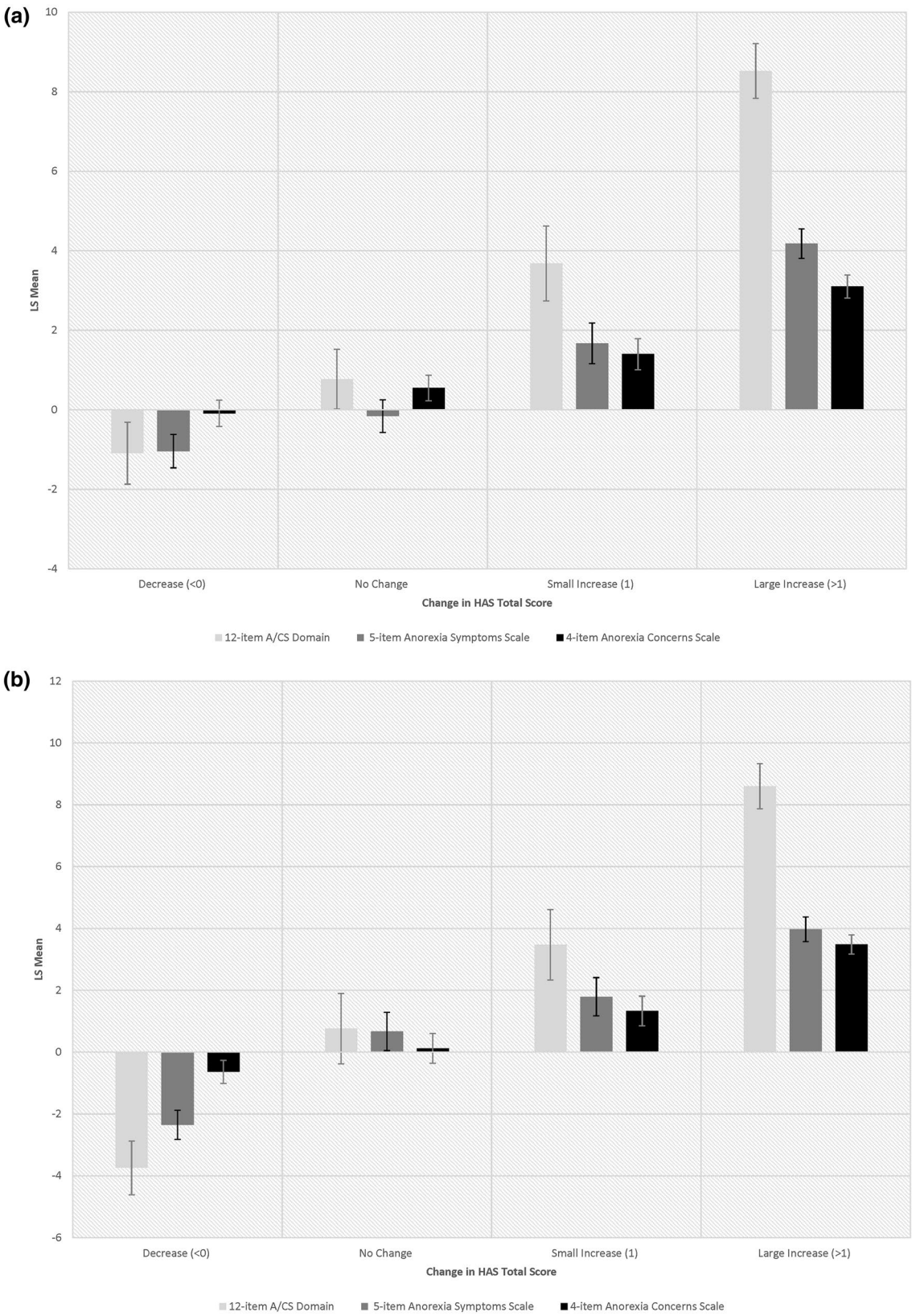

Fig. 3 Responsiveness: changes in FAACT A/CS and Hunger Assessment Scale total score from baseline to week 12: ROMANA1 study population (**a**) and ROMANA2 study population (**b**)

all three scales when using change in weight from baseline to week 12 as a measure of responsiveness (see supplemental material).

Responder definition

Both anchor- and distributionbased analyses were conducted to explore potential responder definitions associated with a meaningful improvement in the three scales. The mean change in the scales between baseline and week 12 were calculated for patients with improvements (increase ≥ 1) on the HAS hungry and appetite items (Fig. 4). The anchor-based estimates across ROMANA1 and ROMANA2 ranged from 2.06 to 2.54 for the 5-item anorexia symptoms scale, from 1.66 to 2.27 for the 4-item anorexia concerns scale, and from 4.26 to 5.82 for the 12-item A/CS domain. Figure 4 also presents the distribution-based estimates. In the ROMANA1 study, these ranged between 0.86 and 3.31 for the 5item anorexia symptoms scale, 0.71 and 2.54 for the 4-item anorexia concerns scale, and 1.62 and 6.11 for the 12-item A/CS domain. In the ROMANA2 study, distribution-based estimates ranged between 0.92 and 3.86 for the 5-item anorexia symptoms scale, 0.74 and 2.92 for the 4-item anorexia concerns scale, and 1.70 and 6.95 for the 12-item A/CS domain.

Based on a triangulation of the anchor- and distribution-based methods, these results suggest a responder definition of two points for both the symptoms and concerns subscales, and a responder definition of four points for the full 12-item A/CS domain.

Discussion

Qualitative content validity of the FAACT A/CS domain was assessed in advanced NSCLC patients, together with the newly identified symptoms and concerns subscales derived from the A/CS domain. The results of the qualitative study suggest that anorexia-related symptoms and concerns were common and highly relevant among this sample of patients with NSCLC and unintended weight loss. The symptoms and concerns related to anorexia and the associated weight loss are significant problems for these patients and have tangible effects on their energy levels, and physical, social, and emotional functioning. However, in the qualitative study sample, vomiting and stomach pain were not reported to be relevant symptoms, and in the factor analyses, these items had lower factor loadings and contributed to poor fit of the models, and therefore the psychometric properties of the 5-item symptoms scales and 4-item concerns scale were evaluated. These results differ from prior work with the A/CS domain, which did identify the items of vomiting and stomach pain as important anorexia-related symptoms

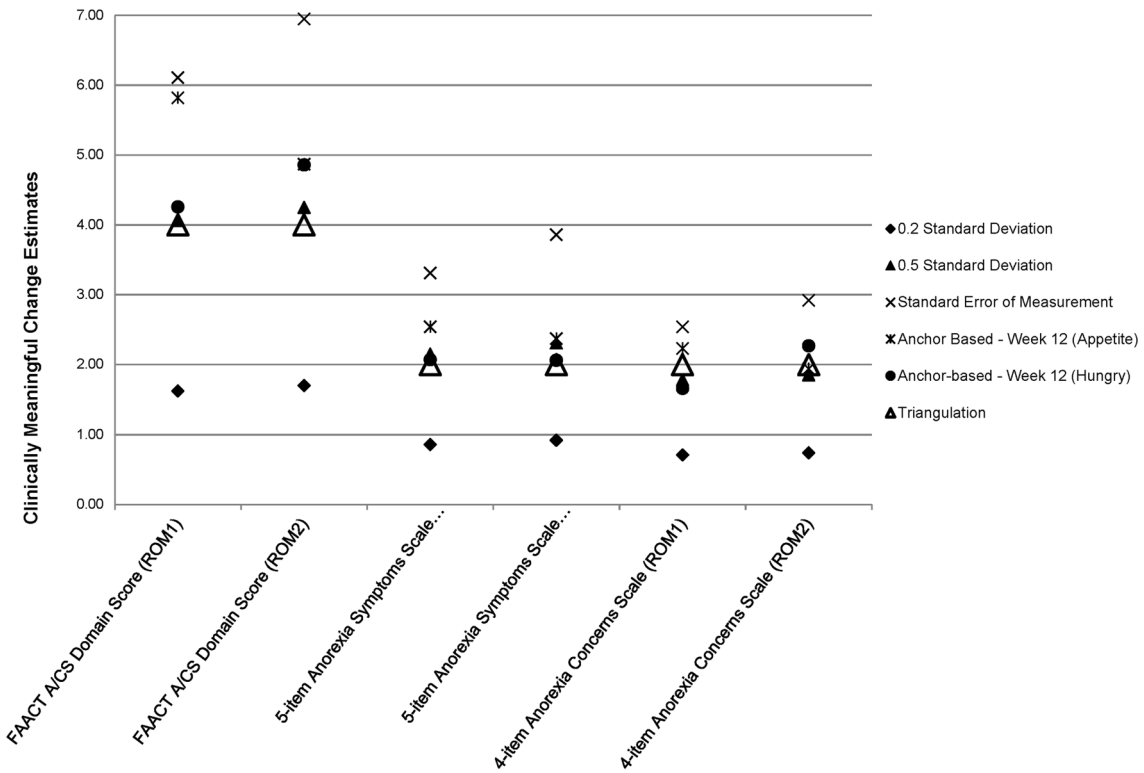

Fig. 4 Triangulation of responder definitions: plot of anchor-based and distribution-based estimates

[19, 20]. It is possible that the differences in patient populations between those studies and the current study contributed to this discrepancy, as previous studies included not only patients with NSCLC, but also other tumor types and patients with HIV. Also, vomiting and stomach pain may reflect later stage than was experienced by this sample of respondents.

The psychometric validity analyses further supported the appropriateness of the A/CS domain, and associated symptoms and concerns subscales, in NSCLC patients using data from the ROMANA1 and ROMANA2 phase III clinical trials. Factor analysis of the FAACT A/CS 12-item scale provided support for separate unidimensional factors for both the 7-item and the 5-item symptoms scales, and the 4-item concerns scale. The psychometric properties of the 5-item symptoms scale were evaluated because this symptoms scale was supported by the qualitative portion of the study in patients with anorexia/cachexia associated with NSCLC. Of note, feedback from participants in the qualitative portion of the study indicated that the general health improving item was not specific to appetite/eating. Factor analyses also suggested poor fit for this item, with low factor loadings in all models tested. Nevertheless, the 12-item A/CS total score, despite its poor model fit, performed comparably to the briefer, better-fitting subscales. The 5-item anorexia symptoms scale, the 4-item anorexia concerns scale, and the full 12-item A/CS domain all demonstrated good psychometric properties, including acceptable internal consistency and test–retest reliability, good construct and known-groups validity, and all scales were responsive to change. Of note, correlations of the A/CS scales with clinical measures were low, however lower correlations were expected for a few reasons. First, the data are gathered using different methods (self-report versus clinical measurement), which can attenuate correlations. Second, PRO measures are, by design, intended to capture information that clinical measures may not. Third, symptom severity is likely going to worsen the clinical outcomes, and therefore timing of the measurement is a factor, and change rather than static clinical outcome status may be more relevant. While any of these three subscale/domain options is suitable for, and likely to be responsive in, future clinical trials, the briefer symptoms or concerns subscales may be more suitable for regulatory use, given their superior model fit and narrower content scope.

Consistent with previous research, a responder definition of 4 points is suggested for the full 12item A/CS domain [20]. A responder definition of two points is recommended for both the anorexia symptoms and concerns subscales.

Interpretation of the results of these analyses may be affected by certain limitations of the studies. First, in the qualitative study, recruitment from this population of very ill patients was challenging; therefore, recruitment may have been biased toward healthier patients. Second, as the psychometric evaluation was a post-hoc analysis of two Phase 3 trials, the data were limited to the variables included in the clinical trials. For example, the HAS was considered to be the best possible criterion variable for test–retest reliability (i.e., defining a stable population), and the HAS appetite item was the best available anchor for responder definition analyses. Future studies should consider anchors that measure the anorexia concept more precisely than those available for this investigation. Despite these limitations, the psychometric evaluation included almost 1000 patients. The large amount of data from these randomized clinical trials yielded results that were extremely similar across the two studies, which highlighted the strength and consistency of the results.

Conclusion

For the 12-item FAACT A/CS domain, this psychometric validation demonstrated good internal consistency, test–retest reliability, construct and known-groups validity, and responsiveness to change. The newly identified 5-item anorexia symptoms and 4-item anorexia concerns subscales, derived from the FAACT A/CS domain, were also found to have good content validity and favorable psychometric properties. These scales may be useful for characterizing the effect of treatment on anorexia symptoms and/or anorexia-related concerns in the NSCLC population.

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