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Latent Transition Analysis of the Symptom Experience of Cancer Patients Undergoing Chemotherapy

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Abstract

Background: Symptom clusters reflect the person's experience of multiple co-occurring symptoms. While a variety of statistical methods are available to address the clustering of symptoms, latent transition analysis (LTA) characterizes patient membership in classes defined by the symptom experience and captures changes in class membership over time.

Objectives: The purposes of this paper are to demonstrate the application of LTA to cancer symptom data and to discuss the advantages and disadvantages of LTA relative to other methods of managing and interpreting data on multiple symptoms.

Methods: Data from a total of 495 adult cancer patients who participated in randomized clinical trials of two symptom management interventions were analyzed. Eight cancer- and treatment-related symptoms reflected the symptom experience. LTA was employed to identify symptom classes and evaluate changes in symptom class membership from baseline to the end of the interventions.

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Results: Three classes, “A (mild symptoms),” “B (physical symptoms),” and “C (physical & emotional symptoms),” were identified. Class A patients had less comorbidity, better physical and emotional role effect, and better physical function than the other classes. The number of symptoms, general health perceptions, and social functioning were significantly different across the three classes and were poorest in Class C. Emotional role functioning was poorest in Class C. Older adults were more likely to be in Class B than younger adults. Younger adults were more likely to be in Class C ($p < .01$). Among patients in Class C at baseline, 41.8% and 29.0%, respectively, transitioned to Classes A and B at the end of the interventions.

Discussion: These results demonstrate that symptom class membership characterizes differences in the patient symptom experience, function and quality of life (QoL). Changes in class membership represent longitudinal changes in the course of symptom management. LCA overcomes the problem of multiple statistical testing that separately addresses each symptom.

Keywords

cancer patients; latent class analysis; latent transition analysis; precision health; symptom management; symptom profile

Patients with chronic conditions, especially advanced cancer, often suffer from multiple symptoms that require intensive management. They report an average of more than 10 concurrent symptoms that originate from the disease or the side effects of cancer treatments (Miaskowski, 2006; Miaskowski, Dodd, & Lee, 2004;). Symptoms are often interrelated, and the inter-relationships may have multiple behavioral, treatment-related, and biological causes. From the perspective of precision health, the patterns among symptoms may be predicted by “omic,” lifestyle, and sociodemographic, and environmental factors.

Kelly and colleagues documented the relationships between inflammatory, immune, and hormonal markers, and cancer-related symptom clusters by reviewing 14 related studies (Kelly et al., 2016). They emphasized the importance of conducting longitudinal studies to validate the relationships between symptom clusters and biomarkers and investigate the biological mechanisms that must be understood to mitigate cancer-related symptoms. This approach requires appropriate statistical methods to identify cancer patients with similar symptom clusters and to track changes in their symptom profiles following symptom management interventions.

Dodd, Miaskowski, and Lee (2004) defined a symptom cluster as three or more co-occurring symptoms, while Kim and colleagues (2005) described clusters as two or more co-occurring symptoms that may or may not share the same etiology. Miaskowski and colleagues (2006) emphasized the importance of symptom cluster research to symptom management and proposed that symptom clusters may be related to functional status, QoL, and demographic and clinical characteristics. However, Barsevick, Whitmer, Nail, Beck, and Dudley (2006) warned of the need to protect against bias from sample selection and the importance of the timing of symptom measures. Addressing these important research areas requires sophisticated approaches to symptom cluster analysis.

There are two types of methods for identifying and analyzing symptom clusters. The first group consists of ways that categorize symptoms, while the second group includes methods that categorize patients based on their experiences with similar symptom profiles (Miaskowski, Aouizerat, Dodd, & Cooper, 2007). Exploratory and confirmatory factor analyses are examples of the first group of methods (Baggott, Cooper, Marina, Matthay, & Miaskowski, 2012; Cleeland, Mendoza, Wang, Chou, & Engstrom, 2000; Miaskowski et al., 2007). Although these methods are frequently used, they are limited to cross-sectional applications and do not permit the evaluation of patient symptom experiences over time. For example, when evaluating the effects of symptom management interventions, symptoms may have high correlations immediately before the intervention, but specific symptoms may not move in parallel with others over time; some may be ameliorated; others may continue or even increase. Symptom clusters may also differ over time based on the treatment process or cancer location. For example, Kim and Abraham (2008) identified two symptom clusters. A psychoneurological cluster and an upper-gastrointestinal cluster presented differently before and after chemotherapy or radiotherapy. As a result of two symptom management interventions (Sikorskii et al., 2007), lung-cancer patients had significantly different symptom patterns compared to those with cancer at other sites and their symptom patterns changed over the course of symptom management intervention. Traditional factor analysis approaches are available to investigate correlations among symptoms over time, but are not able to track individual trajectories of symptom profiles over phases of the disease or treatment that address these concerns.

Some of the methods for grouping patients according to symptoms also deal with cross-sectional data. For example, cluster analysis classifies patients into “like” groups. In several symptom cluster studies (Miaskowski et al., 2006; Walsh & Rybicki, 2006), investigators used cluster analysis to measure distances from one subject to other subjects based on their symptom experiences. These studies address the severity of symptoms, and there are subgroups of patients with a high similarity of cross-sectional symptom profiles. Like factor analysis, cluster analysis uses continuously measured symptoms, but is limited in the use of measures of binary (e.g., presence of symptom) or ordinal (e.g., mild, moderate, and severe) levels of measurement.

Latent class analysis (LCA) can be classified as both the first and second type of methods (Collins & Lanza, 2013; Lanza, Flaherty, & Collins, 2003) because it groups symptoms into clusters and also classifies patients into groups using their symptom profiles. The underlying premise is the existence of an underlying unobserved (latent) variable. Based on correlations among multiple symptoms, LCA provides the conditional probability of the risk of the occurrence of moderate or severe symptoms in class membership which is called “response probability.” A different set of conditional probabilities (i.e., posterior probability) describes the likelihood that each patient belongs to a particular class (group of participants) given their symptom reports. Patients are classified based on the highest values of this posterior probability. These analyses account for multiple symptoms within groups of patients, and latent class membership represents a concise summary of the patient symptom experience.

Latent transition analysis (LTA) extends the LCA framework to handle sequential changes in latent class in longitudinal data (Collins & Lanza, 2013; Lanza et al., 2003). It is used to

estimate the transition probability of shifting one latent class to another over time and permits assessments of how likely patient symptom experience change after treatment. This approach overcomes the restrictions of factor analysis and cluster analysis to cross-sectional correlations or symptom profiles. While consistent factor loadings or clusters are not available over time, LTA can produce identical latent classes memberships across different timepoints by constraining response probabilities. Using LTA, we can track whether one individual with a symptom profile at baseline keeps the same profile or moves to another profile at later observations. Schmiede, Meek, Bryan, and Petersen (2012) proposed the application of latent variable mixture modeling, including LCA and LTA, to classify individuals with heterogeneous outcomes in nursing research and Conley and colleagues (Conley, Jeon, Proctor, Sandler, & Redeker, 2018; Conley, Proctor, Jeon, Sandler, & Redeker, 2017) analyzed symptom clusters among inflammatory bowel disease cross-sectionally and longitudinally with these approaches.

The purposes of this paper are to demonstrate the application of LTA to cancer symptom data and to discuss the advantages and disadvantages of LTA relative to other methods of managing and interpreting data on multiple symptoms. We discuss the interpretations of the identified class memberships and transitions of symptom profiles and ways that they might be used to develop personalized strategies for symptom management.

Methods

Subjects and Settings

This study was a secondary analysis of data obtained from two randomized clinical trials. These included a nurse versus a non-nurse, coach-assisted, symptom management intervention (Trial I) and a second trial of automated telephone monitoring versus nurse-assisted symptom management (Trial II). The authors published inclusion criteria and data on the efficacy of the interventions (Given et al., 2004; Given, Given et al., 2008; Sikorskii et al., 2007). They performed the studies with identical timelines and recruitment criteria, with the exception that Trial I required that patients had caregivers who participated with them. The investigators screened a total of 806 participants to assure that they met minimum symptom criteria. Included participants scored two or higher on the severity of at least one symptom, and were randomly assigned to one of the two clinical trials. Out of the 806 participants, 601 began assessing their symptoms and interference with daily function at the first contact (baseline) and continued with subsequent scheduled six contacts. The six contacts were scheduled for intervention and symptom assessment during 8 weeks—weekly for the first four contacts and biweekly for the fifth and sixth contacts. Since two studies had identical study designs for symptom assessment, our secondary analysis was performed with the combined data with 495 subjects who completed the assessment over all of the scheduled contacts.

Variables and Measures

Demographic data were collected during the baseline interview; comorbid conditions were assessed using a 15-item questionnaire modified from Katz and colleagues (1996). Patient's functional outcomes including physical function, physical role functioning, emotional role

functioning, general health perceptions, and social functioning were assessed at baseline interview using the Medical Outcomes Study Short Form-36 (Ware, Snow, Kosinski, & Gandek, 1993). Symptom severity and interference with daily functioning (i.e., enjoyment of life, relationship with others, general activity, and emotions) were assessed with the M.D. Anderson symptom inventory (MDASI) at each intervention contact. Cleeland and colleagues (2000) showed good reliability, validity, and sensitivity of the MDASI from a validation sample of 527 outpatients with cancer. Given et al. (2008) and Jeon and colleagues (2009) established cutoffs for the MADASI that categorize symptoms into mild, moderate, and severe. The established cutoffs were used to classify symptoms as not present or mild versus moderate or severe.

Data Analysis

We described the proportion of participants who had moderate or severe symptoms and the means of the summed interference scores at the first intervention contact. We calculated mean interference with daily function for each symptom and analyzed symptom profiles with the eight symptoms that had the highest means. We identified class membership of the symptom profiles at baseline using LCA and determined the number of class memberships using goodness-of-fit criteria, including the likelihood-ratio G^2 statistic, Akaike's Information Criterion, and Bayesian Information Criterion, CACI, and the adjusted BIC. We selected the number of class memberships with the lowest scores on those criteria for the optimized LCA model. LCA produces different parameter estimates depending on the starting values due to multimodes of the likelihood function (Lanza, Collins, Lemmon, & Schafer, 2007). Therefore, we fitted LCA with 1,000 random starting values and selected the best-fitted models for 2, 3, and 4 classes. Using the estimated parameters from LCA, patients, we classified patients into one of the class memberships.

To validate the identified symptom classes, we compared clinical outcomes, including the number of symptoms, depressive symptoms, measured with the Center for Epidemiologic Studies Depression (CESD) scale, and SF-36 subscales across these classes. Using the general logit model, we tested the associations between the identified class memberships of symptom profiles and age, comorbid conditions, gender, cancer site, cancer stage, and cancer recurrence.

We performed the longitudinal analysis with eight symptoms at the first, third, and sixth (last) intervention contacts using LTA with constrained parameters for the equal response probabilities across three timepoints. The constrained parameters enable us to obtain an identical symptom profile for each class membership over time. LTA provides the transition probabilities of moving from one class membership to another between the first and the third contact and also between the third and the sixth contact.

The parameter estimations were performed using PROC LCA and LTA (PROC LCA & PROC LTA (Version 1.3.0), which employs the EM (expectation-maximization) algorithm to produce maximum likelihood estimates (Lanza et al., 2003, 2007; Lanza & Collins, 2008). PROC LCA and LTA imputes missing symptom items using full-information maximum likelihood (FIML) with the assumption of missing at random or missing completely at random (Graham, 2009; Yung, & Zhang, 2011).

Results

Table 1 presents the comparison of the demographic and clinical data between the two clinical trials. The majority of the participants were female ($n = 347$, 70.1%), half of whom were diagnosed with breast cancer ($n = 178$, 36.0%). Approximately 83.5% had a late stage cancer, and 22.0% had recurrent cancers.

Table 2 shows the percentages of patients who reported moderate or severe symptoms based on the eight selected symptoms with the highest level of interference with daily function. The participants reported that pain, fatigue, and anxiety had the highest interference with daily function, while pain (39.3%), fatigue (81.2%), and weakness (40.2%) were most prevalent symptoms.

With the dichotomized (moderate or severe vs. mild) 8 symptoms, LCA identified baseline memberships in classes (symptom profiles). We compared the model selection criteria for LCA when the number of classes is 2, 3, and 4. The three-class model was supported with the smaller model selection criteria ($BIC = 320.3$, $CAIC = 346.3$), compared to the four-class model ($BIC = 348.8$, $CAIC = 383.8$). The other criteria were similar between the three- and four-class models but much smaller compared to the two-class model. Therefore, we selected the three-class model based on the criteria. Table 3 shows the class probabilities of class memberships A, B, and C (that is, the proportions of patients that would be classified into one of three class memberships). The symptom class probabilities computed from LCA were 31.9%, 39.6%, and 28.4% for Classes A, B, and C, respectively. We report the estimated response probabilities of moderate/severe symptoms within each of three classes in Table 3. For example, all patients in Class B have moderate or severe fatigue (response probability of 1), while patients in Class A have an estimated .463 probability of having moderate or severe fatigue. Class A has a relatively low response probability for fatigue compared to Classes B and C and very low probabilities for the other seven symptoms. Class B has relatively high probabilities of fatigue, weakness, and pain, but low probabilities of anxiety, depression, and nausea/vomiting. Class C has the greater probabilities across eight symptoms compared to Classes A and B. Therefore, we labeled Class A mild symptoms, Class B physical symptoms, and Class C physical and emotional symptoms. By comparing the posterior probabilities, we classified individuals into Class A ($n = 161$), B ($n = 207$), and C ($n = 127$). The actual proportions of classes identified by comparing posterior probabilities are slightly different from the estimated class membership probabilities, the expected proportions of class in Table 3.

Table 4 presents the comparisons of class membership at the first intervention contact on the total number of symptoms, CESD, and functional health status (SF-36). All of the variables were significantly explained by the class memberships. Using Duncan's multiple range test, we performed comparisons of the variables among the three classes, and we found that there were significant differences among all three classes on most variables including total symptoms, CESD, lack of physical role effect, general health perception, and social function. Not surprisingly, the patients classified into Class A had significantly fewer symptoms ($M = 4.5$, $SD = 2.7$), better physical functioning ($M = 73.3$, $SD = 22.2$), general health ($M = 66.4$, $SD = 21.3$), and social functioning ($M = 79.1$, $SD = 22.1$) compared to

Classes B and C; while Class C had a significantly lower score on the CESD ($M = 17.7$, $SD = 6.9$), and lower emotional role effect ($M = 50.6$, $SD = 41.1$) and social functioning ($M = 53.1$, $SD = 20.0$) compared to Class B. (Note: a higher score on the SF-36 indicates better function).

There was no association between class membership and the demographic or clinical variables including gender, cancer site, cancer stage or recurrence. However, younger adults (age < 60) and patients with two or more comorbid conditions were more likely to be in Classes B or C rather than in Class A (data not shown in tables). The odds ratios of being in Classes C or B rather than Class A were 2.82 (95% CI [1.64, 4.86]) and 1.26 (95% CI [0.80, 12.00]) for younger adults and 2.17 (95% CI [1.30, 3.64]) and 2.51 (95% CI [1.56, 3.97]) for two or more comorbid conditions after controlling for other demographic variables.

The LTA classified three symptom classes (Class A: mild symptoms, Class B: physical symptoms, Class C: physical/emotional symptoms) similarly to the LCA. Since the LTA included more cases with mild symptom profiles from the third and sixth contacts due to the fact that patients improved their symptoms over time, Class A in the LTA has fewer people with moderate/severe symptoms compared to the same class in LCA which includes the baseline symptom profiles only. Therefore, the LTA classified more cases in Class A (22.9%) and fewer cases in Class B (46.8%) and Class C (30.3%) at the first contact compared to the LCA analysis. The symptom class probability of Class A increased at the third (40.7%) and sixth (48.4%), while the class probability of Class C were dramatically reduced at the third (18.7%) and sixth (9.8%). The estimated transition probabilities from one class membership to one or another class membership over time are shown in Table 5. The transition probabilities of staying at Class A over time had a high probability (1.000 at third and 0.882 at sixth) of staying at Class A. The probabilities of transition from Class B to Class A were also substantive (.307 at third and .297 at sixth). The transition probabilities show that participants transitioned from more severe to milder symptom classes.

Discussion

The results of this study demonstrated an application of latent variable modeling approaches to evaluation of multiple correlated symptoms at cross-sectional and longitudinal observations. We identified three subgroups of cancer patients based on their symptom experience at baseline and showed how they transitioned from one subgroup to another at postintervention. The identified patterns of symptom profiles are a concurrence of physical and emotional symptoms (Class C); concurrence of physical symptoms only (Class B); and a group that had one symptom or only fatigue (Class A).

Unlike a previous study (Conley et al. 2017, 2018), we did not identify a group of patients who suffered from emotional symptoms only, while approximately 40% of patients reported physical symptoms, with low chances of anxiety (response probability is .000) and depression (response probability is .284). In this study anxiety and depression usually accompanied physical symptoms and may be due to the stress of physical symptom burden or the cancer experience. The response probabilities (i.e., prevalence in each class) of sleep disturbance, dyspnea, and nausea/vomiting were smaller in Class B (anxiety = 0% and

depression = 28.4%), compared to Class C (anxiety = 88.1% and depression = 74.7%), while the probabilities of fatigue, weakness, and pain were similar between two classes. The differences in sleep disturbance between the classes with and without emotional symptoms might be explained by the comorbidity between anxiety and depression sleep disturbance and insomnia among cancer patients (Palesh et al., 2010; Trill, 2013) and others.

The finding that class memberships differentiated relevant outcomes (total number of symptoms, CESD, physical and emotional functioning, general health and social functioning) suggests that class memberships may be useful in classifying cancer patients who may benefit from targeted interventions for symptoms as well as function and QoL. The identified class memberships of symptom profiles may also represent the stages of symptom burden and the patterns of symptoms at each symptom stage in cancer patients. In conjunction with the identified class memberships, the longitudinal model might demonstrate the process of symptom resolution over time: (a) an experience of emotional distress from the co-occurrence of fatigue with other physical symptoms (Class C); (b) a resolution of emotional distress with a presence of multiple physical symptoms (Class B); and (c) a resolution of physical symptoms with improved physical function (Class A). The transition probabilities estimated from LTA demonstrated the longitudinal process of symptom resolution from Class C to Classes B and A by relieving emotional and physical symptoms, respectively.

LCA provides a minimum number of homogeneous subsets with the assumption of local independence. This assumption means that given class membership, symptom items are conditionally independent. That is, if class membership is known, data on individual symptom items does not add any new information beyond class membership. Thus, the correlated multiple symptoms would be conditionally uncorrelated within each of the identified symptom classes, and the multiple symptoms could be evaluated by a categorical variable of the class membership without a concern about multiple correlated outcomes. This class membership summary overcomes the drawbacks of analyzing each symptom separately; a process that induces inflated Type I error due to multiple tests with correlated symptom variables, or addition of the counts or severities of multiple symptoms into a composite score.

This study also demonstrated the application of LTA to evaluate longitudinal changes in correlated multiple symptoms by characterizing class memberships with independent risks on symptoms. The estimated transition probabilities from the baseline to the post-intervention class memberships could be used to evaluate intervention efficacy on symptom burden. For example, this analysis shows successful reduction in symptom burden over time by multiplying the transition probabilities from the first to the third contacts with the transition probabilities from the third to sixth contacts in Table 5. Approximately 49% of patients in Class C at the first contact were likely to be in Class B at the sixth contact after receiving the symptom management intervention in the trials (i.e., $\text{Class C} > \text{C} > \text{B}: 0.324 = 0.619 \times 0.523$; $\text{Class C} > \text{B} > \text{B}: 0.155 = 0.226 \times 0.687$; $\text{Class C} > \text{A} > \text{B}: 0.012 = 0.115 \times 0.102$). Furthermore, LTA provides person-specific parameters including posterior and transition probabilities which represent the individual risks of moderate-severe symptoms at baseline and their likelihood of improving symptom during the intervention. It

is important to know that the identified class memberships can remain consistent symptom profiles over time by constraining response probability, which keeps identical class memberships at baseline and postintervention.

The symptom profiles identified through LCA and transitions over time, as reflected in LTA, may represent phenotypes that are useful from a precision health perspective. Future research is needed to better understand the “omic,” lifestyle, sociodemographic, treatment, environmental, and other factors that may predict the classification of individuals into symptom clusters and how they change over time. Once these relationships are understood, interventions can be more precisely targeted to individual risk.

Limitations and Recommendations

LCA and LTA have several limitations. The difficulties of calculating statistical power and of identifying the maximum likelihood solution with complex models have been discussed in general applications of the models (Bray, Lanza, & Collins, 2010). There are also some limitations of these models when used to evaluate multiple symptom severities. First, these approaches require optimal cutoffs to categorize continuous measures of symptom severity. In general, loss of information may result from categorizing a continuous variable. However, optimal cutoffs have been defined relative to QoL and these may be more amenable to clinical interpretation due to the nonlinear relationship between symptom severity and QoL (Daut, Cleeland, & Flannery, 1983; Given et al., 2008; Jeon et al., 2009; Paul, Zelman, Smith, & Miaskowski, 2005; Serlin, Mendoza, Nakamura, Edwards, & Cleeland, 1995). Therefore, finding the optimal cutoff is critical to identifying clinically reasonable symptom profiles with continuous measures of symptom severity in LCA and LTA. In this study, we used cutoffs that maximized decrements in life interference due to symptoms and interpreted a presence of symptom as “reaching a symptom severity level that starts substantively decrementing his/her quality of life.” Meanwhile, use of extremely conservative or naïve cutoff levels could produce different patterns of symptom profiles and misinterpretations. Alternatively, Conley and colleagues (2017, 2018) used the Patient Reported Outcomes Measurement Information System (PROMIS), which includes normed symptom scores, by dichotomize with a cutoff of 50. The score of 50 or higher represents a clinically significant symptom relative to healthy population (Cella, Choi, Carcia, Cook, & Gershon, 2014; National Institutes of Health, 2013). Second, LCA and LTA classify patients by comparing posterior probabilities that represent individual likelihoods of class memberships. Most individuals have a substantively larger probability of a specific class membership compared to other class memberships, and this contributes to enhancing the homogeneity of clustered subjects. However, some individuals may have equal or similar posterior probabilities across multiple class memberships, but may not have a high probability of a specific class membership. This limitation presents not only in LCA and LTA but also in other cluster analysis approaches if there are subjects who have equal distances on symptom severity between all clusters. Those poorly defined cases could be addressed by maximizing goodness of fit with an optimal number of classes.

A conceptual model of symptom management (Dodd et al., 2001) emphasized the interplay of the symptom experience, symptom management strategies, and outcomes. They argued

that symptom management should not target only the individual experience of the symptom but also the risk of symptom development. LCA addresses this by classifying patients by the risk of symptoms (i.e., response probability) but individuals in the group may not necessarily have all of the specific symptoms. That is, all patients in Class C did not have to report all physical and psychological symptoms, but they had relatively high risks of those symptoms compared to those in other class memberships. Thus, the estimated specific parameters can be used to estimate individual's risk of experiencing each symptom and may be useful in tailoring symptom management strategies that target patients with specific symptom profiles that adversely influence QoL. Thus, this analysis could be used to classify patients who might have more benefits from symptom management (e.g., Class C in this study), and those who might be at highest risk for adverse symptom profiles.

The observed correlations with clinical outcomes suggest that the identified class membership could also be an important index of summarizing current symptom burden as well as the QoL. This patient-centered approach with LCA and LTA would provide optimized information with individual symptom profiles to develop a strategy of personalized symptom management. Further analysis of the relationships between class memberships and survival or cancer-related outcomes, such as function or healthcare resource utilization, would be necessary to assess whether the class membership could be used for prognostic assessment in cancer patients.

Conclusion

LTA and LCA are important tools to address the importance of symptom clusters to precision health, treatment of cancer and other chronic conditions, recovery, and QoL. Further research is needed to assess the utility of these approaches to precision health and guiding symptom interventions.

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Table 1

Demographic and clinical data from two oncology clinical trials

Variable	Trial I (N = 166)	Trial II (N = 329)
	<i>N (%)</i>	<i>N (%)</i>
Gender/Female	96 (57.8%)	251 (76.3%)
Cancer Site		
Breast	44 (26.5%)	135 (41.0%)
Colon	14 (8.4%)	48 (14.6%)
Lung	42 (25.3%)	49 (14.9%)
Other	66 (39.8%)	97 (29.5%)
Recurrent Cancer	44 (26.5%)	65 (19.8%)
Late Stage Cancer	146 (89.0%)	265 (80.8%)
	<i>Mean (SD)</i>	<i>Mean (SD)</i>
Age	57.8 (11.5)	57.3 (11.8)
Comorbid Conditions	2.12 (1.59)	1.99 (1.55)
The Number of Symptoms	7.09 (2.96)	7.29 (3.45)

Table 2

Percent of moderate/severe symptoms and summed interference score at the first contact

Symptom	Moderate/Severe Symptom	Summed Interference with daily function
	<i>N (%)</i>	<i>Mean (SD)</i>
Pain *	175 (39.3%)	14.6 (12.3)
Fatigue *	402 (81.2%)	14.0 (10.5)
Anxiety *	128 (25.9%)	13.9 (11.1)
Depression *	168 (33.9%)	11.9 (11.3)
Nausea / Vomiting *	64 (12.9%)	11.2 (12.9)
Weakness *	198 (40.2%)	10.7 (9.5)
Sleep Disturbance *	170 (34.4%)	9.5 (9.2)
Dyspnea *	117 (23.6%)	9.2 (10.5)
Poor Appetite	148 (29.9%)	8.4 (9.7)
Diarrhea	53 (10.7%)	7.9 (10.8)
Constipation	91 (18.4%)	6.6 (8.8)
Alopecia	174 (35.1%)	6.2 (8.1)
Cough	85 (17.2%)	5.6 (8.2)
Remembering	169 (34.1%)	5.3 (7.1)
Peripheral Neuropathy	82 (16.6%)	4.8 (7.1)
Dry mouth	84 (17.0%)	3.8 (6.9)

* Note. indicates 8 most frequently reported symptoms which were used in LCA and LTA.

Table 3

Parameter estimates for LCA with three class memberships of symptom profile at the first contact

Three Class Model	Class A	Class B	Class C
Class Probabilities <i>Estimate ± SE</i>	0.319 ± 0.050	0.396 ± 0.044	0.284 ± 0.043
	Response Probability (Moderate/Severe Symptom) <i>Estimate ± SE</i>		
Fatigue	0.463 ± 0.082	1.000 ± 0.000	0.943 ± 0.021
Anxiety	0.026 ± 0.020	0.000 ± 0.000	0.881 ± 0.118
Depression	0.046 ± 0.030	0.284 ± 0.061	0.747 ± 0.041
Weakness	0.055 ± 0.024	0.531 ± 0.070	0.614 ± 0.046
Pain	0.104 ± 0.042	0.524 ± 0.055	0.540 ± 0.049
Sleep Disturbance	0.181 ± 0.040	0.361 ± 0.044	0.506 ± 0.045
Dyspnea	0.087 ± 0.026	0.233 ± 0.046	0.408 ± 0.044
Nausea / Vomit	0.025 ± 0.016	0.090 ± 0.033	0.301 ± 0.041

Table 4

Comparisons of clinical outcomes for three latent classes at the first contact

Clinical Outcomes	Class A: Mild Symptoms <i>Mean (SD)</i>	Class B: Physical Symptoms <i>Mean (SD)</i>	Class C: Physical & Emotional Symptoms <i>Mean (SD)</i>	<i>p</i> -value
Total Number of Symptoms ⁽¹⁾	4.5 (2.7)	7.8 (2.5)	9.7 (2.6)	<.0001
Number of moderate-severe symptoms ⁽²⁾	0.9 (0.7)	3.1 (1.0)	5.0 (1.4)	<.0001
Depression (CESD)	8.2 (5.5)	11.9 (6.0)	17.7 (6.9)	<.0001
Physical Functioning (SF-36)	75.2 (21.2)	53.8 (25.8)	53.7 (25.0)	<.0001
Physical Role Functioning (SF-36)	38.7 (36.4)	17.3 (28.2)	10.3 (17.7)	<.0001
Emotional Role Functioning (SF-36)	82.2 (29.6)	71.2 (36.4)	53.3 (41.6)	<.0001
General Health Perceptions (SF-36)	66.4 (21.3)	52.8 (21.4)	45.8 (22.1)	<.0001
Social Functioning (SF-36)	79.1 (22.1)	63.7 (24.1)	53.1 (20.0)	<.0001

Note.

⁽¹⁾ is the number of reported symptoms with any severity level greater than zero out of 16 symptoms.⁽²⁾ is the number of moderate or severe symptom out of 8 symptoms used in LCA.

Table 5

Transition probabilities of symptom classes from the first to the last contact

Cluster at the 1 st contact	Estimated probability of transition to symptom cluster at the 3 rd contact		
	Class A	Class B	Class C
Class A	1.000	0.000	0.000
Class B	0.307	0.693	0.000
Class C	0.115	0.226	0.619
Cluster at the 3 rd contact	Estimated probability of transition to symptom cluster at the 6 th contact		
	Class A	Class B	Class C
Class A	0.882	0.102	0.016
Class B	0.297	0.687	0.016
Class C	0.025	0.523	0.452