The Breast 77 (2024) 103781

Contents lists available at ScienceDirect

The Breast

journal homepage: www.journals.elsevier.com/the-breast

Psychometric properties of patient-reported outcomes Common Terminology Criteria for adverse events (PRO-CTCAE®) in breast cancer patients: The prospective observational multicenter VIP study

Caterina Caminiti [a], Giuseppe Maglietta [a], Laura Arenare [b], Raimondo Di Liello [c], Gessica Migliaccio [d], Daniela Barberio [d], Michelino De Laurentiis [e], Francesca Di Rella [e], Francesco Nuzzo [e], Carmen Pacilio [e], Giovanni Iodice [e,1], Michele Orditura [f,2], Fortunato Ciardiello [f], Sara Di Bella [g], Luigi Cavanna [h,3], Camillo Porta [i,j], Filippo Giovanardi [k], Carla Ida Ripamonti [l,4], Domenico Bilancia [m], Giuseppe Aprile [n], Tommaso Ruelle [o,p], Francesca Diodati [a], Maria Carmela Piccirillo [b], Elisabetta Iannelli [q], Carmine Pinto [r], Francesco Perrone [b,*]

[a] Clinical and Epidemiological Research Unit, University Hospital, Parma, Italy
[b] Clinical Trial Unit, Istituto Nazionale Tumori, IRCCS Fondazione G.Pascale, Napoli, Italy
[c] Division of Medical Oncology, Ospedale del Mare, Napoli, Italy
[d] Departmental Structure of Clinical Psycho-oncology, Istituto Nazionale Tumori, IRCCS, Fondazione G. Pascale, Napoli, Italy
[e] Experimental and Clinical Senologic Oncology Unit, Istituto Nazionale Tumori, IRCCS Fondazione G.Pascale, Napoli, Italy
[f] Department of Precision Medicine, Università degli Studi della Campania Luigi Vanvitelli, Napoli, Italy
[g] Medical Oncology, ASST Rhodense, Rho (MI), Italy
[h] Medical Oncology, Ospedale Guglielmo da Saliceto, Piacenza, Italy
[i] Interdisciplinary Department of Medicine, Università degli Studi 'A. Moro', Bari, Italy
[j] Polyclinic Consortium University Hospital, Bari, Italy
[k] Medical Oncology, Ospedale Civile, Guastalla (RE), Italy
[l] Supportive Care Unit, istituto Nazionale Tumori, IRCCS, Milano, Italy
[m] Medical Oncology, Ospedale S.Carlo, Potenza, Italy
[n] Medical Oncology, Azienda ULSS 8 Nerica, Ospedale S.Bortolo, Vicenza, Italy
[o] Medical Oncology, IRCCS Ospedale Policlinico San Martino, Genova, Italy
[p] Department of Internal Medicine and Medical Specialties (DIMI), Università di Genova, Genova, Italy
[q] FAVO - Federazione Italiana delle Associazioni di Volontariato in Oncologia, Roma, Italy
[r] Medical Oncology, AUSL-IRCCS, Reggio Emilia, Italy

ARTICLE INFO

Keywords:
Patient-reported outcome measures (PROMs)
Electronic PROMs (ePROMs)
PRO-CTCAE
HADS
EORTC BR-23
Convergent validity
Responsiveness
Breast cancer

ABSTRACT

Patients' self-reporting is increasingly considered essential to measure quality-of-life and treatment-related side-effects. However, if multiple patient-reported instruments are used, redundancy may represent an overload for patients.

Patient-Reported Outcomes Common Terminology Criteria for Adverse Events (PRO-CTCAE) are a tool allowing direct patients' reporting of side-effects.

We tested psychometric properties of a selected list of PRO-CTCAE items, in a cohort of 303 breast cancer patients, using validated instruments for quality of life assessment as anchors.

The analysis of convergent validity with HADS (Hospital Anxiety and Depression Scale) and EORTC BR-23 subscales, and the analysis of responsiveness with the PGIC (Patients Global Impression of Change) score supported

* Corresponding author. Clinical Trial Unit Istituto Nazionale Tumori IRCCS Fondazione G.Pascale, Italy.
E-mail address: f.perrone@istitutotumori.na.it (F. Perrone).
[1] deceased.
[2] Present address: Division of Medical Oncology, Ospedale Civile, Caserta.
[3] Present address: Casa di Cura Piacenza, Internal Medicine and Oncology unit, Piacenza.
[4] Present address: Universita' degli Studi di Brescia, Brescia; Italy.

https://doi.org/10.1016/j.breast.2024.103781
Received 27 February 2024; Received in revised form 19 June 2024; Accepted 18 July 2024
Available online 20 July 2024

that a selected list of PRO-CTCAE symptoms might represent a standardized, agile tool for both research and practice settings to reduce patient burden without missing relevant information on patient perceptions.

Among patients using digital devices, those with a higher education levels required shorter time to fulfil questionnaires.

In conclusion, a selected list of PRO-CTCAE items can be considered as a standardized, agile tool for capturing crucial domains of side-effects and quality of life in patients with breast cancer.

The study is registered on clinicaltrials.gov (NCT04416672).

1. Introduction

Patient-reported outcome measures (PROs) are used in cancer clinical trials mainly to measure the impact of treatments on quality of life (QoL) [1]. Several libraries of PROs are available, either generic or focused on specific clinical settings, and many of them have been validated in different languages, like the European Organization for Research and Treatment of Cancer (https://qol.eortc.org/) or the FACIT (https://www.facit.org/) libraries.

However, in more recent years, reporting of side-effects of treatment has become another important field for the use of PROs. This has been prompted by the acknowledgment that physicians typically tend to underestimate and under-report the side-effects that have a significant and prevalent subjective component [2]. Therefore, to complement reporting of toxicity done by physicians, typically through the use of Common Terminology Criteria for Adverse Events (CTCAE) categories, the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE®) has been developed to allow patient's self-reporting of symptomatic adverse events (AEs) in cancer clinical trials. PRO-CTCAE is an item library comprised of 124 self-reported items reflecting 78 symptomatic AEs drawn from the CTCAE [3,4].

The interest in the use of PROs for the measure of treatment side-effects is also increasing following the suggestion that remote monitoring of symptoms may ultimately improve patients' prognosis [5]. Consequently, the European Society of Medical Oncology has issued guidelines recommending the wider application of PROs in clinical practice, not only within clinical trials [6].

An important advantage of the PRO-CTCAE is that items are intended to stand alone, therefore items and questions can be selected according to specific cancer types, disease stages, and treatments. This is important because not all AEs are relevant to every disease or treatment context, and the large number of items in the PRO-CTCAE library could make it impractical to administer all items to all patients [3]. Based on these considerations, researchers have focused on creating selected lists of PRO-CTCAE [7].

We recently produced the Italian language translation of PRO-CTCAE and tested its content validity and reliability in a sample of Italian speaking patients affected by various types of cancer [8]. We then initiated the Validation of Italian PRO-CTCAE (VIP) Study, a large multicenter prospective project aimed at evaluating the psychometric properties of existing PRO-CTCAE short lists for specific cancer types, using items from the certified Italian version. The project also concerns the creation of short lists for tumor sites for which one is not yet available, and their subsequent psychometric evaluation.

The aim of the present study was to test validity and responsiveness in an Italian cohort of breast cancer patients of a previously selected short list of PRO-CTCAE items.

2. Methods

VIP is an ongoing prospective observational study, promoted by the Federation of Italian Cooperative Oncology Groups (FICOG) and conducted in Italian cancer centres located nationwide. The study is registered on clinicaltrials.gov (NCT04416672). Overall VIP includes 24 cohorts, based on the type of cancer.

The primary objective of the VIP Study is to assess the construct validity (degree to which the instrument accurately measures the underlying phenomenon) and responsiveness (capacity of the instrument to show a change when there has been a change in the underlying phenomenon) of PRO-CTCAE items, Italian version, within each specific cancer type. Here we report the results obtained in the study on the breast cancer cohort.

2.1. Study design

In the breast cohort, construct validity was assessed in two ways. First, by testing convergent validity in terms of correlation of PRO-CTCAE items with two patient-reported tools used as anchors: EORTC breast-cancer specific module BR-23 and Hospital Anxiety and Depressions Scale (HADS). Second, by the known-group analysis testing the correlation of response to PRO-CTCAE items with patient ECOG Performance Status (PS). Responsiveness was tested by verifying the correlation of changes of responses to PRO-CTCAE items with global impression of change given by the patients through the Patients Global Impression of Change (PGIC) scale.

2.2. Study population

Eligible patients for the VIP study are older than 18 years, receiving anticancer treatment, with at least two clinical visits scheduled 2–6 weeks apart. Patients must be able to complete questionnaires on their own using either paper case-report forms (CRFs) or a tablet, be able to understand Italian and sign informed consent. Individuals who have received more than 5 lines of therapy or with psychiatric disorders or major cognitive dysfunctions that could hinder the provision of informed consent are excluded.

2.3. Instruments

In each cohort of the VIP study, four instruments are used: PRO-CTCAE, EORTC QOL tools and HADS at enrolment (visit 1), and PRO-CTCAE and PGIC at the second visit (visit 2), 2–6 weeks later.

PRO-CTCAE represents a patient-reported outcome measurement system of symptomatic toxicity suffered by cancer patients. The PRO-CTCAE library includes 124 items (122 for females and 119 for males) representing 78 symptoms for females and 75 for males (https://healthcaredelivery.cancer.gov/pro-ctcae/overview.html). Each symptomatic AE is evaluated using a combination of one to three attributes among frequency, amount, severity, interference and presence/absence. Cancer-specific PRO-CTCAE short lists have been produced by NCI on the basis of expert consultation, patient representative input, and literature review [4]. In the present breast cancer cohort of the VIP study, a previously published short list of PRO-CTCAE was used, including 48 symptoms described in 76 items [4].

Similarly, QOL cancer specific modules are used when available in the EORTC library. For the breast cohort, the BR-23 disease-specific questionnaire was used. The 23 questions of BR-23 assess 4 symptom scales/items (breast symptoms, arm symptoms, side effects of systemic therapy, hair loss) and 4 functional scales/items (body image, future perspectives, sexual functioning and sexual enjoyment) [9].

HADS is a 14-item questionnaire that measures anxiety and

depression (7 items for each). Each item has four possible responses ranging from 0 to 3 points; two scores are calculated, one for anxiety and one for depression. Each score may vary between 0 and 21; scores between 0 and 7, 8–10 and 11–21 are considered as normal, borderline-abnormal and abnormal, respectively [10].

The Patients' Global Impression of Change (PGIC) Scale is a short tool which asks patients to rate their changes in overall QOL, physical condition, and emotional state on a 7-point scale ranging from "very much better," "moderately better," "a little better," "about the same," "a little worse," "moderately worse," to "very much worse" [11].

2.4. Outcome measures

For convergent validity, two types of comparisons were performed: (a) PRO-CTCAE items concerning anxiety and depression were correlated with overall HADS scores (HADS-A scores for anxiety and HADS-D for depression); and (b) each PRO-CTCAE item was compared with the score of the BR-23 symptom subscale. Since high score for a symptom scale/item represents a high level of symptomatology/problems in both instruments, the EORTC scale was not reverse scored.

For known-group validity, each PRO-CTCAE item reported at visit 1 was compared between patients with good and deteriorated performance status (PS 0 vs 1 or greater) according to the distribution of PS reported at visit 1.

For responsiveness, patients were grouped into three change categories, defined by PGIC response (worse, unchanged, improved) at visit 2. In each category, the change of PRO-CTCAE items at visit 2 with respect to visit 1 was calculated.

2.5. Data collection

Investigators provided baseline and clinical information regarding enrolled patients through electronic case report forms (eCRF) in the web platform of the Clinical Trial Unit at National Cancer Institute of Naples. Patient-reported outcomes were gathered anonymously by means of paper CRFs or an eCRF provided to patients during visits on a tablet. To reduce completion times, conditional branching was applied in the PRO-CTCAE questionnaire, so that when an AE was marked as absent by the respondent, further questions related to that AE (eg. severity and interference with daily activities) were not displayed.

2.6. Sample size calculation

Sample size was determined based on the findings of Dueck et al., and defined separately for each of the two psychometric properties and for each cancer type [4]. Since enrolled patients are expected to contribute to all evaluations, sample size was determined by the highest value of the estimate adjusted for the number of tests performed (Bonferroni correction for multiple comparisons). Thus, with $1\text{-}\beta = 0.80$ and $\alpha = 0.017$, at least 107 patients are required for testing convergent validity, 167 patients are required for testing known-group validity, and 86 for responsiveness. Thus a total of at least 167 patients were included. Furthermore, to account for dropout, we considered the findings by Post et al., and with a dropout rate of 5 %, we estimated that at least 175 patients were necessary [12].

2.7. Statistical analysis

To assess convergent validity, Pearson correlation coefficient and their 95 % CI were computed between each PRO-CTCAE item and functional and symptom scale scores of the EORTC BR-23 questionnaire, and HADS score for anxiety (HADS-A) and depression (HADS-D). A positive correlation implies that both variables have a tendency to increase or decrease together. A negative correlation, however, implies that when one variable increases the other has a tendency to decrease, and vice versa. Correlation coefficients of 0.10 is interpreted as "small", 0.30 as "moderate", and 0.50 or more as "large" effect [13]. An item was considered valid if both correlation values ≥ 0.30 and test values with $p < 0.001$ were verified (to take into account potential collinearity and multiplicity).

For known-group analysis, comparison of PRO-CTCAE items with PS at baseline (PS 0 vs 1+) was tested using Cohen's d coefficient for non-dichotomic items and Cohen's h coefficient for dichotomic ones. Effect sizes (Cohen d or h) of <0.20, 0.20–0.49, 0.50–0.79 and ≥ 0.80 are interpreted as absent, small, medium and large correlation, respectively [13].

Similarly to a previous study (Dueck et al. [4]), responsiveness was investigated by comparing the change from the first to the second visit in 27 PRO-CTCAE items selected a priori for their high potential to be significantly related to global changes in quality of life, physical condition and emotional state. It was measured using a Standardized Response Means (SRMs) and 1-sided Jonckheere-Terpstra test across respondents who reported their PGIC to be worse ("a little worse," "moderately worse," or "very much worse"), unchanged ("about the same"), or improved ("a little better" "moderately better" or "very much better"). SRMs are computed as the mean change score divided by the standard deviation of the change scores for each PRO-CTCAE item.

Missing data were described and no imputation strategy was applied as they were numerically small.

An unplanned exploratory analysis was performed to verify whether age and education level were correlated with time required to complete questionnaires, among patients who used digital devices, applying the Wilcoxon rank sum test. Analyses were performed with R statistical software (vers.4.1.3).

3. Results

From April 29, 2019 to June 18, 2021, 307 breast cancer patients were enrolled by 19 centres (Fig. 1). Of these, 303 (98.7 %) completed the PRO-CTCAE and 294 (95.8 %) the EORTC QLQ-BR23 questionnaires during Visit 1 (102, 33.2 % using the electronic tablet version); 212 (69.1 %) completed the PRO-CTCAE and 206 (67.1 %) the PGIC questionnaires during Visit 2 (33 using the tablet).

Baseline characteristics of patients at both visit 1 and visit 2 are summarized in Table 1. At visit 1, median age was 55 (IQR = 48–63) years, 66.7 % had a high education (high-school or university degree), 81.8 % were classified as ECOG PS 0; 46.9 % was receiving adjuvant therapy, 64.0 % cytotoxic chemotherapy, 80.9 % intravenous drugs, and 2.6 % concomitant radiotherapy.

Distribution of responses given to baseline questionnaires are displayed in appendix (Appendix Tables 1 and 2 for PRO-CTCTAE and HADS, respectively; Appendix Tables 3 and 4 for BR-23).

All participants reported the presence of at least 1 symptom/AE at the first visit, with a median of 29 (IQR 19–39) symptoms/AEs noted. Considering the 63 symptoms for which respondents were required to indicate the frequency/severity/interference (with ordinal likert scale 0–4), 75.6 % (232/307) reported at least 1 symptom with "high" frequency/severity/interference (value 3 or 4). The distribution of item scores is shown in Appendix fig. 1.

3.1. Convergent validity

All nine PRO-CTCAE items referring to anxiety, depression and sadness were significantly correlated with HADS subscales in the expected direction with Pearson correlation coefficients larger than 0.50 (considered a large value), ranging from 0.53 to 0.70 (Fig. 2).

Correlation values of PRO-CTCAE items with QLQ-BR23 subscales are reported in Fig. 3. Only three items on 76 (nail loss and skin burns items with BR-23 body image subscale, and irregular menses with BR-23 systemic therapy side effects subscale) exhibited no correlation between the two scales (ranges from a negative one to a positive one). For the remaining items, correlation coefficients fell in the >0.10 and < 0.30

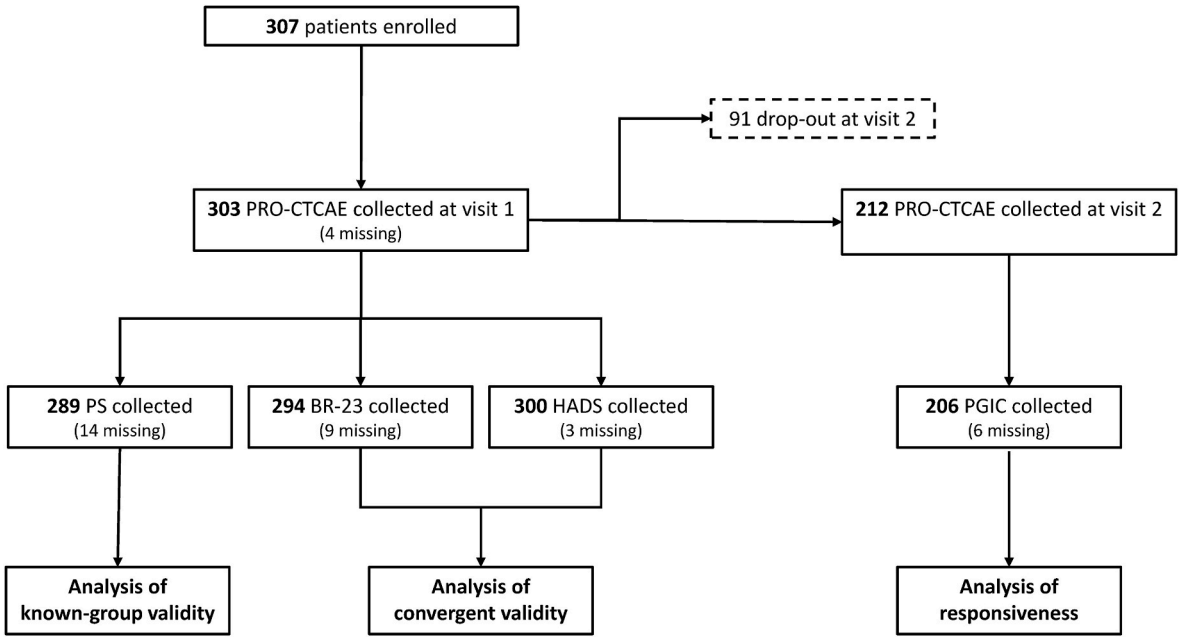

Fig. 1. Study flow.

Table 1
Baseline characteristics of patients.

Patients characteristics	Visit 1 (N = 303)		Visit 2 (N = 212)	
Age at enrollment, median (IQR)	55	(48–63)	55	(47–63)
Age group, n (%)				
<40	25	(8.3)	17	(8.0)
40-64	210	(69.3)	145	(68.4)
>64	68	(22.4)	50	(23.6)
Gender, n (%)				
Female	300	(99.0)	209	(98.6)
Male	3	(1.0)	3	(1.4)
Education level, n (%)				
None	12	(4.0)	9	(4.2)
Elementary school	14	(4.6)	7	(3.3)
Middle school	75	(24.8)	58	(27.4)
High school	155	(51.2)	109	(51.4)
Degree	47	(15.5)	29	(13.7)
ECOG performance status, n (%)				
0	248	(81.8)	186	(87.7)
1	39	(12.9)	26	(12.3)
2	1	(0.3)	0	(0.0)
3	1	(0.3)	0	(0.0)
missing	14	(4.6)	0	(0.0)
Ongoing treatment line, n (%)				
Neo-adjuvant	52	(17.2)	38	(17.9)
Adjuvant	142	(46.9)	96	(45.3)
First line for advanced disease	65	(21.5)	52	(24.5)
Second line for advanced disease	20	(6.6)	13	(6.1)
Third line for advanced disease	24	(7.9)	13	(6.1)
Type of ongoing treatment, n (%)				
Chemotherapy (±other)	194	(64.0)	133	(62.7)
Anti-HER2 (±endocrine)	65	(21.5)	43	(20.3)
CDK4/6 inhibitors (±endocrine)	17	(5.6)	16	(7.5)
ADC-antiHER2	14	(4.6)	10	(4.7)
Endocrine alone	8	(2.6)	7	(3.3)
Anti-angiogenetic (±other)	3	(1.0)	1	(0.5)
Immune checkpoint inhibitors	2	(0.7)	2	(0.9)
Route of administration, n (%)				
Intravenous	245	(80.9)	170	(80.2)
Oral	23	(7.6)	21	(9.9)
Subcutaneous	21	(6.9)	9	(4.2)
Combination	14	(4.6)	12	(5.7)
Concomitant radiotherapy, n (%)				
No	295	(97.4)	205	(96.7)
Yes	8	(2.6)	7	(3.3)

interval (small to medium correlation) for 18 items (23.7 %), between 0.30 and 0.50 (medium to large correlation) for 36 items (47.4 %) and were higher than 0.50 (large correlation) for 19 items (25.0 %). All these correlations were in the expected direction. Overall 89.5 % (68/76) of the items had a high statistical significance ($p < 0.001$), and 72.4 % (55/76) of the items shows both values of Pearson correlation ≥30 and statistically significant at $p < 0.001$.

3.2. Known-group analysis

Results of known-group analysis for non-dichotomic and dichotomic PRO-CTCAE items are summarized in Appendix (Fig. 2a and b and Table 5, respectively). Among the non-dichotomic ones, only some categories of PRO-CTCAE items (gastrointestinal, cutaneous, neurological and gynecologic) had higher mean scores in the ECOG PS 1+ vs 0 group; similarly, for dichotomic ones, only 7/13 symptoms (53.8 %) were more frequent in patients with worse PS. It should be highlighted that in this study the low prevalence of patients in the deteriorated PS group (41/289, 14.2 %) limits the interpretability of this finding.

3.3. Responsiveness analysis

The analysis of responsiveness (Fig. 4) showed similar variation of PRO-CTCAE items and PGIC score, with few exceptions; particularly, numbness/tingling of hands/feet tended to worsen even in patients reporting improved PGIC score, while constipation, nausea, vomiting and sadness tended to improve even among patients reporting worse PGIC score. The SRM values and the test probability are reported in Appendix table 6.

3.4. Exploratory objective

The unplanned analysis on the electronic survey completion times highlights that median time (IQR) measured among 102 patients who used the electronic tablet was 10′15′′ (IQR: 8′04′′ - 13′16″) for baseline PRO-CTCAE, 3′15′′ (IQR: 2′41′′ – 3′59″) for baseline BR-23, 2′47′′ (IQR: 2′13′′ – 3′36″) for baseline HADS, and 10′23′′ (IQR: 8′13′′ – 13′27″) for PRO-CTCAE after Visit 2. The statistical analysis showed that there was no difference in the time for completion of baseline PRO-CTCAE between patients younger and older than 64 (median time 10′15″ and

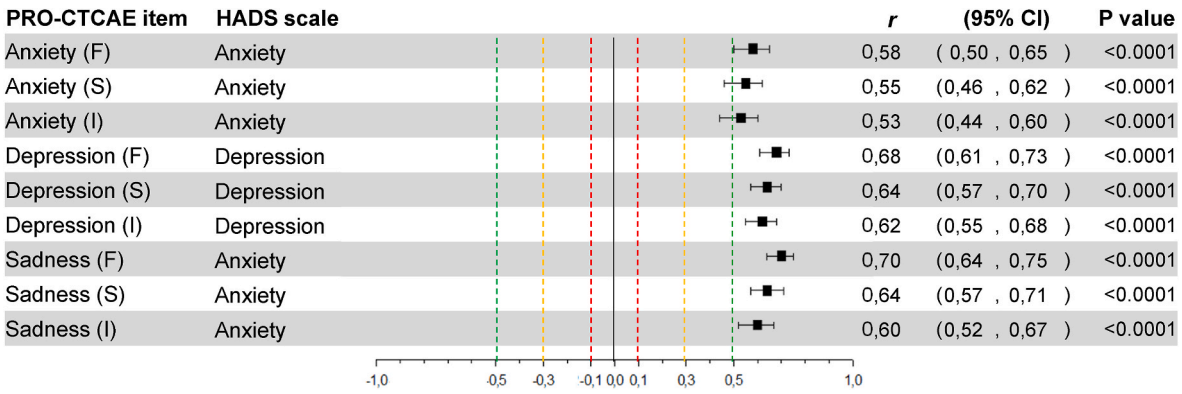

Fig. 2. – Correlation between selected PRO-CTCAE items and HADS subscales for anxiety and depression. Vertical lines identify regions representing small effects (red dashed lines 0.10–0.29), moderate effects (yellow dashed lines 0.30–0.49) and large effects (green dashed linies 0.50 or more).

10′13″, respectively, p = 0.35); on the contrary, patients with a higher education level (high-school or university degree) were able to complete the questionnaire in a shorter time as compared to those with elementary or primary school (median 9′53″ vs 11′15″, respectively p = 0.045).

4. Discussion

In this multicenter, prospective observational study in breast cancer patients undergoing treatment prevalently based on chemotherapy, we validated the Italian version of the cancer-specific short list of PRO-CTCAE® using widely used instruments (EORTC-BR23, HADS, ECOG PS, and PGIC scale) as anchors. Participating patients were consecutively enrolled in various cancer centres located all over the country, including both large academic and community hospitals, which makes results applicable to different contexts.

Comparing convergent validity results with those obtained by Dueck et al. in patients receiving treatment for different cancer types, we recorded a higher percentage of items (68/76, 89.5 % vs 87/124, 70.2 %) exhibiting correlations highly statistically significant ($p < 0.001$) with quality of life [4]. This supports the need for disease-specific instruments to measure PROs.

The VIP project contributes to the development of patient-reported instruments in line with current recommendations, such as those contained in the European Society of Medical Oncology (ESMO) Clinical Practice Guidelines on the use of PRO Measures (PROMs) in clinical practice [6].

Firstly, ESMO recommends that the selection of outcomes to be explored should be meaningful (either prevalent or impacting on QOL) and actionable (by modifying anticancer treatment or adding supportive care). In the present study the use of PRO-CTCAE allowed to identify a number of symptoms (dry mouth, taste disturbance, nausea, diarrhea, dry skin, skin irritation, nail problems, hair loss, pain, joint pain, fatigue, insomnia, anxiety, depression, sadness, hot flushes, sweating excess or reduction, and symptoms representing an impairment for sexual life - vaginal dryness, painful intercourses, decrease of libido) that are reported either as frequent or as severe by over 10 % of breast cancer patients. Most of these symptoms may be either prevented or alleviated, and their identification through a systematic use of PRO-CTCAE is crucial to prompt a possibly effective reaction of physicians that may ultimately induce prescription of appropriate palliative treatments, or advise on non-drug based strategies.

Secondly, ESMO recommends that PROMS should be valid, reliable and responsive to change. Our data support validity for many PRO-CTCAE symptoms, showing their correlation with validated anchors like the HADS or the scores calculated by using the EORTC BR-23 questionnaire. Responsiveness to patient-reported impression of changes (PGIC) was also good, with few symptoms going in the opposite direction: peripheral neuropathy (which is hard to prevent and treat in clinical practice and may worsen over the time also in patients who have clinical benefit from chemotherapy), gastrointestinal symptoms (constipation, nausea and vomiting that can be prevented or managed quite well also in patients who are not benefiting from treatment) and sadness, which might be improved by a placebo-like effect also in absence of a significant clinical benefit. Less good in the present study was the performance of PRO-CTCAE items in the known-group analysis, but this analysis may be limited by the use of performance status as known-group that is substantially limited to two categories (0 and 1 with very few cases over 1), which might not be sensitive enough to detect associations with reported symptoms, also considering that deteriorated performance status usually represents a contraindication to active anticancer treatment.

Two further ESMO recommendation, with low strength of evidence, suggest that a set of core items should be used in the entire patient population, and additional cancer-specific modules should be used, paying attention to limiting the number of items to avoid burden on patients and to favor patient participation. In the present breast cancer patient cohort, some of the symptoms that exhibited good properties in terms of validity (dry mouth, taste disturbance, decreased appetite, nausea, diarrhea, skin irritation, hair loss, pain, concentration, headache, insomnia, fatigue, anxiety, depression) are included in the list of 20 core symptoms of the PRO-CTCAE library [4]. Other symptoms (dry skin, nail problems, joint pain, dizziness, sadness, vaginal dryness, decreased libido, time to orgasm, unable to orgasm, painful intercourse, sweating abnormalities and hot-flushes) reflect more breast cancer specific conditions, including the type of drugs used in the treatment of this type of cancer. This might help to define a breast-cancer specific set of symptoms able to recapitulate the same information retrieved by using, for example, the EORTC BR-23 and the HADS instruments.

Finally, while the last ESMO recommendation emphasizes the opportunity of offering more than one mode of administration, to ensure that vulnerable populations are able to have access to the proposed instrument, the use of electronic PROs has been proposed as a tool to improve monitoring of symptoms and communication on quality of life for metastatic breast cancer patients [14]. Our unplanned analysis on time required to fulfill PRO-CTCAE questionnaires at baseline (including 48 symptoms described in 76 items) suggests that older age does not impair the ability of using the electronic device, while a higher education level is correlated with shorter time for questionnaire completion. However, a limitation of this study is that we did not collect data on time to completion of paper CRFs, and only one-third of patients used digital devices. For these reasons we plan to perform this analysis on a much larger data-set, combining cohorts of patients with different cancer types within the VIP study. Other limitations of this study should be considered. Firstly, we recorded a nearly 30 % drop-out rate at the second visit, probably due to the pandemic situation, although we cannot exclude that drop-out patients might have different clinical conditions.

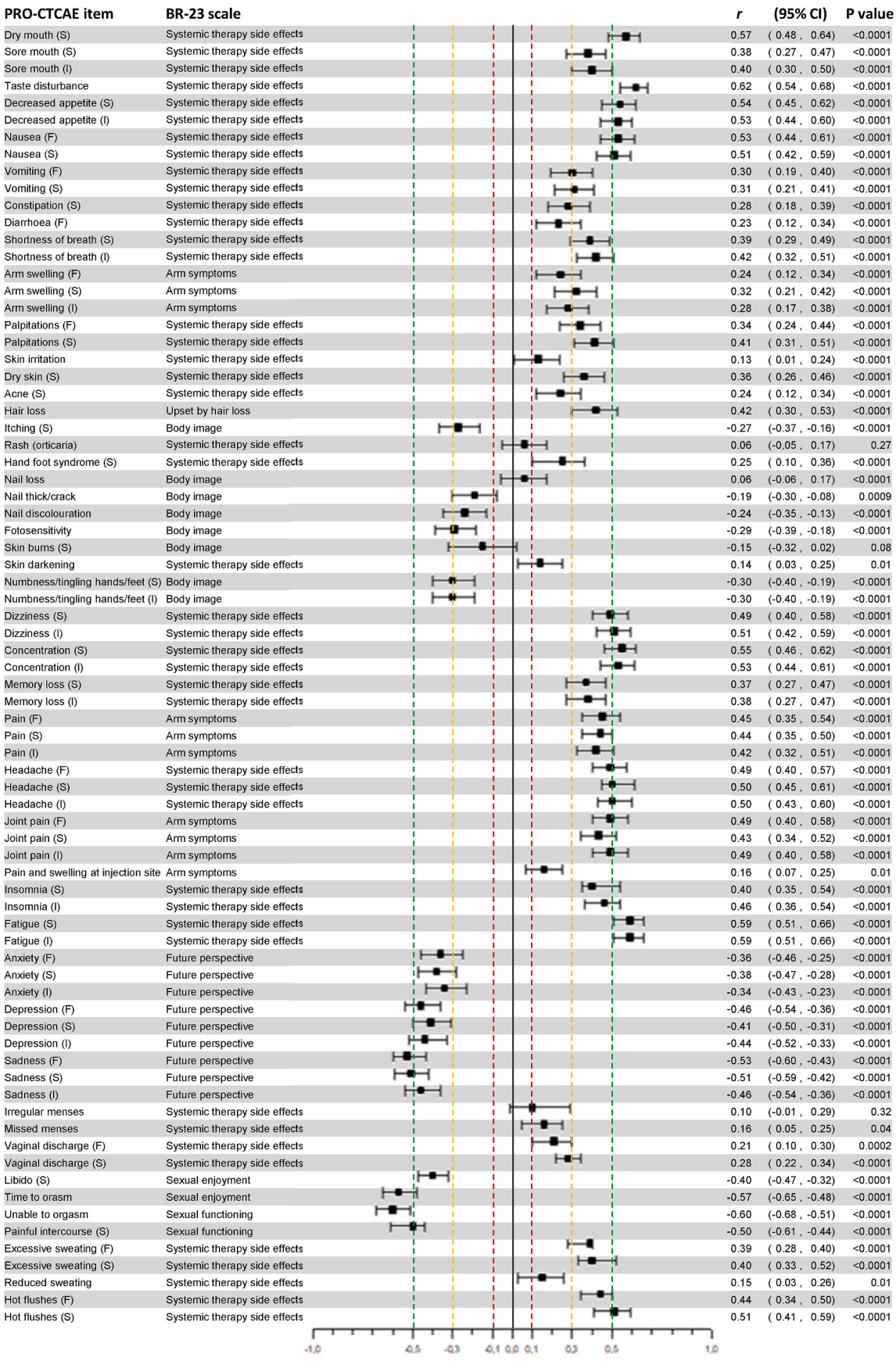

Fig. 3. Correlation between selected PRO-CTCAE items and BR-23 subscales. Vertical lines identify regions representing small effects (red dashed lines 0.10–0.29), moderate effects (yellow dashed lines 0.30–0.49) and large effects (green dashed linies 0.50 or more).

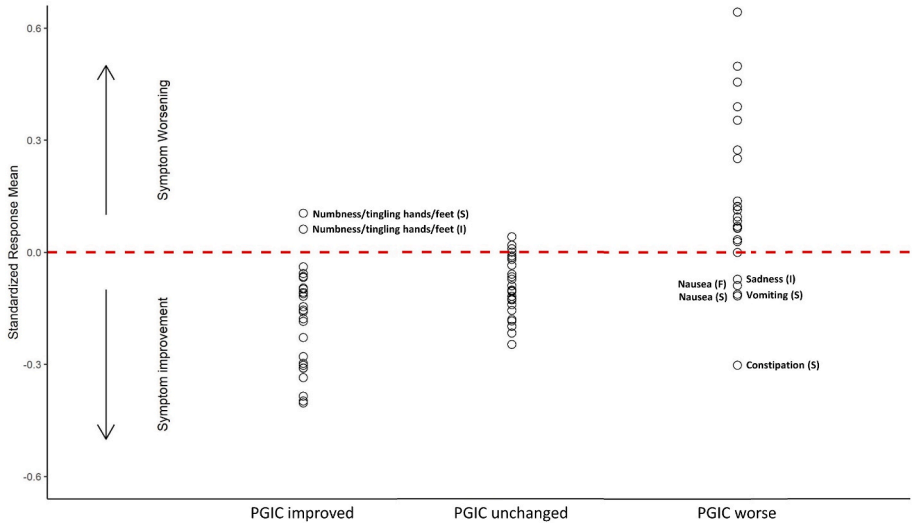

Fig. 4. – Bivariate distribution of standardized response mean to selected PRO-CTCAE items and PGIC score.

Secondly, the small number of participants with impaired ECOG PS precluded the possibility to verify the meaningfulness of PRO-CTCAE for patients with more severe disease.

5. Conclusion

In conclusion, the subjective dimensions of cancer and its treatment, such as quality of life and side-effects, are now regarded as essential components of cancer care. The knowledge about psychometric properties of available instruments and about relationships among their items may be important to allow integration of different instruments in order to capture complete and not redundant descriptions of clinically relevant domains, both for side-effects and quality of life. For breast cancer patients, the specific PRO-CTCAE short list can be considered as a standardized, agile tool for both trial and clinical settings.

Data availability

The datasets generated and/or analysed during the current study are available in the Zenodo repository https://zenodo.org/records/10435813.

Ethical approval

The study was approved by ethical committees at all participating centres; the first approval was by the committee operating at the coordinating centre on July 4th, 2018 (code 16/18-OSS).

Acknowledgments and funding source

The VIP study is promoted by FICOG (Federation of Italian Cooperative Oncology Groups). The study is partially supported by: Italian Ministry of Health – Ricerca corrente funds (grant L4/10); and by unrestricted grants from AstraZeneca, Bayer, Incyte and Pfizer. All the funders played no role in study design, data collection, analysis and interpretation of data, or the writing of this manuscript.

CRediT authorship contribution statement

Caterina Caminiti: Conceptualization, Data curation, Formal analysis, Methodology, Validation, Writing – original draft. **Giuseppe Maglietta:** Formal analysis, Validation, Visualization, Writing – original draft. **Laura Arenare:** Data curation, Formal analysis, Validation, Visualization, Writing – original draft. **Raimondo Di Liello:** Data curation, Writing – review & editing. **Gessica Migliaccio:** Investigation, Writing – review & editing. **Daniela Barberio:** Investigation, Writing – review & editing. **Michelino De Laurentiis:** Investigation, Writing – review & editing. **Francesca Di Rella:** Investigation, Writing – review & editing. **Francesco Nuzzo:** Investigation, Writing – review & editing. **Carmen Pacilio:** Investigation, Writing – review & editing. **Giovanni Iodice:** Data curation, Investigation. **Michele Orditura:** Investigation, Writing – review & editing. **Fortunato Ciardiello:** Investigation, Writing – review & editing. **Sara Di Bella:** Investigation, Writing – review & editing. **Luigi Cavanna:** Investigation, Writing – review & editing. **Camillo Porta:** Investigation, Writing – review & editing. **Filippo Giovanardi:** Investigation, Writing – review & editing. **Carla Ida Ripamonti:** Investigation, Writing – review & editing. **Domenico Bilancia:** Investigation, Writing – review & editing. **Giuseppe Aprile:** Investigation, Writing – review & editing. **Tommaso Ruelle:** Investigation, Writing – review & editing. **Francesca Diodati:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Maria Carmela Piccirillo:** Conceptualization, Validation, Writing – original draft, Writing – review & editing. **Elisabetta Iannelli:** Conceptualization, Supervision, Writing – review & editing. **Carmine Pinto:** Conceptualization, Funding acquisition, Investigation, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing. **Francesco Perrone:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing.

Declaration of competing interest

Michelino De Laurentiis declares: honoraria or consultation fees for speaker, consultancy or advisory roles from Eli Lilly, Seagen, Therapeutics, GSK, Roche, Novartis, Genetic, Pfizer, Pierre Fabre, MSD, Menarini Stemline, Sophos Biotech, Max Farma, Celltrion Healthcare, Gilead, Daiichi Sankyo; institutional financial interests, financial support for clinical trials or contracted research, from: Novartis, Pierre Fabre, Pfizer, Roche, Stemline Therapeutics.

Fortunato Ciardiello declares: honoraria or consultation fees for speaker, consultancy or advisory roles from Amgen, Merck KGaA, MSD, Pierre Fabre, Pfizer, Roche, Servier; institutional financial interests, financial support for clinical trials or contracted research, from: Amgen, Merck KGaA, MSD, Pierre Fabre, Pfizer, Roche, Servier.

Lugi Cavanna declares honoraria from Roche and Pfizer.

Filippo Giovanardi declares honoraria from Eli Lilly, AstraZeneca, Roche, Seagen, Novartis.

Maria Carmela Piccirillo declares: honoraria for speaker activities from Astellas, Pfizer, Ipsen, Astrazeneca; financial support to institutional research activities from AstraZeneca, Bayer, Roche.

Francesco Perrone declares: institutional grants or contracts from Roche, Bayer, AstraZeneca, Pfizer, Incyte, Tesaro/GSK, Merck; consulting fees from Bayer, Pierre Fabre, Astra Zeneca, Incyte, Ipsen, Clovis, Astellas, Sanofi, Roche, Pfizer; leadership in scientific society: President of AIOM 2023–2025.

All the other authors declares no competing interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2024.103781.

References

[1] Ciani O, Meregaglia M, De Lorenzo F, Perrone F, Pinto C. Patient-reported outcome measures in Oncology drugs approved by the European medicines agency, 2017-2021. JAMA Netw Open 2023;6:e2251564.
[2] Di Maio M, Basch E, Bryce J, Perrone F. Patient-reported outcomes in the evaluation of toxicity of anticancer treatments. Nat Rev Clin Oncol 2016;13:319–25.
[3] Basch E, Reeve BB, Mitchell SA, Clauser SB, Minasian LM, Dueck AC, et al. Development of the National Cancer Institute's patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE). J Natl Cancer Inst 2014;106.
[4] Dueck AC, Mendoza TR, Mitchell SA, Reeve BB, Castro KM, Rogak LJ, et al. Validity and reliability of the US national cancer institute's patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE). JAMA Oncol 2015;1:1051–9.
[5] Caminiti C, Maglietta G, Diodati F, Puntoni M, Marcomini B, Lazzarelli S, et al. The effects of patient-reported outcome screening on the survival of people with cancer: a systematic review and meta-analysis. Cancers 2022;14.
[6] Di Maio M, Basch E, Denis F, Fallowfield LJ, Ganz PA, Howell D, et al. The role of patient-reported outcome measures in the continuum of cancer clinical care: ESMO Clinical Practice Guideline. Ann Oncol; 2022.
[7] Veldhuijzen E, Walraven I, Belderbos J. Selecting a subset based on the patient-reported outcomes version of the common terminology criteria for adverse events for patient-reported symptom monitoring in lung cancer treatment: mixed methods study. JMIR Cancer 2021;7:e26574.
[8] Caminiti C, Bryce J, Riva S, Ng D, Diodati F, Iezzi E, et al. Cultural adaptation of the Italian version of the patient-reported outcomes common terminology criteria for adverse event (PRO-CTCAE(R)). Tumori 2022:3008916221099558.
[9] Sprangers MA, Groenvold M, Arraras JI, Franklin J, te Velde A, Muller M, et al. The European Organization for Research and Treatment of Cancer breast cancer-specific quality-of-life questionnaire module: first results from a three-country field study. J Clin Oncol 1996;14:2756–68.
[10] Costantini M, Musso M, Viterbori P, Bonci F, Del Mastro L, Garrone O, et al. Detecting psychological distress in cancer patients: validity of the Italian version of the Hospital Anxiety and Depression Scale. Support Care Cancer 1999;7:121–7.
[11] Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol 1998;16:139–44.
[12] Post WJ, Buijs C, Stolk RP, de Vries EG, le Cessie S. The analysis of longitudinal quality of life measures with informative drop-out: a pattern mixture approach. Qual Life Res 2010;19:137–48.
[13] Cohen J. Statistical power analysis for the behavioral sciences. second ed. Hillsdale, NJ: Lawrence Erlbaum Associates, Publishers; 1988.
[14] de Ligt KM, Koppert LB, de Rooij BH, van de Poll-Franse LV, Velikova G, Cardoso F. Seizing the moment: the time for harnessing electronic patient-reported outcome measures for enhanced and sustainable metastatic breast cancer care is now. Breast 2024;74:103676.