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Symptom clusters in advanced cancer patients: an empirical comparison of statistical methods

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Abstract

Purpose: To investigate the consistency of symptom cluster composition in advanced cancer patients using different statistical methodologies for all patients across five primary cancer sites, and to examine which clusters predict functional status, a global assessment of health and global quality of life.

Methods: Principal components analysis and exploratory factor analysis (with different rotation and factor selection methods) and hierarchical cluster analysis (with different linkage and similarity measures) were used on a dataset of 1562 advanced cancer patients who completed the EORTC QLQ-C30.

Results: Four clusters consistently formed for many of the methods and cancer sites: tense-worry-irritable-depressed (emotional cluster); fatigue-pain; nausea-vomiting; and concentration-memory (cognitive cluster). The emotional cluster was a stronger predictor of overall quality of life than the other clusters. Fatigue-pain was a stronger predictor of overall health than the other clusters. The cognitive cluster and fatigue-pain predicted physical functioning, role functioning, and social functioning.

Conclusions: The four identified symptom clusters were consistent across statistical methods and cancer types, although there were some noteworthy differences. Statistical derivation of symptom clusters is in need of greater methodological guidance. A psychosocial pathway in the management of symptom clusters may improve quality of life. Biological mechanisms underpinning symptom clusters need to be delineated by future research. A framework for evidence-based screening, assessment, treatment, and follow-up of symptom clusters in advanced cancer is essential.

Introduction

Advanced cancer patients experience symptom clusters (SCs), defined as groups of two or more concurrent symptoms that co-occur independently of other clusters, which may or may not share a common etiology (1-3). Several reviews have highlighted the predictive ability of SCs in compromising patient outcomes like quality of life (QOL) and functional status, often in a multiplicative rather than additive manner (4-7). Although identification of SCs can result in effective symptom management interventions, there is no accepted 'best practice' approach for identifying SCs(4). The large number of statistical methods that have been used to discover cluster composition, with little guidance regarding justification of choice of method ((8, 9) are two exceptions), is a major barrier to the conceptual validity and clinical utility of statistically-derived SCs (8, 10).

Some studies involving advanced cancer patients have directly compared the cluster compositions produced by different statistical approaches (11-13). Aktas and colleagues (11) found that cluster composition was consistent across different approaches, whereas Chen and colleagues (13) found that greater similarity in results was produced by hierarchical cluster analysis (HCA) and principal components analysis (PCA) than between these methods and exploratory factor analysis (EFA). Furthermore, in research to date the patient samples used have either been homogeneous with respect to primary cancer site (e.g., 14, 15), or heterogeneous but of insufficient size (e.g., 12, 16) to allow comparison of cluster composition between sites.

Dong et al (4) reported that some studies had empirically examined predictors and outcomes of SCs, but that this was done in a piecemeal fashion and without guidance from an

over-arching framework. Examples of relevant frameworks are Wilson and Cleary's (17) model and the theory of unpleasant symptoms (18), both of which posit that physiological factors cause symptoms, which in turn influence functional status. Wilson and Cleary further propose that functional status in turn influences general health perceptions and impacts on overall QOL. Thus symptoms are posited to determine QOL as mediated by functional status (e.g., physical, social and role) and perceived health.

The present study had three broad aims. The first was to examine the extent to which different statistical methodologies differ in the cluster composition solutions they produce. To this end we report the results of 150 variants of PCA, EFA and HCA, using data from the European Organisation for the Research and Treatment of Cancer QOL Questionnaire (EORTC QLQ-C30) (19). Our second aim was to examine the consistency of SC composition across five primary cancer sites. Our third aim was to determine which SCs predict functional status, a global assessment of health and global QOL, and whether there is evidence for the mediating associations posited by the Wilson and Cleary model.

Method

Data

All analyses described below were conducted on a pooled data set obtained from several international sources, covering a range of study types and countries (Table 1). Only patients with advanced cancer (mean age 61.6 years, range 18-90) and complete QLQ-C30 data were included in the analysis (6 randomised controlled trials, 9 observational/validation studies). If a patient completed the QLQ-C30 on more than one occasion, an on-treatment observation was included in the analysis if available (because we expect patients receiving treatment to experience a range of problems). If no on-treatment observation was available, a follow-up

observation was included, and in the absence of both a pre-treatment observation was used. The total number of patients in the data set for analysis was 1562. Demographic, disease and treatment variables are shown in Table 1.

[Table 1 here]

Instrument

The EORTC QLQ-C30 version 3 (19)comprises 30 items that form five functioning sub-scales, three multi-item symptom sub-scales, five single-item symptoms, a financial difficulties item, and a global health and QOL sub-scale. For the functioning and symptom items, responses are made on a four-point scale (1 = "Not at all", 2 = "A little", 3 = "Quite a bit", 4 = "Very much"), and for the global health and QOL items responses are made on a seven-point scale (1 = "Very poor" through 7 = "Excellent"). Items 1-5 have no specified recall period, whereas items 6-30 have a recall period of the past week. Using this instrument for the present purposes has several benefits, including: a range of symptoms relevant to advanced cancer patients; and items assessing functional status, health and QOL. Of note, the inclusion of three fatigue items allowed us to examine how cluster composition changes with slight changes to item content. We dealt with these items in five ways: (1) as three separate items, all included; (2) as a mean of the three items; (3) Item 10 only; (4) Item 12 only; and (5) Item 18 only.

Physical functioning (Items 1-5), role functioning (Items 6, 7) and social functioning (Items 26, 27) were scored as the mean of the relevant items. Global health and QOL were analysed as separate variables.

Statistical methods

1. Consistency of cluster composition

Kim, Abraham, and Malone (8) described several statistical methods that have been employed to establish SC composition in advanced cancer: (1) principal components analysis (PCA); (2) common factor analysis; (3) cluster analysis; (4) latent class analysis; and (5) structural equation modelling. We employed these methods with two exceptions: latent class analysis classifies observations rather than variables, and is thus not directly comparable to principal components and factor analysis (although it can be compared to cluster analysis, which can produce clusters of observations or variables; and structural equation modelling requires a priori specification of a theoretical model, which we argue is inappropriate for SC research at this stage. Skerman et al (9) recommended the use of factor analysis, which unlike PCA and cluster analysis is based on a theoretical model, thus aligning with the view of symptom clusters as having biopsychosocial mechanisms. Because there is no resolution regarding whether symptoms in a cluster require a common aetiology, and because the other methods have been widely used, here we examined all three.

To address Aims 1 and 2, the following methods of statistically identifying clusters (intended to be indicative of past research rather than exhaustive) were employed:

(1) PCA (SAS v9.3): only oblique rotation methods (direct oblimin and promax) were used, as clusters were expected to have non-zero correlations with one another, making orthogonal rotation inappropriate (9). The number of factors extracted was determined using a scree plot, parallel analysis and the minimum average partial test (20) (the latter two are seldom used in

symptom cluster research, but we deemed it worthwhile comparing them). We therefore performed a maximum[1] of 30 (2 rotation methods × 3 factor selection methods × 5 methods for handling fatigue) PCAs.

(2) Exploratory factor analysis (EFA; SAS v9.3): the same rotation and factor selection methods were used as for PCA. The principal axis factoring method of extraction was used (the other most common method, maximum likelihood, assumes normally distributed data, which we expected our data to violate and we did not consider) (9). We therefore performed a maximum of 30 (2 rotation methods × 3 factor selection methods × 5 methods for handling fatigue) EFAs.

(3) Cluster analysis (SPSS v21): the hierarchical agglomerative method[2] was used to examine clusters of variables(21). Three linkage methods were used: single (nearest neighbour); average (between), and; average (within). Three measures of similarity were used: Euclidean distance; cosine, and; Pearson correlation. Previous research has also drawn attention to the different similarity thresholds used to determine what clusters form (11, 13), typically on the basis of correlation. Because SPSS presents similarity for some of the methods employed here as rescaled distances rather than correlations, we employed two arbitrary thresholds for the interpretation of clusters: one lower (rescaled distance < 10) and one higher (rescaled distance < 15). We therefore performed a maximum of 90 (3 linkage × 3 similarity measures 2 thresholds × 5 fatigue scores) HCAs.

[1] This is a maximum because different factor selection methods may produce the same number of factors, which results in identical factor solutions. For example, if all three methods suggest the same number of factors, only 10 PCAs are required. If any two are the same, only 20 PCAs are required.

[2] K-means cluster analysis has been used in the SC literature but this requires a priori specification of the number of clusters, so was not considered in the present analysis, which is more exploratory. This is not to say that K-means cluster analysis is inappropriate for SC research.

Each analysis was conducted on the total sample and subsets representing the five primary cancers with sufficiently large numbers (breast, colorectal, lung, myeloma and prostate), giving a total of 6×(30+30+90)=900 cluster solutions.

Internal consistency was assessed for each cluster and each primary site using Cronbach α.

2. Symptom clusters as predictors of self-reported functioning, health and QOL

The degree to which SCs predicted physical, role and social functioning, and global health and QOL (Aim 3), was assessed using path analysis (Mplus v6) with maximum likelihood estimation and robust standard errors, which take into account non-normality (22). We operationalised SCs as the mean of the symptom scores for a given cluster. If substantially different cluster compositions were observed in the first part of the analysis, separate path analyses featuring these alternative clusters as predictors were conducted. We controlled for treatment status (two dummy variables with pre-treatment as reference), age and sex (except for breast and prostate).

Figure 1 shows a simplified graphical representation of the path model. The functioning domains were modelled as potential mediators of the associations between SCs and global health and QOL, and health was modelled as a potential mediator of the associations between SCs and functioning with QOL. All direct and indirect paths were estimated.

Results

All symptoms had prevalence (item score > 1) greater than 15%, except vomiting in the myeloma sub-sample, so all were retained for all analyses.

1. Consistency of cluster composition

We first present an exemplar analysis in detail, followed by a summary of all 900 separate combinations. The exemplar comprises a PAF (with oblimin rotation and number of factors determined by parallel analysis) and a HCA with single linkage and Euclidean distance used as the similarity measure (with both high and low thresholds examined), both conducted on the total sample.

The Kaiser measure of sampling adequacy was high (>.95) for all PCA and PAF analyses. For the exemplar, parallel analysis and MAP suggested the extraction of three factors. The scree plot suggested one or possibly three factors.

Factor loadings are shown in Table 3 for the three factors: (1) fatigue (where the three fatigue items had the highest loadings), pain, appetite, diarrhoea, and dyspnoea; (2) the emotional items; and (3) nausea, vomiting and constipation. Memory, concentration and insomnia had low loadings on all factors.

The dendrogram (Figure 2) illustrates the HCA results. Using the lower threshold, three clusters were observed: (1) emotional; (2) cognitive; and (3) nausea and vomiting (we considered the fatigue items as a unit rather than a cluster). Using the higher threshold, two clusters were observed: (1) the combination of the emotional and cognitive clusters; and (2) nausea, vomiting and constipation. None of the other symptoms (fatigue, dyspnoea, pain, appetite, sleep and diarrhoea) formed clusters within these thresholds. Note that there was little difference between

the distance at which the emotional/cognitive cluster formed and where a fatigue and pain cluster formed, although the latter was right on the threshold and the former below it. This highlights the sometimes arbitrary nature of the decision regarding the level of similarity that defines clusters, and suggests that a better approach, where possible, is to select clusters on the basis of large discontinuities rather than arbitrary thresholds. Using this principle, the first (three-cluster) solution may be more appropriate.

Table 4 summarises the results of all analyses. This table shows the number of times each cluster occurred exclusively (e.g., tense, worried, irritable and depressed only) and the total number of times each cluster occurred (e.g., any cluster containing tense, worried, irritable and depressed). Exclusive clusters occurred more frequently for HCA than PCA or EFA. The emotional and nausea/vomiting clusters were the most common, followed by the fatigue/pain and cognitive clusters. In several instances the emotional and cognitive items formed a single cluster, and nausea and vomiting clustered with constipation and occasionally lack of appetite. Dyspnoea, insomnia, and diarrhoea did not cluster consistently with any other symptoms.

A noteworthy result is that when the "weak" item was used to represent fatigue it tended to cluster with appetite loss, whereas when "rest" or "tired" were used they tended to cluster with pain.

2. Symptom clusters as predictors of functioning and QOL

Because of their consistency across cancer sites, we included the same clusters (emotional, nausea/vomiting, fatigue/pain and cognitive) as predictors of functioning and QOL for the total

and cancer site sub-samples. Although some clusters were highly correlated, we assessed multicollinearity using the variance inflation factors, all of which were acceptable

The results of the path analysis on the total sample are shown in Table 5. The emotional cluster predicted social functioning and overall QOL. The fatigue/pain cluster predicted the three aspects of functioning, health and QOL. The cognitive cluster predicted the three aspects of functioning. The nausea/vomiting cluster weakly predicted all outcomes. The emotional, fatigue/pain and cognitive clusters all predicted QOL indirectly via social functioning and health. The fatigue/pain and cognitive clusters also predicted QOL indirectly via role functioning and health.

Table 6 summarises the results of the path analyses conducted separately on the five cancer sites. The most robust result is that fatigue/pain strongly predicted physical, role and social functioning for all sites, and also predicted health for all sites except prostate, and QOL for breast cancer patients. The emotional cluster was the only other strong predictor of QOL (for lung). The cognitive cluster predicted functioning for breast cancer patients, and social functioning for colorectal and lung cancer patients.

Discussion

To our knowledge, this is the first study to examine the consistency of SC composition in patients with advanced cancer across a number of primary cancer sites using different statistical methods, and to explore their associations with QOL and functioning. Our results align with previous studies that have observed consistency in cluster composition across statistical

techniques (11, 13-15) and with reviews of SCs in advanced cancer patients (4, 5, 7), extending this research by demonstrating a strong degree of consistency across primary cancer sites. Notwithstanding this consistency, some methods may be preferred for theoretical reasons; Skerman et al provide guidance in this regard (9).

We found four core sets of symptoms that clustered with relative consistency across methods and cancer sites: tense-worried-irritable-depressed (emotional), nausea-vomiting, concentration-memory (cognitive) and fatigue-pain. All but fatigue-pain represent sub-scales in the established structure of the QLQ-C30 (19), highlighting that the SC concept is closely related to some of the constructs that were built into this instrument in its development.

Trouble sleeping, dyspnoea and diarrhoea did not cluster consistently with any other symptoms. Appetite loss was observed in some analyses to cluster with nausea-vomiting and in others with fatigue. Specifically, when fatigue was represented by the "weak" item, it tended to be associated with appetite, but when represented by "rest", "tired", all three fatigue items or their mean, it was more often associated with pain, and appetite tended to cluster with nausea-vomiting. This illustrates how cluster composition can be determined by subtle differences in symptom representation. Advanced cancer patients have been shown to causally relate the symptoms of fatigue, loss of appetite and weight loss (23), yet the experience of fatigue has been proposed to have three distinct transitional stages, from tiredness to fatigue to exhaustion/weakness (24). Similarly, although dyspnoea did not consistently cluster with other symptoms in our analyses, it has been associated with anxiety in other research (25-27). Anxiety is not explicitly represented in the QLQ-C30. We speculate that if anxiety had been explicitly

represented in our dataset, the emotional cluster composition may have also included anxiety and dyspnoea.

Constipation often clustered with nausea-vomiting in the breast, lung, and prostate sub-scales. The cause of nausea-vomiting in advanced cancer patients is often central (from the brain), e.g., due to biochemical disturbances and treatment (28). Medications used for chemotherapy induced nausea may be constipating which may contribute to this clustering. Constipation in advanced cancer patients shares some of these causes, but also has local causes, e.g., gut motility or pelvic floor dysfunction (29, 30). Diarrhoea, in contrast, is commonly associated with some treatments and is largely an acute symptom in advanced cancer patients (31). This may explain why constipation often clustered with nausea-vomiting, whereas diarrhoea did not cluster consistently with any symptom.

The strongest predictor of QOL in this sample was the emotional cluster, highlighting the importance of addressing psychosocial aspects in SC management. In addition, the fatigue-pain cluster strongly predicted health and all three aspects of functioning for every cancer site, consistent with previous research (32-35). We found weak associations between depression and fatigue-pain across cancers, despite previous findings that fatigue-pain-depression were associated with reduced physical function and co-occurred in clinical practice (33). Furthermore, previous studies suggest links between emotional symptoms, fatigue and pain, specifically: association between depression and severity/burden of multiple physical symptoms (36); cognitive-behavioural intervention efficacy in treating pain, fatigue, and sleep disturbance (37, 38), and; association between pro- and anti- inflammatory cytokine genes and a cluster of pain, fatigue, sleep, disturbance, and depression (39).

Recent literature has highlighted the role of systemic inflammation and pro-inflammatory cytokines involved in the pathophysiology of associated cancer symptoms such as fatigue (40) and pain (32, 41), consistent with the "biological factors" in Wilson and Cleary's model (17) and the "influencing factors" in the theory of unpleasant symptoms (18) . Although Aktas et al (34) suggested the fatigue–pain cluster is likely influenced by cancer site, we observed it across cancer sites, supporting the role of pro-inflammatory cytokines as a common underlying mechanism. Although pharmacologic treatments have been effective in improving cancer-related fatigue in patients with advanced cancer (42), the strength of the relation between systemic inflammation and SCs needs to be examined further within the context of trials exploring interventions targeted to pro-inflammatory cytokine pathways.

The clinical relevance of our results is manifold. Knowledge of SCs may allow oncologists and palliative care teams to provide more targeted and higher-quality care. Identification of patient subgroups with higher cluster severity may be useful in targeting high-risk individuals for intervention. Few interventions to date have specifically targeted SCs (37, 43). Given the association of the emotional and fatigue-pain clusters with QOL and functioning, separate clinical pathways for psychosocial and fatigue-pain management may be warranted. Interventions involving physical activity (44, 45) and systematic self-monitoring of physical symptoms (46) should be included in a fatigue-pain management pathway for advanced cancer patients, yet the interaction between pain and fatigue warrants further investigation. Furthermore, the observed association between the cognitive cluster and functioning is important. Although cognitive failure (47) and cognitive disorders (48) are highly prevalent in advanced cancer patients, particularly acute cognitive issues such as delirium (49), it is a neglected aspect of clinical care and limited inventions exist to improve these symptoms at present(50, 51).

The QLQ-C30 differs from other instruments that have been used in previous research in that its item phrasing and response scale ("Not at all"-"Very much") do not clearly represent a particular dimension (e.g., severity, frequency, importance, distress) (8, 10, 52). How respondents interpreted the QLQ-C30 questions is unknown, and more generally the issue of what factors respondents consider when answering such items need to be empirically addressed (53).

To date, quantitative studies in the field of SCs have yielded a lack of consistency in conceptual, methodological and statistical approaches, which makes drawing firm conclusions and translating findings into clinical practice difficult (8, 54). Our study attempted to resolve some of the methodological inconsistencies in the literature using a large heterogeneous sample, however, further research regarding the clinical basis for confirmatory modelling for patient outcomes is required. Causal modelling of the kind reported here may be of particular value. For example, Gundy et al tested several alternative models for the QLQ-C30, including some that estimated structural paths from symptom burden to functioning and QOL (55). Future avenues for research include examining the effect of other variables on the composition and predictive nature of SCs, such as treatment, country, and a spiritual domain as a moderator of patient-reported outcomes. Inconsistency in how these variables were assessed the pooled data set used here precluded thorough control of these variables. In particular, type and stage of treatment may partly determine symptom cluster composition. This limitation of the present research is worthy of further attention.

In conclusion, we found four robust clusters in a large sample of advanced cancer patients, although the practice of statistically deriving SCs should make use of appropriate methodological guidance. There was a significant association between distinct SCs and QOL and

function. Knowledge of cluster composition and their associations with QOL and function is vital in the management of SCs to improve patient outcomes. A psychosocial pathway in the management of SCs may improve QOL.

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Table 1. Number of patients with each primary cancer site

	Frequency				%
	Pre-treatment	On treatment	Follow-up	Total	
	n=427	n=715	n=420	n=1561	
Sex					
Male	254	339	249	842	54
Female	172	376	171	719	46
Primary cancer site					
Colorectal	21	204	36	261	17
Breast	56	95	99	250	16
Myeloma	46	63	82	191	12
Lung	57	94	34	185	12
Prostate	57	8	11	176	11
Oesophagus/stomach	35	89	0	124	8
Other	43	19	54	116	8
Gynaecological	15	60	0	75	5
Genito-urinary	6	39	0	45	3
Head and neck	31	1	2	34	2
Liver/bile/pancreas	17	11	0	28	2
Sarcoma	0	26	0	26	2
Leukaemia	17	0	0	17	1
Malignant melanoma	5	3	0	8	1
Missing	-	-	-	26	2
Treatment type					
Chemotherapy				794	
Radiotherapy				427	
Analgesics				186	
Surgery				32	
Other/none				11	
Country					
Norway	213	18	141	372	24
USA	46	63	79	188	12
Canada	0	174	0	174	11
UK	0	168	4	172	11
Sweden	18	5	142	165	11
Australia	22	138	0	160	10
Greece	72	48	0	120	8
Spain	10	6	28	44	3
Brazil	42	0	0	42	
Turkey	0	13	23	36	2
France	0	31	1	32	2
Germany	0	17	2	19	1
Taiwan	0	17	0	17	1
New Zealand	4	12	0	16	1
Italy	0	5	0	5	0

Table 2. Items of the EORTC QLQ-C30

Symptoms	8. Were you short of breath? 9. Have you had pain? 10. Did you need to rest? 11. Have you had trouble sleeping? 12. Have you felt weak? 13. Have you lacked appetite? 14. Have you felt nauseated? 15. Have you vomited? 16. Have you been constipated? 17. Have you had diarrhea? 18. Were you tired? 20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television? 21. Did you feel tense? 22. Did you worry? 23. Did you feel irritable? 24. Did you feel depressed? 25. Have you had difficulty remembering things?
Physical functioning	1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase? 2. Do you have any trouble taking a long walk? 3. Do you have any trouble taking a short walk outside of the house? 4. Do you need to stay in bed or a chair during the day? 5. Do you need help with eating, dressing, washing yourself or using the toilet?
Role functioning	6. Were you limited in doing either your work or other daily activities? 7. Were you limited in pursuing your hobbies or other leisure time activities?
Social functioning	26. Has your physical condition or medical treatment interfered with your family life? 27. Has your physical condition or medical treatment interfered with your social activities?
Health	29. How would you rate your overall health during the past week?
Quality of life	30. How would you rate your overall quality of life during the past week?

Table 3. Factor loadings for the exploratory factor analysis with principal axis factor extraction and oblimin rotation for the total sample. Loadings in bold represent the highest loading for each item, provided it was greater than 0.4 (56).

Item	**Factor 1**	**Factor 2**	**Factor 3**
rest	**0.94**	-0.03	-0.09
weak	**0.83**	0.03	-0.00
tired	**0.81**	0.06	-0.04
pain	**0.55**	0.13	0.04
appetite	**0.45**	0.01	0.36
diarrhoea	**0.34**	0.04	0.28
worried	-0.00	**0.92**	-0.12
tense	0.04	**0.82**	0.00
depressed	0.06	**0.77**	0.02
irritable	-0.05	**0.73**	0.13
vomiting	0.00	0.02	**0.81**
nausea	0.15	-0.05	**0.75**
constipation	-0.09	0.11	**0.61**
concentration	0.23	0.36	0.28
sleep	0.18	0.33	0.20
memory	0.13	0.32	0.33

Table 4. Summary of cluster composition for the 150 separate analyses for the total sample and five primary cancer sites. The # clusters column shows the number of times (out of 150) the items clustered, and the # exclusive clusters column shows the number of times the items formed a cluster without any other items. Cronbach α is shown for each primary cancer site and cluster.

Cluster	Primary site	Cluster composition	# clusters	# exclusive clusters	α
1. Emotional	All	Tense, worried, irritable, depressed	**148**	**50**	.90
	Breast	Tense, worried, irritable, depressed	**147**	**78**	.92
	Colorectal	Tense, worried, irritable, depressed	**149**	**92**	.89
		+ concentration	**56**	**25**	.87
	Lung	Tense, worried, irritable, depressed	**135**	**16**	.87
		+ concentration, memory	**91**	**17**	.88
		+ concentration, memory, sleep	**71**	**12**	.89
	Myeloma	Tense, worried, irritable, depressed	**148**	**18**	.85
		+ concentration, memory	**122**	**37**	.86
	Prostate	Tense, worried, irritable, depressed	**132**	**57**	.94
2. Nausea/vomiting	All	Nausea, vomiting	**148**	**55**	.84
		+ constipation	**73**	**31**	.77
	Breast	Nausea, vomiting	**150**	**15**	.91
		+ constipation	**135**	**57**	.85
	Colorectal	Nausea, vomiting	**146**	**59**	.77
		+ appetite	**83**	**34**	.75
	Lung	Nausea, vomiting	**106**	**13**	.76
		+ constipation	**64**	**32**	.67
	Myeloma	Nausea, vomiting	**94**	**14**	.50
	Prostate	Nausea, vomiting	**124**	**16**	.82
		+ constipation	**92**	**26**	.90
		Vomiting, constipation	**111**	**13**	.68
3. Fatigue & pain	All	Fatigue, pain	**92**	**22**	.88
	Breast	Fatigue, pain	**95**	**22**	.89
	Colorectal	Fatigue, pain	**77**	**19**	.86
	Lung	Fatigue, pain	**94**	**15**	.85
	Myeloma	Fatigue, pain	**98**	**32**	.85
	Prostate	Fatigue, pain	**77**	**51**	.87
4. Cognitive	All	Concentration, memory	**83**	**35**	.77
	Breast	Concentration, memory	**96**	**58**	.84

	Colorectal	Concentration, memory	**59**	**18**	.61
	Lung	Concentration, memory	**115**	**22**	.74
	Myeloma	Concentration, memory	**138**	**16**	.70
	Prostate	Concentration, memory	**105**	**19**	.83

Table 5. Standardised regression parameter estimates for the path analysis conducted on the total sample. For all cluster variables, a higher score means worse symptoms. For the functioning, health and quality of life variables, a higher score means better functioning, health or quality of life.

Cluster	Physical	Role	Social	Health	QOL
Emotional	0.00	0.05	0.13**	-0.02	-0.06**
Nausea/vomiting	-0.01	-0.00	0.01	0.04	-0.01
Fatigue/pain	-0.62**	-0.72**	-0.48**	-0.33**	-0.08*
Cognitive	-0.19**	-0.07*	-0.24**	0.05	0.05

* p <. 05, ** p < .01

Table 6. Summary of the results of the path analyses for the primary cancer site sub-samples. The clusters listed were those that were statistically significant ($p<.05$), and those flagged with an asterisk had comparatively large standardised parameter estimates, indicating strong associations).

	Outcome				
Primary site	**Physical**	**Role**	**Social**	**Health**	**QOL**
Breast	FP*, Cog	FP*, Cog	FP*, Cog	FP*, NV	FP
Colorectal	FP*	FP*	FP, Cog	FP*	-
Lung	FP, Cog	FP*	FP, Emo, Cog	FP	Emo
Myeloma	FP*	FP*	FP*	FP, Emo	-
Prostate	FP*	FP*, NV	FP*, Emo, Cog	-	-

FP = fatigue/pain; Cog = cognitive; Emo = emotional; NV = nausea/vomiting

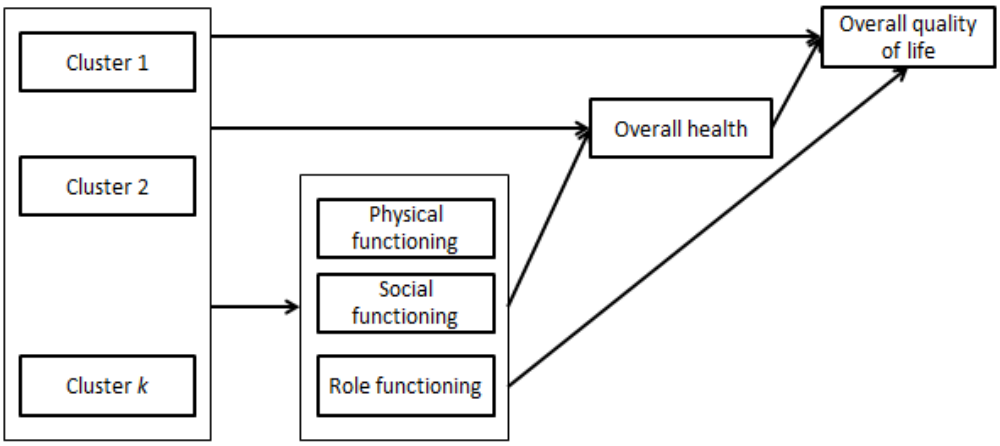

Figure 1. A simplified representation of the model tested using path analysis. Although not represented here, all direct and indirect paths from clusters to functioning to overall health to overall quality of life were estimated.

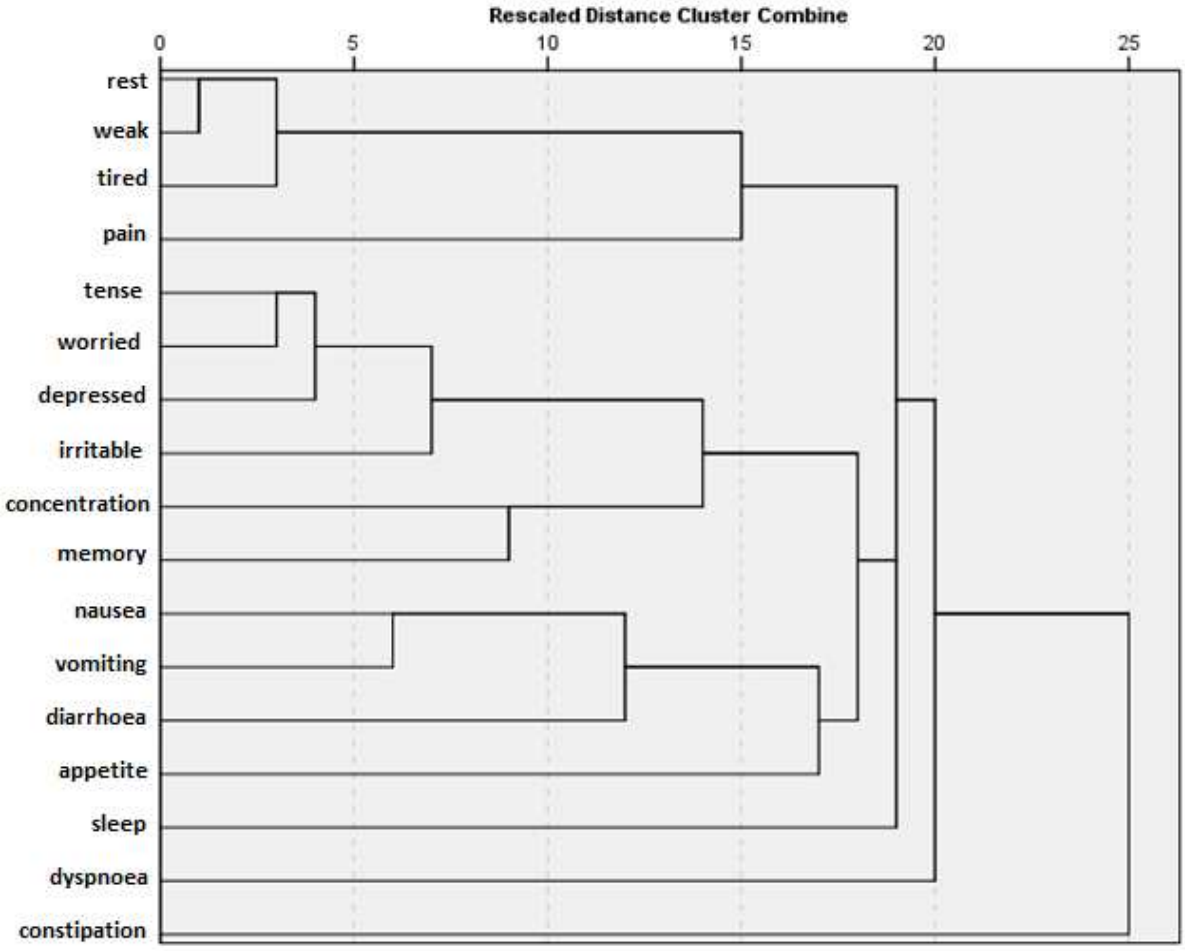

Figure 2. Dendrogram illustrating the results of the hierarchical cluster analysis. The distance at which the branches join indicates similarity (shorter branch represents greater similarity).