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ORIGINAL ARTICLE

Co-occurrence of symptoms after radiochemotherapy in locally advanced cervix cancer patients: a cluster analysis

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ABSTRACT

Background: State of the art combined radiochemotherapy and image-guided brachytherapy for locally advanced cervical cancer (LACC) has shown improved disease control and survival as well as a significant reduction of organ related morbidity. However, LACC cancer survivors are still experiencing a spectrum of symptoms. The aim of this study was to identify co-occurring symptoms in cervix cancer survivors by using patient-reported outcome and physician assessed morbidity.

Materials and method: EMBRACE I is a multicenter prospective observational study with 1416 LACC patients (2008–2015). Information on physician-assessed morbidity and patient-reported outcome was assessed at baseline and at regular follow-ups up with the CTCAE v.3 and EORTC-C30/CX24, respectively. Patients with at least 2 years of follow-up were included and data from 3 months to 2 years was used in the analysis. Factor analysis was used on both EORTC and CTCAE data with symptoms and follow-ups as observations. The extracted factors represent clusters of symptoms. Subsequently, regression models were built to investigate associations between the symptom clusters and QOL.

Results: The analysis included 742 patients. Despite the differences in the definition of physician-assessed and patient-reported symptoms, similar clusters are identified by the two assessment methods. Three main organ-related clusters are recognized for urinary, gastro-intestinal and vaginal morbidity. Furthermore, a general symptoms cluster where fatigue, pain, insomnia, neuropathy, and hot flashes have large weights is found. Lastly, a cluster with nausea, vomit and lack of appetite is also identified. The general, gastrointestinal and nausea clusters show significant associations with general QOL.

Conclusions: This analysis on both PRO and physician-assessed morbidity found a cluster associated with general symptoms and organ-related symptom clusters (urinary, gastrointestinal, vaginal). This shows that LACC survivors experience a variety of co-occurring symptoms. Our analysis also shows that the cluster of general symptoms is associated with a decrease in QOL.

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Radiotherapy; locally advanced cervical cancer; symptom clusters; quality of life; patient reported outcome

Introduction

Implementation of external-beam radiotherapy (EBRT) together with image-guided brachytherapy in the treatment of locally advanced cervical cancer (LACC) has shown improvement in local control and survival as well as reduction of major morbidity as compared to previous experience with non-image-guided brachytherapy [1–3]. However, overall treatment outcome is still associated with a wide spectrum of symptoms, which can be related to cancer, to its treatment or to other factors. These symptoms may have a significant impact on quality of life (QOL). Together with physician-assessed side effects, patient-reported outcome is becoming increasingly important for understanding the relevance of such symptoms and the corresponding effect on QOL [4,5].

There is increasing evidence that multiple symptoms occur concurrently in clusters, although this is not necessarily associated with a shared etiology [6–11]. Multiple co-occurring symptoms are often referred to as a symptom cluster. This concept has been defined in the literature [12,13] as stable groups of co-occurring symptoms that have stronger relationships within the cluster than between clusters. This implies that each cluster must have a distinct group of symptoms belonging to it and these symptoms need to co-exist together in patients [14]. Examples of symptoms clusters identified in the literature can be the cluster of insomnia and fatigue [15], the gastrointestinal symptom cluster [16] or

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pain, fatigue, and head and neck specific symptom clusters related to dry mouth and mucus [17].

Several methodologies have been proposed in the literature to identify symptom clusters [18,19]. These methods range from clinically predefined clusters through correlations to statistical approaches such as Exploratory Factor Analysis (EFA) and hierarchical clustering [20].

It has been shown that understanding symptom clusters is essential for planning interventions and symptom management after treatment [21]. Suggestions on how to provide effective treatment for the fatigue cluster have been proposed [15,22] and the importance of considering symptoms clusters for symptom management has also been discussed [23].

Along this line, it seems natural to move from addressing single symptoms to clusters of symptoms. Nonetheless, in clinical studies, morbidity reporting is usually based on individual symptoms or aggregation of endpoints based on organ systems [24], rarely looking at the co-occurrence of related symptoms.

For LACC patients, a number of reports have already described the incidence of individual symptoms after treatment [3,25–30] and analyzed patient and treatment-related risk factors [31–33], but a detailed analysis of the correlations between organ-related and general symptoms was never carried out. Furthermore, the longitudinal association between symptoms and QOL was also recently reported [34] but only looking at individual symptoms. The aim of this analysis was to identify clusters of co-occurring symptoms over time in LACC patients after radiochemotherapy using both physician-assessed symptoms and patient reported outcomes. Furthermore, the analysis aimed to investigate the association between the clusters and QOL in LACC survivors. To this end data from the international prospective study on MRI-guided brachytherapy (EMBRACE-I) are used.

aterial and methods

Patients and treatment

The EMBRACE-I cohort was used to derive clusters of symptoms and evaluate association between symptom clusters and QOL. EMBRACE-I (NCT00920920) is a multicentre, prospective, and observational study with 1416 patients enrolled from 2008 to 2015 in 24 centers (www.embracestudy.dk). The full list of centers is available in the Supplementary Material. The study was approved by the respective National or Institutional Ethics Committees of each participating center. Patients with biopsy proven LACC International Federation of Gynecology and Obstetrics (FIGO) stage IB-IVB [35] were eligible for the study. Treatment consisted of EBRT with concomitant chemotherapy and IGABT. More details on study design, patient selection, and treatment are available elsewhere [1].

Assessment of symptoms and side effects

Information on morbidity and patient-reported outcome (PRO) was prospectively assessed at baseline and regularly during follow-up every three months for the first year after treatment, every six months until the third year, and every year onward. Assessments were censored at any recurrence of the disease. Data on PRO and QOL were evaluated with the European Organization for Research and Treatment of Cancer (EORTC) QOL general (QLQ-C30) and cervical cancer-specific module (QLQ-CX24) questionnaires. Patients scored symptoms with four categories:" not at all"," a little"," quite a bit", and" very much". Global health/general QOL was scored using a 7-point scale ranging from" poor" to" excellent". Physician-assessed morbidity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0 [36] which has 5 categories, from Grade 1 (mild symptoms) to Grade 5, corresponding to death.

Statistical methods and analysis

Patients treated according to protocol were included in this analysis when at least two years follow-up was available. The analysis consisted of three steps. First, correlations between symptoms were calculated using Pearson's correlation coefficient r to validate the hypothesis of intercorrelation. Correlations are large if $r \geq 0.5$, moderate if $r \in [0.4, 0.5)$ and weak if $r \in [0.2, 0.4)$.

Secondly, clusters of symptoms co-existing in different follow-ups and patients were determined with Exploratory Factor Analysis [37]. In this step, all symptoms and side effects recorded in the EMBRACE I study were considered except for the fistulae. Fistulae were not included in this analysis as the manifestation of this condition is dependent on the type and outcome of management, which was not reported in the EMBRACE I database. EFA identifies unobserved latent variables called factors representing the shared variation among the observed correlated variables. In this analysis, EFA was applied to each follow-up separately as well as to the data set from all follow-ups. The number of factors to be estimated has been determined using the Kaiser rule [38]. The factors resulting from the EFA correspond to the clusters of symptoms. Symptoms with weights ≥ 0.6 are highly correlated with the factors, whereas the correlation of symptoms with weights < 0.2 is considered low. More details on the EFA are available in the Supplementary Material.

The main advantage of this methodology over other clustering techniques is that it can ease the understanding of the data by reducing the number of observed variables (symptoms) through the identification of unobserved factors (clusters). As the number of factors to be estimated is determined *via* the Kaiser rule and subsequently factor analysis is applied to the data, the cluster of symptoms and the weights of each symptom in a cluster are statistically estimated. Data-driven estimation of symptom clusters allows objective cluster estimation compared to clinical-based symptom clustering. Other statistical methods for symptom cluster estimation have been proposed in the literature (e.g., hierarchical clustering or principal component analysis) and are based on classical methodologies for statistical clustering.

In contrast to EFA, these clustering techniques have a primary aim to identify groups of similar observations instead of reducing the number of variables.

Lastly, these clusters were used to build a regression model for detecting associations between the occurrence of clusters and QOL. Scores on global health/general QOL were transformed to a continuous scale according to the EORTC manual (score 0–100) [39]. Two regression models were built at each follow-up time for EORTC and CTCAE data respectively. For each regression model, QOL was used as the dependent variable and the estimated clusters of symptoms as predictors. The resulting p-values from the regression analysis were corrected for multiple testing using the Benjamini-Hochberg procedure [40].

Results

From the EMBRACE-I cohort, 54 patients were excluded prior to this analysis for the following reasons: 17 were registered without further information, 34 did not receive treatment as planned, and 3 were falsely excluded without subsequent information registered. Furthermore, 637 patients had less than 2 years follow-up, resulting in 742 patients available for this analysis. The median age was 48 [range:22:83] years. Patients with WHO performance status $= 1$ and ≥ 2 were 167 (23%) and 12 (2%). $FIGO_{2009}$ distribution was: IB $= 130$ (17%), IIA $= 29$ (4%), IIB $= 421$ (57%), IIIA $= 5$ (1%), IIIB $= 96$ (13%), IVA $= 14$ (2%), IVB $= 47$ (6%) and 49% of the patients were node positive at diagnosis. Detailed information on patients, disease and treatment are reported in the Supplementary Material. Patient characteristics of the patients included in this analysis can be found in Table 1.

Figure 1 shows the correlations between EORTC symptoms as well as CTCAE. Correlation is large for fatigue, pain, and pain in the lower back and moderate correlations are observed for 1) fatigue and insomnia, 2) diarrhea and difficulty in bowel control, 3) urinary frequency and incontinence, and 4) vomit, nausea and lack of appetite. In the CTCAE data, additional weak correlations are found between bladder spasms and bladder bleeding, as well as between bladder frequency and bladder incontinence.

Figure 2 shows the results of EFA applied to the EORTC and CTCAE data respectively. The clusters of symptoms are displayed as columns with the corresponding weights for each symptom. High weights on symptoms indicate strong relationship between the corresponding cluster and the symptom. For both CTCAE and EORTC data, three clear organ-related clusters are identified for urinary, gastro-intestinal (GI) and vaginal morbidity. Furthermore, a cluster corresponding to general symptoms is also found. Symptoms in the general symptoms cluster are defined as unspecific symptoms typically not related to a specific organ system [41]. In addition, a cluster of symptoms related to nausea is identified in the EORTC data (symptoms related to nausea and vomiting were not captured with CTCAE reporting in EMBRACE I).

For the general cluster, fatigue has highest weight in both data sets, together with pain for the EORTC data and insomnia for the CTCAE data. Furthermore, in the CTCAE results, the symptoms with highest weights for the urinary cluster are cystitis and bladder bleeding, for the GI cluster proctitis and rectal bleeding and for the vaginal cluster vaginal stenosis and dryness. For the EORTC results, the highest weights are observed for urinary incontinence and difficulty emptying the bladder for the urinary cluster and for difficulty in bowel control and diarrhea for the GI cluster. In the vaginal clusters the highest weights are found for discharge and soreness and lastly in the nausea cluster nausea and vomiting have the highest weights.

The results on the regression models evaluating the association between the clusters of symptoms and QOL are reported in Table 2. The general cluster is a significant predictor for QOL at all follow-ups considering both CTCAE and EORTC data. For EORTC data, the cluster of gastro-intestinal symptoms and the nausea cluster are significantly associated with QOL at two and three follow-ups respectively. The cluster of gastro-intestinal symptoms is also significant for the CTCAE data at three follow-ups.

Discussion

This analysis is focused on LACC survivors (disease-free until at least 2 years) and comprises prospective patient-reported and physician-assessed outcome. The main finding is the identification of different clusters of symptoms through the use of EFA. These results are also in line with the observations from clinical routine with LACC patients after pelvic radiotherapy [42]. Lastly, associations of the clusters of general, GI, and nausea symptoms with QOL are also identified in our analysis.

Previous works hypothesized that it is possible to cluster symptoms according to clinically observed associations in cancer patients [12,14,43,44] and several research works have found clinically relevant clusters for different cancer sites. For example, clusters associated with fatigue and pain have been found in cohorts of patients from ovarian [9,45], lung [46,47], prostate [48], and breast [49–51] cancer. Similarly, in this analysis, a cluster of general symptoms including fatigue and pain is found in cervical cancer patients. Prevalences for individual persistent symptoms for LACC patients in EMBRACE I were previously published [34].

Identification of clusters of symptoms

The correlation coefficients between symptoms shown in Figure 1 provide motivation for working with clusters of symptoms to reduce the dimensionality of the data set. In this work, the clusters of symptoms are identified based on longitudinal data of symptoms for all patients.

The EFAs on both PRO and physician-assessed morbidity found clusters of symptoms associated with general and organ-related symptoms after treatment. These two sets of results are very concordant despite different information recorded in CTCAE and EORTC symptoms. Similar clusters of symptoms are found in both data sets: 1) general symptoms (fatigue, pain, insomnia, and pain to the lower back); 2)

Table 1. Patient-, disease- and treatment-related characteristics in the cohort eligible for analysis. Abbreviations: BMI:body mass index; EBRT VXGy: volume treated with X Gy external beam radiotherapy dose; HDR: high dose rate; PDR: pulsed dose rate; IC: intracavitary; IC/is: intracavitary/interstitial.

	Included pat $n = 742$			Excluded pat $n = 637$	
	Parameters	Values	Percentage	Values	Percentage
Age (years)	Median	48		51	
	Min	22		21	
	Max	83		92	
BMI	NA	0	0%	19	3%
	Underweight (<18.5)	39	5%	26	4%
	Normal (18.5–24.9)	344	47%	265	42%
	Overweight (25–29.9)	216	29%	177	28%
	Obese (30+)	136	19%	143	22%
Smoking status	NA	25	3%	49	8%
	No	494	67%	396	62%
	Yes	223	30%	192	30%
WHO performance status	PS0	563	76%	422	68%
	PS1	167	23%	180	29%
	PS2	10	1%	22	4%
	PS3	2	<1%	1	<1%
Comorbidities	NA	0	0%	12	2%
	No	541	73%	433	68%
	Yes	201	27%	192	30%
FIGO 2009 stage	IB	130	17%	119	19%
	IIA	29	4%	40	6%
	IIB	421	57%	287	45%
	IIIA	5	1%	8	1%
	IIIB	96	13%	99	16%
	IVA	14	2%	21	3%
	IVB	47	6%	51	8%
Chemotherapy	NA	0	0%	31	5%
	No	32	4%	41	6%
	Cisplatin	696	94%	541	85%
	Other	13	2%	24	4%
	of which reduced cycle	8	61%	13	54%
EBRT prescribed dose	NA	0	0%	33	5%
	<47.5 Gy	594	80%	446	70%
	>47.5 Gy	148	20%	158	25%
EBRT technique	3D-CRT	472	64%	322	53%
	IMRT/VMAT	270	36%	281	47%
EBRT lymph node boost	No	478	64%	391	65%
	Yes	264	36%	214	35%
Para-aortic irradiation	NA	0	0%	32	5%
	No	637	86%	492	77%
	Yes	105	14%	113	18%
Brachytherapy dose rate	HDR	429	58%	336	57%
	PDR	313	42%	258	43%
Brachytherapy technique at 1^{st} fraction	IC	503	68%	370	62%
	IC/IS	239	32%	224	38%

organ-specific (gastrointestinal, urinary, and vaginal symptoms). Additionally, the nausea symptom cluster is extracted from the EORTC data. Also, the weights of the symptoms are shared across CTCAE and EORTC: for example, the weights of the general cluster on insomnia, fatigue and hot flashes are high in both EORTC and CTCAE, pointing to a strong influence of these symptoms in the cluster.

Currently, the common underlying mechanisms and etiology for symptom clusters are only partly understood. The relationship between the major symptoms in the general cluster such as fatigue and pain with hot flashes and insomnia has been previously reported [22,52,53]. In the EORTC data, the general cluster also includes symptoms such as peripheral neuropathy and shortness of breath. Shortness of breath is a multifactorial symptom of high relevance for oncological patients [54]. This work shows that it is also usually co-occurring with fatigue and with a decrease in quality of life. Sensory peripheral neuropathy symptoms (numbness or tingling in hands or feet) are well-known toxic effects of chemotherapy. It has been shown that chemotherapy-treated colorectal cancer survivors with peripheral neuropathy experience more fatigue [55]. Psychological distress could be a mechanism underlying the relationship between peripheral neuropathy and fatigue [55] and neuropathic pain may have influence on sleep and mood disturbances [56,57]. Lastly, CTCAE items for these symptoms were not recorded in EMBRACE I, however our results point to their importance for patients, and therefore assessment of these symptoms by physicians could be considered in future studies.

The influence of limb edema on the general symptoms cluster differs between the EORTC and the CTCAE results: the weights of this symptoms is 0.4 in the EORTC results, but it is negligible in the CTCAE results. This can be explained by the discrepancy between the clinical definition of this symptom and patients' perception. In fact, the proportion of patients with any symptomatic persistent limb edema was lower in CTCAE compared to EORTC [34].

Lastly, as for the nausea cluster, the main symptoms are lack of appetite, nausea and vomiting. Evidence of persistent nausea symptoms in EMBRACE I survivors have been

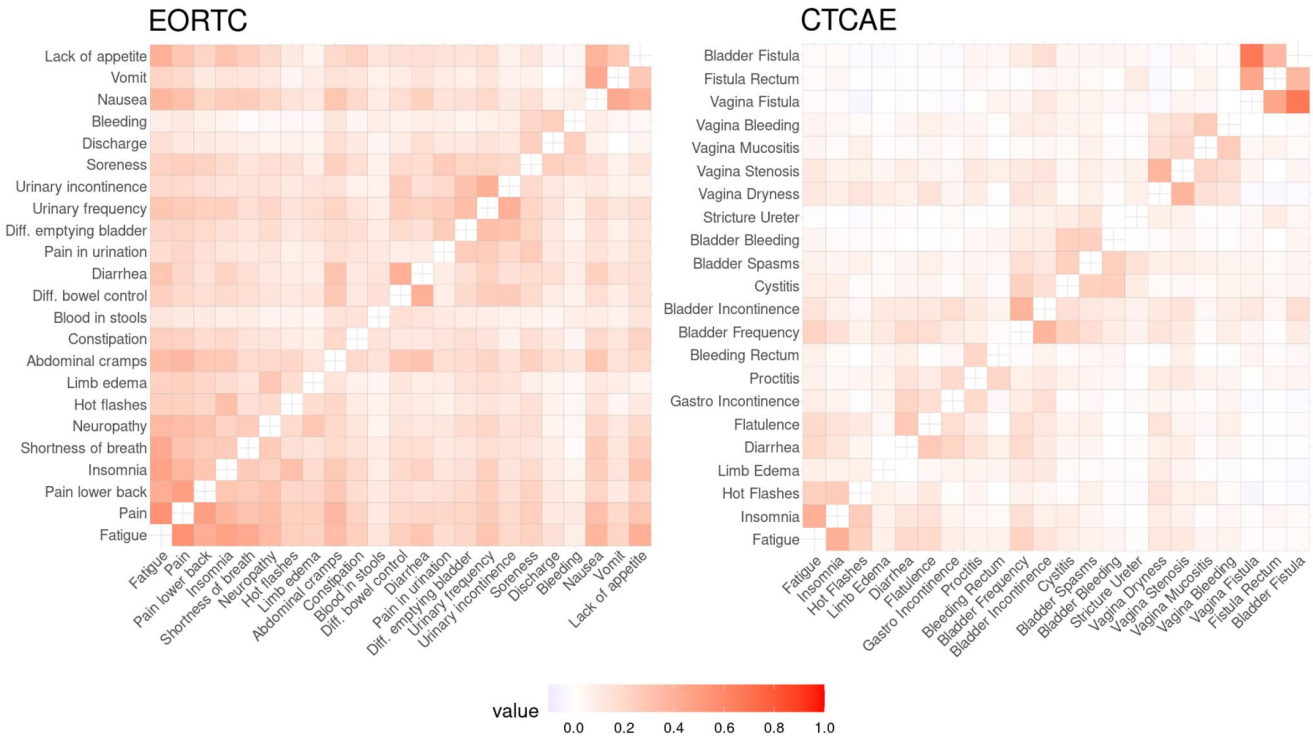

Figure 1. Correlation values between the occurrence of the symptoms in the EORTC data (on the left) and in the CTCAE data (on the right). The red colour indicates positive correlation with darker shades representing higher correlation.

previously reported in 1.1% of patients [58]. Nausea can be related to irradiation of the bowel part, and associations with nausea and QOL and symptoms such as pain and fatigue have been shown in the literature [59–61]. Furthermore, nausea can also be caused by other conditions not captured by EORTC data such as medications.

This analysis did not include an evaluation of the possible association of symptom clusters and treatment-related parameters. However, it can be observed that the majority of symptoms with high -eights in clusters have previously been shown to correlate with treatment parameters (e.g., cystitis, bladder bleeding, vagina stenosis, proctitis, rectal bleeding, bowel control, diarrhea and fatigue) [26,30–33,62,63]. This emphasizes the hypothesis that treatment induces co-occurring symptoms, while symptoms related to other risk factors unrelated to treatment could possibly manifest with a lower level of co-occurrence. In light of these results, we suggest that risk factor analysis including symptom clusters instead of single symptoms might be considered in order to understand the association with treatment-related parameters.

Association between clusters of symptoms and QOL

Previous analyses within EMBRACE-I have already shown the association of persistent pain, fatigue, insomnia, and peripheral neuropathy on QOL in LACC survivors [34,64]. Here, the relationship between QOL and the clusters of symptoms is quantified at each follow-up through regression models where QOL is the dependent variable and the clusters of symptoms are the independent variables. Association between clusters of symptoms and QOL however is also influenced by patient-specific components such as psychological factors and by the environment, such as demographic and social characteristics. Such factors are not always easily captured in the context of clinical trials.

As shown in Table 2, and in concordance with the results already shown in EMBRACE-I for individual symptoms [34], the cluster of general symptoms has a higher impact on QOL than organ-related symptom clusters. Furthermore, the gastrointestinal symptoms cluster for both EORTC and CTCAE data is a significant predictor for QOL. The nausea symptom cluster is also significantly associated with QOL. The other clusters of symptoms are not significant in predicting QOL in this analysis. However, it is important to stress that even when not significant in predicting QOL in this analysis, symptoms associated with the urinary and vaginal clusters are still relevant for patients and can affect their daily life activities and well-being. For this reason, it is essential to report these symptoms during follow-up and apply dose constraints during treatment planning to decrease the occurrence of morbidity. In addition, if not directly impacting overall QOL, vaginal symptoms have a profound influence on the sexual activity of LACC survivors [65]. Furthermore, common symptoms such as vaginal stenosis can also prevent thorough gynecological examinations during follow-ups needed to check recurrence of the disease.

Strengths and limitations

The exploratory factor analysis carried out in this work provides stable statistical clusters of symptoms and side effects for LACC survivors. The advantage of considering a follow-up period of two years also offers the possibility to validate the robustness of these clusters over time and to better

Figure 2. Factor analysis results for the EORTC data (on the top) and the CTCAE data (on the bottom). Each vertical box represents one of the symptoms clusters identified by factor analysis. The length of bars indicates the loadings (weights) on the symptoms.

Table 2. Regression coefficients and standard deviations for the association between QOL and the estimated clusters of symptoms in the EORTC and CTCAE data sets. Significance levels are reported after multiple testing correction. *** significant at $p < 0.001$, ** significant at $p < 0.01$, and * significant at $p < 0.05$.

		General symptoms	Gastro-intestinal	Urinary	Vaginal	Nausea
EORTC	3M	−12.64 (1.01) ***	−2.36 (0.99) *	1.06 (0.94)	0.77 (1.01)	−1.61 (0.97)
	6 M	−14.11 (0.94) ***	−1.15 (0.85)	1.92 (0.91)	0.49 (0.88)	−3.45 (0.9) ***
	9 M	−14.77 (1.04) ***	−2.96 (1.07) **	2.86 (0.93) **	−0.89 (1.10)	−3.33 (0.88) ***
	12 M	−15.77 (1.02) ***	−1.54 (1.02)	1.44 (1.06)	−0.18 (1.19)	−0.35 (1.02)
	18 M	−15.17 (0.91) ***	−0.32 (0.91)	−0.28 (1.01)	−0.16 (0.98)	−4.9 (0.83) ***
	24 M	−16.21 (0.98) ***	−0.70 (0.88)	1.24 (0.93)	−1.19 (0.96)	−1.31 (0.89)
CTCAE	3M	−6.95 (1.23) ***	−1.22 (1.12)	1.17 (1.01)	0.61 (1.09)	–
	6 M	−10.56 (1.09) ***	−1.34 (1.12)	−0.33 (1.24)	0.78 (1.17)	–
	9 M	−7.89 (1.17) ***	−2.9 (1.12) *	−3.24 (1.29)	−0.31 (1.31)	–
	12 M	−10.93 (1.10) ***	−1.91 (1.05)	−0.69 (1.27)	0.99 (1.06)	–
	18 M	−12.42 (1.15) ***	−3.09 (1.30) *	−0.15 (1.08)	2.61 (1.13)	–
	24 M	−11.10 (1.11) ***	−2.76 (1.11) *	0.19 (1.22)	0.58 (1.24)	–

understand which clusters have the major contribution in decreasing QOL. However, symptoms with a later onset (especially urinary) [66,67] are not captured in this analysis.

Furthermore, factors such as medication after treatment and/or development of non-cancer related diseases after treatment may impact QOL or clustering of symptoms. However, post-treatment information about medication or other diseases was not collected in the EMBRACE I study, and the impact or bias of these factors could therefore not be evaluated in this analysis.

Lastly, the clinical application of these findings remains challenging. For example, the prevalence of the fatigue cluster in oncology has been reported several times [47–49,51] and attempts to assess the general cluster in routine follow-up have been proposed [68–70] together with various strategies to address this cluster in the clinic [15,22]. The weights of the symptoms in each cluster discussed in Section 3 provide motivation to explore further the underlying causes of co-occurring symptoms and to explore holistic approaches to the management of general symptoms, e.g., cognitive-behavioral interventions. Lastly, informing patients about these results could help the patients to be better prepared for the symptoms they might have and thus to cope better with them.

Future work

Future work should be directed to developing a method able to directly account for the time patterns of symptom clusters. Additionally, associations between the symptom clusters and treatment parameters have not yet been investigated for this data set and such analysis could also benefit by the results from the EFA. Lastly, future analysis could be directed to identify patient-specific risk factors for certain clusters that in turn are relevant for overall health and QOL [71]. To conclude, this work shows that LACC survivors experience a variety of symptoms that tend to occur together in clusters of symptoms. The use of symptom clusters in addition to individual symptoms may have value for the evaluation of morbidity outcomes in clinical trials. e.g., Accounting for symptom co-occurrence in a total toxicity burden score might be more effective in comparing the overall treatment burden of different treatment approaches than in comparing individual symptoms. Total toxicity burden scores such as those presented in [72,73] that include information on symptom severity and timing can indeed be even more effective when informed by clusters of symptoms with major impact on QOL.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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