



Original research

Facilitating the interpretation of the multidimensional EORTC QLQ-FA12 fatigue questionnaire: Establishing thresholds for clinical importance

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ABSTRACT

Objective: Cancer-related fatigue is among the most burdensome side-effects of cancer and its treatment. The Fatigue Questionnaire of the European Organization for Research and Treatment of Cancer (EORTC QLQ-FA12) is a widely used measure to assess fatigue multidimensionally. However, interpretation of its scores can be challenging. Therefore, thresholds for clinical importance (TCI) for the three fatigue dimensions assessed by this questionnaire were developed.

Methods: A standardized approach was followed for the derivation of TCI. Three anchor items regarding limitations in daily life, need for help/care, and worries to the patient, their partner and/or family were completed by patients with various cancer types, in addition to the EORTC QLQ-FA12. Receiver Operating Characteristic curves and Youden's J were estimated to determine the most suitable TCIs.

Results: Complete data of the EORTC QLQ-FA12 and the anchor items were available for $N = 1111$ patients (age 67.2 ± 12.6 years; 61.2% female) from two observational studies. The derived TCIs for the physical, emotional, and cognitive fatigue scores (scale 0–100) were 43, 28, and 25, respectively. Subgroup analyses, categorized by gender and age, yielded consistent results. The sensitivity of the thresholds ranged from 0.87 to 0.94; the specificity from 0.67 to 0.80. Areas under the curve were all ≥ 0.89 .

Conclusion: The analyses established TCIs for the three dimensions of the EORTC QLQ-FA12. TCIs can be used in research and clinical practice to facilitate interpretation of individual patient scores at a single point in time. TCIs may indicate which patients experience a fatigue level that warrants additional clinical attention.

1. Introduction

Cancer-related fatigue is one of the most frequently reported and distressing symptoms experienced by patients with cancer [1]. It is characterized by a substantial and persistent feeling of exhaustion that can manifest in physical, emotional, or cognitive domains, and is not sufficiently alleviated by sleep or rest. Fatigue adversely affects functional performance, mood, and overall well-being [2,3], leading to reduced daily functioning and a potentially diminished adherence to cancer therapy [2,3]. Studies report that fatigue affects up to 85% of patients with cancer throughout the disease trajectory, with a pooled

prevalence of 49%–52% in patients during therapy [4,5]. Even years after the end of treatment, fatigue remains a prevalent complaint among more than 25% of patients [6,7].

As there are no objective measurements for fatigue, and clinicians often underestimate its severity, patients' self-reports are essential for systematically assessing fatigue [8]. A widely used questionnaire to measure fatigue multidimensionally is the Fatigue Module of the quality of life questionnaire [9] from the European Organization for Research and Treatment of Cancer (EORTC QLQ-FA12). It has been shown to be one of the most valid fatigue measures available, making it a recommended tool for both research and clinical practice [10]. However, the

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interpretation of the 0–100 points metric scores derived from this questionnaire can be challenging, as they do not necessarily indicate the clinical relevance of symptoms [11].

In recent years, the use of patient-reported outcome measures (PROMs) has increased, with these measures becoming an integral part of clinical outcome assessments in oncological trials [12,13]. Consequently, attempts have been made to facilitate the interpretation of questionnaire scores. In addition to the endeavors to identify minimally important differences (MIDs) to detect important changes in patient scores over time [14], Giesinger and colleagues [11] defined thresholds for clinical importance (TCIs) to foster a more intuitive interpretation of an absolute score from a patient at a single point in time [11]. In this sense, TCIs reflect that the underlying symptom a) causes limitations in daily life, b) indicates the need for help or care, or c) causes worry to the affected person or the family/partner [15]. Conceptually, TCIs aim to enhance the interpretation of PROM scores at the individual patient level and at a single point in time. They therefore represent an approach to interpreting PROM scores that is distinct from MIDs and from group-level comparisons (e.g., normative or reference data). In contrast, the MID is the smallest change in the given PROM score that is meaningful to patients. Estimates of MIDs typically rely on external criteria such as patients rating of changes [16], clinical variables, or on group level-statistics such as 0.5 Standard Deviations [14]. Thus, MIDs represent thresholds to interpret score differences and score changes, and TCIs are absolute thresholds indicating whether a single score from an individual patient is clinically meaningful.

In principle, TCIs can be used for research purposes, e.g. in cancer clinical trials, as well as in clinical practice. Initially, TCIs were intended to aid symptom screening in clinical practice, aimed to enhance the interpretability of PROM scores, and indicate to the clinical team clinically relevant symptom levels of individual patients (i.e. screening purposes). In cancer clinical trials and other empirical studies, TCIs may be further used to define outcomes (i.e. as response criteria in proportion of responder, or time to deterioration/improvement analysis) or to aid statistical analyses of PROM scores which rely on binary criteria (Odds Ratios, Hazard Ratios, Logistic Regression, etc.). The current use and application of TCIs for the EORTC measures has been described in detail elsewhere [17]. Thus far, TCIs have been established for the subscales of the EORTC QLQ-C30 [11], its computer-adaptive version [EORTC CAT core; [18]] and the EORTC QLQ-C15-PAL [19], all widely used questionnaires for assessing quality of life and symptom burden in (specific populations of) patients with cancer [20].

To date, there exist no TCIs that represent the multidimensionality of fatigue. However, there is a strong need to develop more nuanced TCIs that are able to reflect the potential origins and the multidimensionality of this common cancer side effect. The present manuscript therefore aims to identify TCIs for the EORTC QLQ-FA12 that assess the physical, emotional, and cognitive dimensions of fatigue.

2. Material and methods

2.1. Sample

Patient data from two longitudinal observational studies were pooled and analyzed to depict a comprehensive patient population and timespan of potential fatigue burden, ranging from the active treatment phase to the early survivorship phase. Patients enrolled in the LIFT study ('Longitudinal Investigation of cancer-related fatigue and its treatment') answered the EORTC QLQ-FA12 and the anchor items on average two years after a cancer diagnosis, either via an online survey or in paper-pencil format. Patients were included in LIFT if they were at least 18 years old, diagnosed with any primary tumor and treated with systemic cancer therapy or radiotherapy. Recruitment for this study took place between August 2021 and September 2022.

Patients of the MERLIN study (German acronym; in English: 'Recognizing and alleviating fatigue and exhaustion in time') answered

the variables of interest during their active treatment via an online study portal (computer-based health evaluation system; CHES [21]). MERLIN eligibility criteria permitted individuals to participate who had been diagnosed with cancer of any type or stage, were at least 18 years old, and had started systemic cancer therapy or radiotherapy within the first month. The recruitment phase started in October 2022 and ended in August 2024. Details of the study procedures have been published elsewhere [22,23].

Both studies were registered in ClinicalTrials.gov (LIFT: NCT04921644; MERLIN: NCT05448573) and have been conducted in accordance with the Declaration of Helsinki. Approvals by the Ethics Committee of the Medical Faculty of Heidelberg University, Germany, were obtained before recruitment started (for LIFT: S-526/2018 in August 2018; for MERLIN: S-336/2022 in May 2022).

2.2. Measures

2.2.1. EORTC QLQ-FA12

The EORTC QLQ-FA12 assesses fatigue with 12 items, each to be answered on a four-point Likert scale with response categories of 'not at all', 'a little', 'quite a bit', 'very much'. The scores of the dimensions 'physical' (5 items), 'emotional' (3 items), and 'cognitive' (2 items) fatigue are transformed to a scale of 0–100 according to the scoring manual, with higher scores indicating higher CRF levels [9]. The last two items of the EORTC QLQ-FA12 are single items that do not score on any of the dimensions and therefore did not contribute to the development of the TCIs.

2.2.2. Anchor items for establishing TCIs

The methodology employed in this study is consistent with those of previous studies that have developed thresholds for the EORTC QLQ-C30 and the EORTC QLQ-C15-PAL [11,19]. To develop suitable anchor items for TCIs, an international interdisciplinary expert panel, comprising of 150 patients and health care professionals providing quantitative and qualitative data, evaluated different aspects of clinical importance of symptom burden. Details of the considerations underlying this selection of criteria can be found elsewhere (Giesinger et al., 2018). In line with the previous studies, aspects of clinical importance were operationalized with the three anchor items as follows:

- Limitations: Has your SYMPTOM/PROBLEM limited your daily life?
- Need for help: Have you needed any help or care because of your SYMPTOM/PROBLEM?
- Worries: Has your SYMPTOM/PROBLEM caused you or your family/partner to worry?

For each dimension of fatigue, the three anchor items substituted 'symptom/problem' with the dimension-specific wording. The exact wording of the anchor items can be found in the Appendix A. The standard EORTC response format as described above (ranging from 'not at all' to 'very much') was employed for each anchor item. The questions were pretested for comprehensibility on a sample of 15 randomly chosen outpatients at the National Center for Tumor Diseases (NCT), Heidelberg, Germany, before being implemented in the studies.

Clinically important fatigue (i.e., a 'positive case') of the respective dimension was defined as a patient's response of 'quite a bit' or 'very much' to at least one of the three anchor items. Patients who responded 'not at all' or 'a little' to all three anchor items were considered as having no clinically important fatigue (i.e. designated as 'negative case').

2.3. Statistical analyses

The potential thresholds were generated with SPSS Statistics (Version 29.0). Sensitivity and specificity values were calculated and visualized using receiver operating characteristic (ROC) analyses. Hereby, the EORTC QLQ-FA12 dimension scores were designated as

Table 1
Study population characteristics.

Characteristics	
Mean age at measurement timepoint (SD)	67.2 (12.6)
	N (%)
Gender	
• Female	680 (61.2)
• Male	431 (38.8)
Time since diagnosis	
• ≤ 3 months (MERLIN)	298 (26.8)
• ≥ 24 months (LIFT)	813 (73.2)
Cancer entity	
• Breast	393 (36.4)
• Colon/rectum	158 (14.6)
• Prostate	129 (11.9)
• Melanoma	54 (5.0)
• Lung	50 (4.6)
• Lymphoma	39 (3.6)
• Ovary and cervix	39 (3.6)
• Stomach	27 (2.5)
• Leucemia	26 (2.4)
• Thyroid	26 (2.4)
• Kidney	23 (2.1)
• Pancreas	17 (1.6)
• Oesophagus	16 (1.5)
• Liver	14 (1.4)
• Other	69 (6.4)
• Missing*	31
Under treatment	
• No	486 (43.7)
• Yes	625 (56.3)
◦ Chemotherapy	234
◦ Radiotherapy	101
◦ Hormonotherapy	318
◦ Immune therapy	62
◦ Targeted therapy	73
◦ Other	41
Educational level	
• University degree	328 (30.7)
• Higher Secondary education (high school diploma) or vocational training	135 (12.6)
• Lower secondary education	333 (31.2)
• Compulsory or less	246 (23.0)
• Other	27 (2.5)
• Missing*	42
Living situation	
• Alone	189 (17.0)
• With partner	818 (73.6)
• With child(ren)	291 (26.2)
• With parent(s)	36 (3.2)
• Other	18 (1.6)

Note. $N_{\text{total}} = 1111$. Living situation and active treatment: Multiple selection possible. 'Age' refers to the age at the time of fatigue measurement.

*Missing values not included in calculation of percentages.

predictors, while the binary criterion of clinical importance was utilized to define positive/negative cases. For each dimension, the threshold that yielded the highest Youden's J index [the sum of sensitivity and

Table 3

Number of patients with clinically important fatigue burden (positive cases) and those without (negative cases).

	Total	Positive cases	
		N	%
EORTC QLQ-FA12 subscale			
Physical fatigue	1109	480	43.3%
Emotional fatigue	1110	289	26.0%
Cognitive fatigue	1109	153	13.8%
In one dimension		207	18.6%
In two dimensions		173	15.6%
In all three dimensions		123	11.1%

Note. Of $N=1,111$ included patients, $N=2$ (vs. 1) did not report values for physical or cognitive (vs. emotional) fatigue or the anchor items.

specificity minus one; [24]) was identified. In instances where the difference in Youden's J between two adjacent thresholds was less than 0.05, the threshold that exhibited higher sensitivity was selected. Areas under the curve (AUCs) were calculated in order to determine the diagnostic accuracy, i.e. the ability of the EORTC QLQ-FA12 to discriminate between negative and positive cases. AUCs above 0.80 are considered to indicate excellent discrimination [25]. Further explorative analyses were conducted to investigate the stability in TCIs and diagnostic accuracy across subpopulations defined by age (below/above 60 years), and gender (male/female). AUCs were calculated for each dimension of the EORTC QLQ-FA12.

3. Results

A total of $N = 1111$ patients (61.2 % female; $M_{\text{age}} = 67.2$ ($SD = 12.6$)) were included in the analysis. About three quarters (73.2 %) were participants of the LIFT study, i.e. assessed around 24 months after diagnosis. The most prevalent cancer diagnoses were breast cancer (35.4 %), followed by colon/rectum cancer (14.2 %), and pancreas cancer (11.6 %). Details of the study population characteristics are depicted in Table 1. Patients demonstrated the highest mean scores in the physical fatigue dimension of the scale, independent of their gender and age (Table 2).

According to the anchor item criteria, 43.3 % of the patients were identified as 'positive cases' for physical fatigue, whereas 26.0 % and 13.8 % were identified as 'positive cases' for emotional and cognitive fatigue, respectively. More than one in ten patients was defined as a 'positive case' in all dimensions of fatigue (Table 3). As depicted in Table 4 and Fig. 1, the TCI for physical fatigue was found to be 43 points (sensitivity=0.94, specificity=0.74), for emotional fatigue 28 points (sensitivity=0.93, specificity=0.70), and for cognitive fatigue 25 points (sensitivity=0.90, specificity=0.77). The AUC of the ROC curve ranged from 0.91 for emotional and cognitive fatigue to 0.92 for physical fatigue, indicating excellent discriminatory properties of the proposed methodology.

In the subsamples, the sensitivity values ranged from 0.87 (cognitive

Table 2
Distribution of the EORTC QLQ-FA12 scores.

	Complete sample ($N = 1111$)	Only women ($N = 680$)	Only men ($N = 431$)	Age < 60 years ($N = 449$)	Age ≥ 60 years ($N = 662$)
Physical fatigue					
• M (SD)	49.4 (27.8)	52.2 (27.7)	44.9 (27.9)	50.4 (27.7)	48.7 (28.1)
• Median (IQR)	47.0 (27.0; 73.0)	53.0 (33.0; 73.0)	40.0 (27.0; 67.0)	53.0 (33.0; 73.0)	47.0 (27.0; 67.0)
Emotional fatigue					
• M (SD)	29.1 (29.2)	32.1 (30.1)	24.4 (27.0)	31.3 (30.4)	27.7 (28.3)
• Median (IQR)	22.2 (0.0; 44.4)	33.3 (0.0; 55.6)	11.1 (0.0; 44.4)	22.2 (0.0; 55.6)	22.2 (0.0; 44.4)
Cognitive fatigue					
• M (SD)	18.9 (23.7)	20.9 (24.9)	15.7 (21.1)	22.5 (25.3)	16.4 (22.2)
• Median (IQR)	16.7 (0.0; 33.3)	16.7 (0.0; 33.3)	0.0 (0.0; 33.3)	16.7 (0.0; 33.3)	0.0 (0.0; 33.3)

Note. IQR = Interquartile Range, describing the span between the 25 % quartile (Q1) and the 75 % quartile (Q3). All EORTC QLQ-FA12 scores ranging from 0 to 100 with higher scores indicating more fatigue.

Table 4

Results of the receiver operator characteristic analyses and thresholds for clinical importance (TCI).

EORTC QLQ-FA12 subscale	AUC [95 % CI]	TCI	Sensitivity [95 % CI]	Specificity [95 % CI]	Youden's J
Physical fatigue	0.92 [0.90; 0.94]	43	0.94 [0.92;0.96]	0.74 [0.70;0.78]	0.68
Emotional fatigue	0.91 [0.89; 0.93]	28	0.93 [0.90;0.96]	0.70 [0.64;0.75]	0.63
Cognitive fatigue	0.91 [0.88; 0.93]	25	0.90 [0.85;0.94]	0.77 [0.71;0.84]	0.67

Note. Scoring above the TCI indicates a clinically relevant symptom burden in the respective fatigue dimension. AUC = area under curve, TCI = threshold for clinical importance, CI = confidence interval.

fatigue in males) to 0.96 (emotional fatigue in patients <60 years), whereas specificity values ranged from 0.67 (emotional fatigue in females) to 0.92 (cognitive fatigue in patients <60 years; Table 5). All sensitivity and specificity values of the TCIs are depicted in Tables 4 and 5. More details of the analyses can be found in the Appendix (Tables B1 to B9). AUCs indicated excellent discrimination between positive and negative cases, as they were all higher than 0.89 (Tables 4 and 5).

When the ROC curves and Youden's J were calculated for the population separated by gender and age, the TCIs remained mainly unchanged (see Table 5 and Appendix, Tables B1 to B9). The only exception to this was a change in the optimal TCI for cognitive fatigue in patients aged below 60 years (Table 5). In this subgroup, applying the above-described criteria would indicate a TCI of 42 points, deviating from the optimal threshold of 25 points in the overall sample. When the calculations were performed separately per study sample (LIFT or MERLIN), the TCIs remained largely unchanged (Appendix, Table C1).

4. Discussion

To enable a more intuitive outcome interpretation in clinical trials of research and to foster screening options to identify clinically relevant fatigue levels of individual patients in clinical practice, TCIs for the physical, emotional and cognitive dimensions of the EORTC QLQ-FA12 were determined. The application of anchor items, indicating whether patients' fatigue-related symptoms were limited their daily life, caused worry to them or their partner/family, or required help or care, constituted a robust methodology for defining TCIs in this population.

According to the anchor item criteria, physical fatigue emerged as the most relevant dimension, whereby 43.3 % of study participants indicated clinically relevant physical fatigue, compared to 26.0 % and 13.8 % for clinically relevant emotional and cognitive fatigue, respectively. This aligns with findings reporting physical fatigue as the most frequently perceived and assessed form of fatigue among patients with

cancer [26,27]. In addition to the TCI of the EORTC QLQ-C30 fatigue subscale, TCIs for the different EORTC QLQ-FA12 dimensions may help identify the most burdensome facets of fatigue and inform further treatment decisions. This is of particular relevance considering that clinical guidelines suggest a tailored treatment of fatigue which targets the underlying cause of fatigue [28,29].

Furthermore, our study results suggest that TCIs remain robust across gender and age. This robustness of TCIs was also found in a sensitivity analysis comparing the results of the LIFT study (post-treatment) and the MERLIN study (on-treatment). The only exceptions to this were the TCI for cognitive fatigue in patients under 60 years old, and in the analysis of cognitive fatigue in MERLIN data only. However, since these subpopulations comprised only 77 'positive cases' of patients in the overall sample (42 'positive cases' in the MERLIN sample), increasing the overall TCI to 42 (which is the adjacent TCI to 25), rather than maintaining it at 25, would not have been considered appropriate. This might overestimate clinically relevant cognitive fatigue symptoms in some patients, but is from the patient perspective a rather conservative approach.

Interestingly, the analyses revealed no differences in TCIs between female and male patients, despite women reporting higher fatigue scores in all dimensions and scoring above the TCIs more frequently. This result indicates that female and male participants report similar 'limitations in daily life', 'worries', and 'need for help/care' in accordance with lower or higher levels of fatigue. In clinical practice, this finding may underscore that TCIs are robust in its concept and may not need to be adapted according to patient characteristics. Furthermore, these observations are consistent with the results of previous studies [7,30] suggesting that female patients may have a higher prevalence of clinically important fatigue symptoms. In line with this finding, female gender has been considered a risk factor for developing fatigue [31,32].

Reiterating the intended use of TCIs, it should be emphasized that they can facilitate outcome interpretation in clinical research. For

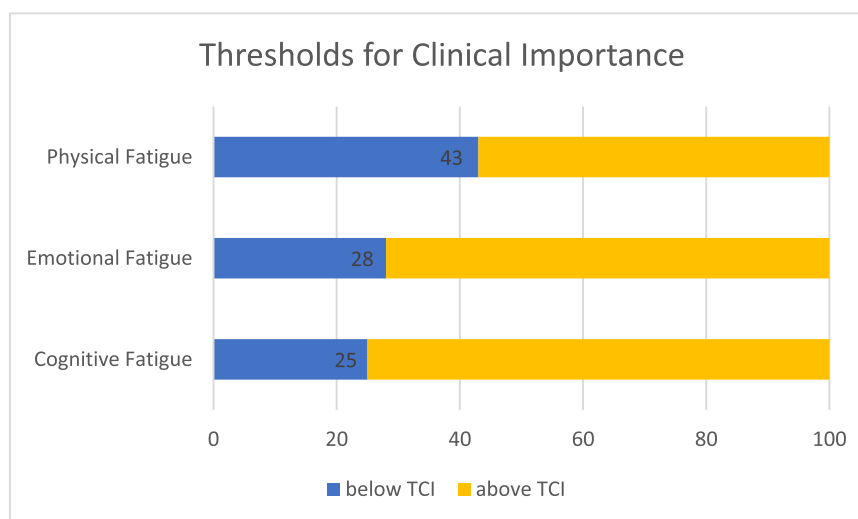


Fig. 1. Thresholds of clinical importance for the three fatigue dimensions. *Note.* Patient scoring in the yellow range of the bar (above the TCI for the respective fatigue subscale) indicate clinically important fatigue levels.

Table 5

Results of the receiver operator characteristic analyses and thresholds for clinical importance (TCI) for each dimension of fatigue differentiated by gender and age.

EORTC QLQ-FA12 subscale	AUC[95% CI]	TCI	Sensitivity [95% CI]	Specificity [95% CI]	Youden's J
Physical fatigue					
• Female	0.92 [0.90; 0.94]	43	0.94 [0.91; 0.96]	0.72 [0.67; 0.77]	0.66
• Male	0.92 [0.89; 0.95]	43	0.94 [0.89; 0.97]	0.76 [0.70; 0.83]	0.70
• <60	0.92 [0.89; 0.94]	43	0.95 [0.92; 0.98]	0.72 [0.66; 0.79]	0.67
• ≥60	0.92 [0.90; 0.94]	43	0.93 [0.90; 0.96]	0.75 [0.70; 0.80]	0.68
Emotional fatigue					
• Female	0.90 [0.88; 0.93]	28	0.93 [0.89; 0.96]	0.67 [0.60; 0.73]	0.60
• Male	0.92 [0.89; 0.94]	28	0.93 [0.88; 0.98]	0.74 [0.65; 0.83]	0.67
• <60	0.92 [0.90; 0.95]	28	0.96 [0.92; 0.99]	0.69 [0.61; 0.77]	0.65
• ≥60	0.90 [0.87; 0.92]	28	0.90 [0.86; 0.95]	0.70 [0.63; 0.77]	0.60
Cognitive fatigue					
• Female	0.91 [0.87; 0.94]	25	0.91 [0.85; 0.96]	0.77 [0.69; 0.85]	0.68
• Male	0.89 [0.84; 0.95]	25	0.87 [0.78; 0.97]	0.79 [0.67; 0.90]	0.66
• <60	0.93 [0.89; 0.97]	42	0.80 [0.71; 0.89]	0.92 [0.85; 0.97]	0.72
• ≥60	0.89 [0.85; 0.93]	25	0.88 [0.81; 0.96]	0.80 [0.71; 0.89]	0.68

Note. Scoring above the thresholds indicates a clinically relevant symptom burden in the respective fatigue dimension. Thresholds are between values that patients can score on the EORTC QLQ-FA12 scales. AUC = area under curve, TCI = threshold for clinical importance, CI = confidence interval.

example, they can serve as a tool to calculate prevalence estimates of symptom burden in study samples or as a responder definition in clinical studies [17]. Regarding the latter, it might be suggested to use TCIs for a-priori definition of secondary or exploratory endpoints, but not yet for primary endpoints as the TCIs still need to be validated in further studies. A successful integration of TCIs in the definition of clinical study endpoints has been shown in various examples [33,34]. Further, TCIs have previously been used as screening criteria in electronic patient report outcome assessments, and directly influenced clinical decision making [35,36]. A similar application is envisioned for the TCIs of the EORTC QLQ-FA12. Importantly, TCIs are not intended to aid the interpretation of group-level data, such as mean scores of full samples [11, 17]. Instead, they can facilitate the interpretation of individual patient-level data at a single point in time. In a previous review [17], the miss-application of TCIs to group level data was identified frequently, which the authors want to warrant against. Regarding the application in clinical practice, TCIs may facilitate the interpretation and communication of results by patients and health care professionals and may help to guide treatment decisions. In particular, they may help to overcome the challenge that patients and clinicians regularly face with the lack of interpretation guidelines of PROM data regarding clinical meaningfulness [37]. In the specific case of fatigue, effective communication and education remain frequently overlooked aspects of fatigue management, despite being defined as key elements in international guideline recommendations [1,23,38,39]. Following this, patients identified with clinically important fatigue, as determined by the TCIs, should not only receive education regarding fatigue, but also be offered treatment options. Although this is generally recommended for all cancer patients, the focus could be directed towards patients who score above the TCI if time and personal resources are limited.

5. Limitations and strengths

Some limitations should be noted. Firstly, patients vary to what degree and how they experience exhaustion or tiredness. Furthermore, given that this is the inaugural study to investigate these dimension-specific TCIs for fatigue, external validation is required. Further investigation into potential influencing factors, such as treatment and tumor type, could be beneficial in strengthening the robustness of the proposed TCIs. Further, it is important to note that the utilization of TCIs in clinical practice does not replace a thoughtful examination of a patient's fatigue through a diagnostic assessment, as recommended by international guidelines for fatigue management [1,39,40]. Nevertheless, the comprehensive sample size, encompassing patients with diverse cancer diagnoses and treatment modalities, along with varying stages throughout the cancer trajectory, facilitated the identification of robust

TCIs. This may assist in identifying patients who are more likely to experience a higher symptom burden that is of clinical significance.

6. Conclusion

The application of the TCIs for the EORTC QLQ-FA12 will facilitate the interpretation of scores by health professionals and patients alike, thereby enhancing the instrument's utility in clinical research and in daily clinical practice. Furthermore, TCIs enable to identify clinically important symptom burden in patients who may necessitate clinical attention.

CRedit authorship contribution statement

Karen Steindorf: Writing – review & editing, Methodology, Investigation, Funding acquisition, Conceptualization. **Johannes M. Giesinger:** Writing – review & editing, Methodology, Formal analysis. **Imad Maatouk:** Writing – review & editing, Conceptualization. **Marlena Milzer:** Writing – review & editing, Investigation, Data curation. **Micha J. Pilz:** Writing – review & editing, Methodology, Formal analysis. **Jens Lehmann:** Writing – review & editing, Methodology. **Martina E. Schmidt:** Writing – review & editing, Investigation, Funding acquisition, Conceptualization. **Lisa M. Storz:** Writing – review & editing, Visualization, Methodology, Formal analysis. **Patricia Blicke:** Writing – review & editing, Writing – original draft, Visualization, Investigation, Data curation, Conceptualization.

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

During the preparation of this work the authors used deepL Write in order to optimize sentences written in academic English. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Declaration of Competing Interest

The authors declare the following financial interests/personal

relationships which may be considered as potential competing interests: JL reports consultancy for Evaluation Software Development and an investigator-initiated research grant from Takeda to his university in his name, both outside of the submitted work. All remaining authors have declared no conflicts of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.ejca.2025.116134](https://doi.org/10.1016/j.ejca.2025.116134).

Data availability

Data can be made available to scientific colleagues upon reasonable request.

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