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Symptom Clusters in Breast Cancer Survivors: A Latent Class Profile Analysis

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Abstract

OBJECTIVES: To identify symptom clusters in breast cancer survivors and to determine sociodemographic and clinical characteristics influencing symptom cluster membership.

SAMPLE & SETTING: The authors performed a cross-sectional secondary analysis of data obtained froma community-based cancer registry–linked survey with 1,500 breast cancer survivors 6–13 months following a breast cancer diagnosis.

METHODS & VARIABLES: Symptom clusters were identified using latent class profile analysis of four patient-reported symptoms (pain, fatigue, sleep disturbance, and depression) with custom PROMIS® short forms.

RESULTS: Four distinct classes were identified: symptoms within normal limits (class 1), pain with fatigue and sleep disturbance (class 2), depression with fatigue and sleep disturbance (class 3), and all high symptom burden (class 4). The authors identified four clinically relevant and actionable symptom clusters in early-stage breast cancer survivorship. Certain sociodemographic and clinical characteristics place patients at risk for physical late effects and mental health issues.

IMPLICATIONS FOR NURSING: Common symptom clusters may lead to better prevention and treatment strategies that target a group of symptoms. Results also suggest that certain factors place patients at high risk for symptom burden, which can guide tailored interventions.

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Lee, Ross, and Griffith contributed to the conceptualization and design. Jensen completed the data collection. Lee provided statistical support. All authors provided analysis and contributed to the manuscript preparation.

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Keywords

breast cancer; survivors; symptom clusters; symptom burden

Patients with breast cancer commonly experience multiple symptoms, including pain, fatigue, sleep disturbance, and depression. These symptoms not only affect patients at diagnosis and during cancer treatment, but also may persist or develop after treatment ends (Marshall et al., 2016). In studies of breast cancer survivors, the prevalence rates of these symptoms have been reported as follows: pain = 34%–97% (Bao et al., 2018; Ellis, 2013; Hamood, Hamood, Merhasin, & Keinan-Boker, 2018; Seib et al., 2017), fatigue = 31%–86% (Ellis, 2013; Fabi et al., 2017; Mao et al., 2018; Seib et al., 2017), sleep disturbance = 38%–75% (Lowery-Allison et al., 2018; Otte et al., 2016; Seib et al., 2017), and depression = 20%–55% (Avis, Levine, Case, Naftalis, & Van Zee, 2015; Seib et al., 2017).

Often, these symptoms are identified, studied, and managed independently, despite that they rarely occur in isolation. Better clarity on the prevalence and severity of co-occurring symptoms, or symptom clusters, will inform symptom management more effectively (Miaskowski et al., 2017). A symptom cluster has been defined as “two or more symptoms that are related to each other and that occur together. Symptom clusters are composed of stable groups of symptoms that are relatively independent of other clusters, and they may reveal specific underlying dimensions of symptoms” (Kim, McGuire, Tulman, & Barsevick, 2005, p. 278).

Chronic symptom clusters may have long-term effects on the quality of life of breast cancer survivors (Roiland & Heidrich, 2011). Identifying symptom clusters and their relationship to patient characteristics may lead to a better interpretation for clinical presentation of breast cancer survivors’ overall symptom experience and provide greater insight into the planning of future interventions. In effect, understanding symptoms as a cluster may guide healthcare providers to develop more targeted and effective interventions for an entire group of symptoms, rather than focusing on a single symptom (Kwekkeboom, 2016). Several studies have identified subgroups of breast cancer survivors with distinct symptom clusters, but results vary in terms of number of symptoms (ranging from 3 to 46), measurement methods (e.g., Symptom Bother Scale–Revised, the Short Form of the Profile of Mood States), and statistical methodology (e.g., factor analysis, cluster analysis) (Avis, Levine, Marshall, & Ip, 2017; Ellis, 2013; Marshall et al., 2016; Mazor et al., 2018; Phligbua et al., 2013; Roiland & Heidrich, 2011; Seib et al., 2017; Shi et al., 2011). Using well-validated and reliable patient-reported outcomes measures in conjunction with latent class analysis, an advanced statistical method, is key for accurate symptom cluster identification.

The purposes of this study were (a) to identify distinct latent classes of four highly prevalent symptoms (pain, fatigue, sleep disturbance, and depression) in breast cancer survivors and (b) to explore which sociodemographic and clinical factors predict symptom cluster membership. This study was guided by the theory of unpleasant symptoms (TUS) (Lenz, Pugh, Milligan, Gift, & Suppe, 1997). This model proposes that physiologic factors, such as the presence of disease, and situational factors, such as employment status and socioeconomic class, interrelate to influence the development of symptoms. These

symptoms can occur individually or concurrently. These symptoms can then affect performance; in the case of cancer survivors, this could mean decreased quality of life or interference in the ability to live life fully (Roiland & Heidrich, 2011). In the current study, the authors focused on the influential factors and symptoms. The influential factors and symptoms examined in this study are detailed in Figure 1.

Methods

This study was a cross-sectional secondary analysis of data from the Measuring Your Health (MY-Health) study, a prospective cohort study. In the parent study, data were collected to evaluate the health and well-being of a diverse cohort of individuals with cancer (Jensen et al., 2016). Participants in the MY-Health study were recruited through four Surveillance, Epidemiology, and End Results (SEER) registries located in California (two), Louisiana, and New Jersey between 2010 and 2012. Participants were eligible for the study if they (a) were aged 21–84 years at the time of initial diagnosis of one of seven types of cancer (i.e., female breast cancer, prostate cancer, colorectal cancer, non-small cell lung cancer, non-Hodgkin lymphoma, uterine cancer, and cervical cancer) and (b) had the ability to read and speak English, Spanish, or Mandarin. Further details regarding the study design, study procedures, and participant descriptions are published elsewhere (Jensen et al., 2016). The survey was completed by 5,506 people with cancer. For this analysis, the authors restricted eligibility to women diagnosed with breast cancer within the past 6–13 months. Of 1,662 women with breast cancer, a total of 1,500 participants were included following exclusion of 137 participants diagnosed greater than 13 months prior to the study and 25 participants who had died during the survey period.

Measures

Sociodemographic variables included age at diagnosis, race, ethnicity, marital status, education, employment status, and income. Clinical variables included stages of cancer, cancer treatment (i.e., surgery, chemotherapy, or radiation therapy), and the number of self-reported common comorbidities documented in breast cancer populations (Fu et al., 2015).

Symptoms were measured using PROMIS® (Patient-Reported Outcomes Measurement Information System) measures, which have been extensively validated in patients with cancer (Cella et al., 2010). This MY-Health study administered custom PROMIS short forms assessing pain interference (10 items), fatigue (14 items), sleep disturbance (10 items), and depression (10 items). In the current study, the internal consistency of the instrument was high (pain: Cronbach alpha = 0.98; fatigue: Cronbach alpha = 0.96; sleep disturbance: Cronbach alpha = 0.95; depression: Cronbach alpha = 0.97). The PROMIS measures are scored on a five-point Likert-type scale ranging from 1 (never) to 5 (always), with higher scores indicating higher symptom severity. The PROMIS measures are calibrated and standardized to a t-score metric, with a mean of 50 and standard deviation of 10 centered on the general U.S. population. The measure offers clinically relevant symptom thresholds (pain: less than 50 is normal, 50–59 is mild, 60–69 is moderate, and 70 or greater is severe; fatigue and sleep disturbance: less than 50 is normal, 50–54 is mild, 55–74 is moderate, and

75 or greater is severe; depression: less than 55 is normal, 55–64 is mild, 65–74 is moderate, and 75 or greater is severe) (Cella et al., 2014).

Statistical Analysis

Latent class analysis is a statistical method for identifying unobserved (i.e., latent) subgroups, which are called classes, within a population using multiple observed variables. The latent class model approach is useful to identify subgroups of individuals sharing similar patterns of symptom characteristics. In the current study, latent class profile analysis (LCPA) was conducted because continuous variables were analyzed (Vermunt & Magidson, 2002). The LCPA identified latent classes of participants based on the four symptom variables (i.e., pain, fatigue, sleep disturbance, and depression). Estimation was carried out with the robust maximum-likelihood and expectation-maximization algorithms (Muthén & Shedden, 1999). Statistical fit indexes were used to evaluate model fit and to determine the final number of latent classes. The model that fits the data best was selected by a combination of the following criteria: (a) the lowest Akaike information criterion (AIC) (Akaike, 1974), (b) the lowest Bayesian information criterion (BIC) (Schwarz, 1978), (c) the lowest Vuong–Lo–Mendell–Rubin likelihood ratio test (VLMR), (d) the lowest parametric bootstrapped likelihood ratio test (BLRT), and (e) entropy to be 0.8 or greater (Celeux & Soromenho, 1996; Nylund, Asparouhov, & Muthén, 2007). Next, the authors performed multinomial logistic regression to determine sociodemographic and clinical factors that predict class membership. Unadjusted models were estimated for sociodemographic and clinical variables shown to be influential in the literature (i.e., age at diagnosis, race, ethnicity, marital status, education, employment status, income, stages of cancer, surgery, chemotherapy, radiation therapy, and the number of comorbidities). Variables with a significant relationship in univariate analyses were retained in multivariate analyses of predicted inclusion in a class. Mplus, version 7.2, was used for LCPA, and other analyses were conducted with IBM SPSS Statistics, version 25.0.

Results

Sample Characteristics

Data for 1,500 breast cancer participants were examined in this analysis (see Table 1). Sample participants were predominantly younger at diagnosis, White, non-Hispanic, married or cohabiting, college graduates, employed, and in a high-income group ($40,000 or more). The largest proportion of participants had stage I breast cancer and were treated with surgery, chemotherapy, or radiation therapy. Participants reported an average of 0.94 (SD = 1.11, range = 0–6) comorbid conditions, with arthritis, rheumatism or other joint disease, diabetes, and hypertension being the most prevalent.

Prevalence and Severity of Symptoms

The prevalence rates of four symptoms have been reported as follows based on the established thresholds (i.e., pain, sleep disturbance, and fatigue thresholds of 50 and depression threshold of 55) (Cella et al., 2014): pain = 64%, sleep disturbance = 61%, fatigue = 51%, and depression = 32%. The mean symptom scores were as follows:

- Pain: 53.74 (SD = 10.17, range = 41–78.2)
- Fatigue: 51.71 (SD = 10.41, range = 34.5–75)
- Sleep disturbance: 51.83 (SD = 9.77, range = 31.7–76.1)
- Depression: 49.84 (SD = 10.1, range = 38.4–80.2)

Identification of Symptom Clusters

Four distinct subgroups of breast cancer survivors were identified based on their ratings of symptom severity and types of symptoms. The results of statistical fit indexes for the candidate models are shown in Table 2. The four-class solution was chosen because the fit index for BIC was smaller compared to those of the two- and three-class models. In addition, the fit index for VLMR was not significant in the five-class model, corroborating that the four-class model fit the data better than the five-class model (Nylund et al., 2007). Latent classes were named based on established symptom cut points (Cella et al., 2014). As summarized in Table 3 and illustrated in Figure 2, class 1 (57%), labeled symptoms within normal limits, was characterized by all four symptoms within normal limits. Class 2 (19%), labeled pain with fatigue and sleep disturbance, was characterized by mild sleep disturbance and moderate pain and fatigue, but no elevated depression (within normal limits). Class 3 (11%), labeled depression with fatigue and sleep disturbance, was characterized by mild fatigue and moderate sleep disturbance and depression, but pain within normal limits. Class 4 (13%), labeled all high symptom burden, was characterized by moderate levels of all four symptoms.

Sociodemographic and Clinical Variables and Symptom Cluster Groups

Unadjusted models were significant for age at diagnosis, race, ethnicity, marital status, education, employment status, income, surgery, chemotherapy, radiation therapy, and the number of comorbidities. These variables were retained in the adjusted model. Table 4 displays multinomial logistic regression results with predictors for each class, using class 1 (symptoms within normal limits) as the reference.

Comparison of class 2 versus class 1: Age at diagnosis, employment status, history of chemotherapy, and the number of comorbidities significantly predicted the likelihood of reporting a pain-related symptom cluster (class 2). Women aged younger than 65 years diagnosed with breast cancer (versus women aged 65 years or older) were more likely to be in class 2 versus class 1 (odds ratio [OR] = 2.12, 95% confidence interval [CI] [1.29, 3.49], $p = 0.003$). Those who were not working (versus those who were working) were more likely to be in class 2 (OR = 1.69, 95% CI [1.13, 2.52], $p = 0.011$). Survivors who received chemotherapy (versus those who received no chemotherapy) were 2.41 times (95% CI [1.63, 3.55], $p < 0.001$) more likely to be in class 2 versus class 1. Participants with an additional comorbid condition were 1.74 times more likely (95% CI [1.47, 2.07], $p < 0.001$) to be in class 2 versus class 1.

Comparison of class 3 versus class 1: Age at diagnosis, education level, and employment status significantly predicted the likelihood of reporting a depression-related symptom cluster (class 3). Participants aged younger than 65 years at diagnosis (versus those

aged 65 years or older) had a higher likelihood of membership in class 3 versus class 1 (OR = 2.31, 95% CI [1.23, 4.32], p < 0.001). Survivors who had completed some college had a higher likelihood of membership in class 3 versus class 1 than those who had completed at least an undergraduate degree (OR = 1.98, 95% CI [1.19, 3.29], p = 0.008). Those who were not working (versus those who were working) were more likely to be in class 3 versus class 1 (OR = 1.98, 95% CI [1.2, 3.29], p = 0.044).

Comparison of class 4 versus class 1: Age at diagnosis, education level, employment status, history of chemotherapy, and the number of comorbidities predicted the likelihood of reporting high symptom burden (class 4). Women aged younger than 65 years at diagnosis had a higher likelihood of membership in class 4 than those aged 65 years or older at diagnosis (OR = 5.17, 95% CI [2.73, 9.78], p < 0.001). Survivor groups with lower education levels (less than a college degree) were more likely to be in class 4 versus those in class 1 with an undergraduate degree (OR = 2.89, 95% CI [1.31, 6.36], p = 0.008; OR = 2.18, 95% CI [1.11, 4.41], p = 0.03; and OR = 2.46, 95% CI [1.4, 4.32], p = 0.002, respectively). Those who reported not working were about 3 times (95% CI [1.85, 4.73], p < 0.001) more likely to be in class 4 compared to those who reported working. Survivors who received chemotherapy were more likely to be in class 4 versus class 1 than those who did not receive chemotherapy (OR = 2.69, 95% CI [1.66, 4.38], p < 0.001). With each increment of one comorbid condition, women were 1.88 times (95% CI [1.54, 2.29], p < 0.001) more likely to be in class 4 versus class 1.

Discussion

This is the first known study to identify four latent classes and to demonstrate the relationship of latent class membership with covariates in breast cancer survivors using an LCPA approach with a large sample. Four distinct classes in early-stage breast cancer survivorship as they end treatment and transition into follow-up care were identified. These classes represent the symptom experience of breast cancer survivors based on the severity of the symptoms in the clusters: class 1 (symptoms within normal limits), class 2 (pain with fatigue and sleep disturbance), class 3 (depression with fatigue and sleep disturbance), and class 4 (all high symptom burden). Other studies (Avis et al., 2017; Ellis, 2013; Marshall et al., 2016; Mazor et al., 2018; Phligbua et al., 2013; Roiland & Heidrich, 2011; Seib et al., 2017; Shi et al., 2011) have identified symptom clusters in breast cancer survivors; however, little consistency exists in the number (ranging from 2 to 7) and types of symptom clusters identified. Limitations across studies may be attributed to differences in the number of symptoms assessed, instruments, and statistical methodology.

The results of this study provide further evidence regarding who is at risk for experiencing symptom clusters. As in past studies (Avis et al., 2017; Ellis, 2013; Roiland & Heidrich, 2011; Shi et al., 2011), survivors in this study who experienced the more highly symptomatic clusters (class 2, class 3, and class 4) were younger in age (younger than age 65 years at diagnosis) than those who were asymptomatic (class 1). These age- related differences may reinforce other findings that younger patients often have more invasive forms of breast cancer and receive more aggressive cancer treatment, which are related to greater side effects and long-term late effects (Ademuyiwa, Cyr, Ivanovich, & Thomas,

2016). In addition, younger survivors may have higher expectations regarding the resumption of full family, social, and vocational roles; such expectations may increase the perception of symptoms (Baker, Denniston, Smith, & West, 2005; Champion et al., 2014). Based on these results, healthcare providers might consider concentrating more on younger patients who experience high symptom burden.

In addition, individuals who were more highly educated appeared to be less likely to be in the symptomatic groups (class 2, class 3, class 4) compared to the symptoms within normal limits group (class 1). The association between lower education level and higher symptom burden is consistent with previous research (Roiland & Heidrich, 2011; Shi et al., 2011). This may be explained by the fact that higher education was linked to higher levels of knowledge, leading to better understanding of how to interpret and manage worsening symptoms (Culter & Lleras-Muney, 2010; Davies, Marcu, Vedsted, & Whitaker, 2018). Employment status was another important factor associated with symptom burden in the current study. This is an important finding, given that a large number of breast cancer survivors (about 43%–93%) return to work either full- or part-time within one year of diagnosis (Islam et al., 2014). In addition, evidence from studies regarding the relationship between employment status and symptom clusters is contradictory (Ellis, 2013; Seib et al., 2017; Shi et al., 2011). In the current study, unemployed survivors were more likely to be found in more symptomatic cluster groups (class 2, class 3, class 4) than those who were employed, and the strongest association between employment status and symptom clusters was found in those with the highest symptom burden (class 4). One plausible explanation is that individuals with higher socioeconomic status, measured as higher education and employment, may be more likely to engage in healthy lifestyle behaviors (e.g., physical activity) (Naik et al., 2016; Park et al., 2015). Those with higher economic status also may be better able to access appropriate healthcare services and communicate with clinicians after treatment has ended, thereby facilitating better symptom management (DiMartino, Birken, & Mayer, 2017). Because of the cross-sectional approach in this study, it is difficult to determine whether employment status is truly protective against problematic co-occurring symptoms or whether individuals who experience worse symptoms are more likely to leave the workforce (Ellis, 2013; Seib et al., 2017; Shi et al., 2011). Future research investigating longitudinal changes in survivors' employment over time is needed to investigate the link between employment and symptom clusters.

A major gap in understanding symptom experience in these breast cancer survivors is whether the symptoms reported are residual symptoms from previous cancer treatment identified in the breast cancer survivors. In the current study, history of chemotherapy predicted membership in class 2 (pain with fatigue and sleep disturbance) and class 4 (all high symptom burden), characterized by a moderate level of pain. This finding is consistent with previous studies where chemotherapy status contributed to membership in a high symptom burden group (Avis et al., 2017; Roiland & Heidrich, 2011; Shi et al., 2011). In addition, similar levels of symptom severity were found between survivors who had completed chemotherapy and those still receiving treatment (Avis et al., 2017; Shi et al., 2011). It is possible that healthcare providers and patients concentrate more on identifying symptoms during active cancer treatment rather than after completion of the cancer treatment. Findings from this study add to the evidence for the need to assess residual

symptoms from cancer therapy among survivors who may require additional symptom assessment and management in the transition from active cancer treatment to long-term follow up.

In the current study, the number of comorbidities was reported as a significant predictor of symptom clusters (class 2 and class 4), characterized by a moderate level of pain. The finding of greater risk for higher symptom burden in cancer survivors with comorbid conditions is consistent with previous studies (Roiland & Heidrich, 2011; Seib et al., 2017; Shi et al., 2011). Seib et al. (2017) showed that peripheral somatic symptoms were higher among breast cancer survivors who reported comorbidities. Another study in cancer survivors found that the likelihood of high symptom burden increased with the number of comorbidities (Shi et al., 2011). These results imply that comorbid illnesses are clinically important factors when assessing the symptom clusters among breast cancer survivors. Special emphasis should be directed to breast cancer survivors with comorbid illnesses who experience progressive symptoms burden, particularly from pain.

This study has several limitations. Because this analysis is cross-sectional, the authors did not explore symptom cluster membership over time or causality between membership and risk factors (e.g., whether employment status triggers worse symptoms or the reverse). A longitudinal design needs to be included in further studies. In addition, this is a secondary data analysis, which limited the ability to assess other factors, most importantly whether any participants were still undergoing current treatment or were experiencing cancer progression or recurrence at the time that they completed the survey. Although symptom burden in early-stage breast cancer survivorship may persist whether or not cancer treatment is completed, the presence of earlier treatment-related symptoms is associated with late symptom distress after termination of therapy (Avis et al., 2015; Shi et al., 2011). Unfortunately, no data regarding the presence of previous treatment- related symptoms or the terminations of therapy were available for this secondary analysis.

Despite the limitations, there were several strengths of this study, including a large sample size that increased the likelihood that all relevant patterns were represented (Wurpts & Geiser, 2014). The current study yielded a representative sample of breast cancer survivors, allowing generalizable symptom cluster results related to early-stage breast cancer survivorship. In addition, given the review of the literature and identification of symptom consistencies between the current findings and those of more recent studies (Matthys et al., 2019; Ricci, Flores, Kuroyama, Asher, & Tarleton, 2018; Sikorskii et al., 2018), the results accurately reflect contemporary symptom profiles in breast cancer survivors despite that data were collected seven years ago. Other strengths of this study included the novel analysis method, LCPA. Much of the symptom cluster literature has focused on using variable-centered approaches, such as regression and factor analysis, with relationships between variables of interest in a population (Kim, Abraham, & Malone, 2013; Miaskowski et al., 2017). Unlike the variable-centered approaches that limit the interpretation of findings to individuals, person-centered approaches focusing on similarities or relationships among individuals, exemplified by latent class analysis, are beneficial in symptom research where data often include heterogeneous groups of individuals with multiple co-occurring symptoms, or symptom clusters (Howard & Hoffman, 2017). In addition, to promote

consistent reporting of symptom clusters across populations, a psychometrically sound and standardized measurement system, such as PROMIS, is the best possible option for accurate symptom assessment at this time (Cella et al., 2010). The findings in the current study indicate the usefulness of LCPA and PROMIS measures for determination of symptom clusters that might provide information to guide clinical management of breast cancer survivors.

Future research is needed to further understand potential predictors of multiple symptoms, such as types of cancer treatment (e.g., mastectomy versus lumpectomy), onset of symptoms during active cancer therapy, and health behaviors (e.g., physical activity, diet). Longitudinal assessment of concurrent multiple symptoms over time will provide information about whether clusters and/or cluster membership change throughout the survivorship trajectory. In addition, the authors found no study that focused on the evaluation of benefits of targeted interventions for a symptom cluster among breast cancer survivors. The direct intervention of one symptom (e.g., strategies to improve sleep) might indirectly improve other symptoms in a cluster (e.g., decreasing fatigue). In addition, it is not clear which targeted interventions —specifically for the symptom clusters involving pain, fatigue, sleep disturbance, and depression—are clinically feasible and effective. Testing the effectiveness of innovative symptom management intervention to treat single or multiple symptoms within symptom clusters should be considered. Finally, future studies of symptom clusters would benefit from the addition of biologic and genetic markers (e.g., cytokines, genomic DNA), providing insight into the underlying biologic and genetic/epigenetic mechanisms of multiple co-occurring symptoms.

Implications for Nursing

The results of this investigation have implications for nursing because there is strong evidence that the symptom clusters the authors identified exist at several different levels of severity. The approach of focusing on symptom clusters in clinical practice may provide useful insights leading to the development of innovative and effective targeted interventions for subgroups of breast cancer survivors experiencing the same symptom cluster. Healthcare providers might specifically target single or multiple symptoms within a cluster to decrease the negative impact of multiple, co-occurring symptoms on patient outcomes. Grouping breast cancer survivors might also be beneficial to clarify which subgroup might be at high risk of poorer outcomes. In terms of promoting symptom recognition, education for patients and their caregivers could focus on the monitoring of symptom clusters rather than on individual symptoms. Ultimately, if patients and their caregivers understand that symptoms may occur in clusters, this awareness may facilitate better self-management, which will result in better quality of life for breast cancer survivors.

Conclusion

This analysis identified several levels of symptom clusters in female breast cancer survivors, which adds to the knowledge of complex co-occurring symptom relationships. Results may lead to the development of tailored interventions that can target multiple symptoms simultaneously, which will improve patient outcomes, including quality of life. In addition,

findings related to demographic and clinical factors that place a group at high risk for symptom burden can be used to identify those most at risk of experiencing the symptom cluster and hasten appropriate care.

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KNOWLEDGE TRANSLATION

- Four symptom clusters were identified in breast cancer survivors: symptoms within normal limits (class 1), pain with fatigue and sleep disturbance (class 2), depression with fatigue and sleep disturbance (class 3), and all high symptom burden (class 4).
- In the relationship between symptom clusters and covariates, significant differences among the four latent classes were found for age, education level, employment status, history of chemotherapy, and number of comorbid conditions.
- The study demonstrated the usefulness of latent class profile analysis and PROMIS® measures for identification of symptom clusters that might guide and support the development of targeted interventions.

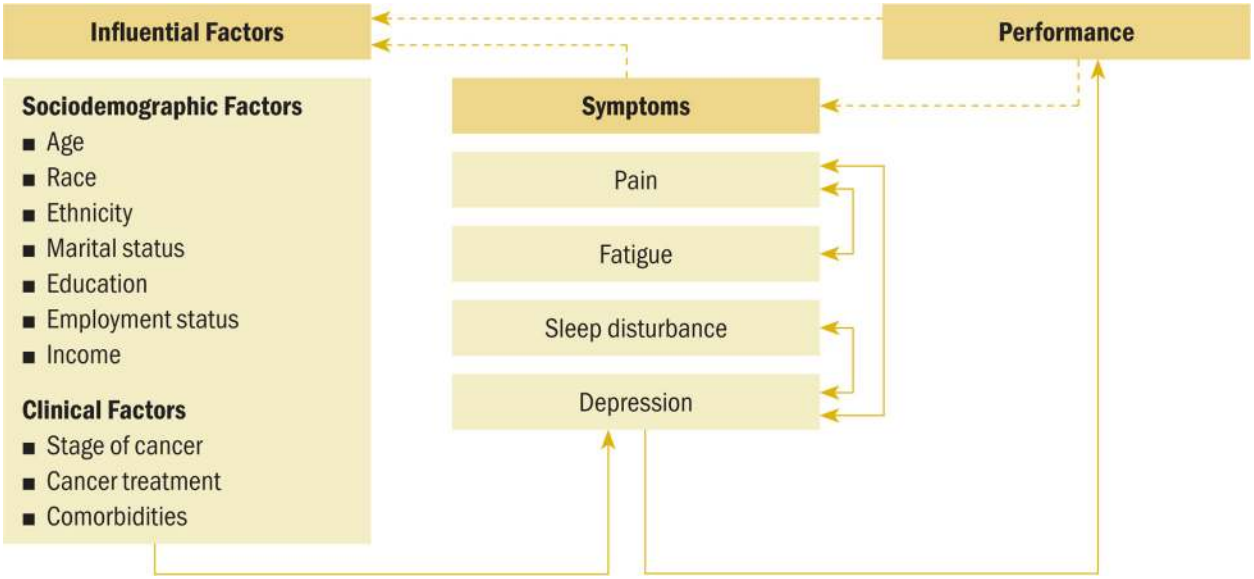

FIGURE 1. The Theory of Unpleasant Symptoms Adapted for the Analysis of Symptom Clusters in Breast Cancer Survivors

Note. Dashed lines indicate feedback, solid lines indicate influences, and double-barbed arrows indicate interaction.

Note. Based on information from Lenz et al., 1997.

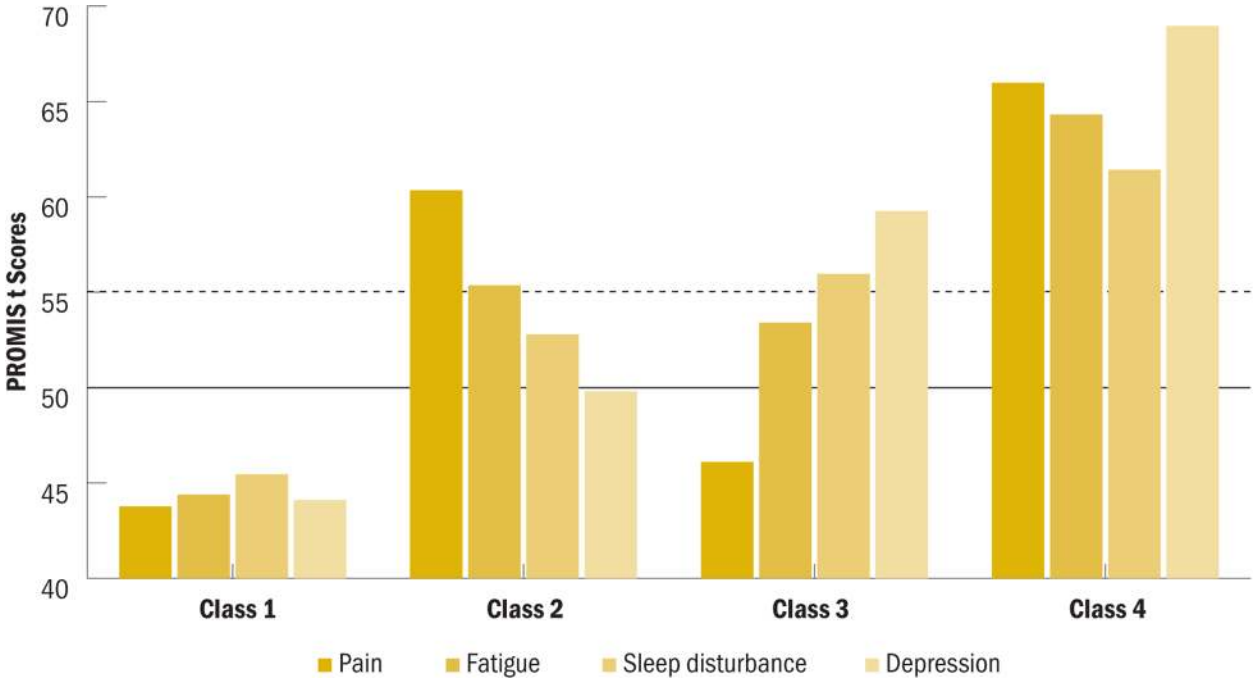

FIGURE 2. Difference in Symptom Distress Among the Latent Classes

class 1—symptoms within normal limits; class 2—pain with fatigue and sleep disturbance; class 3—depression with fatigue and sleep disturbance; class 4—all high symptom burden; PROMIS—Patient-Reported Outcomes Measurement Information System

Note. The dashed line indicates the depression threshold; the solid line indicates the pain, fatigue, and sleep disturbance thresholds.

TABLE 1.

Sample Characteristics (N = 1,500)

Characteristic	n	%
Age at diagnosis (years)		
21–49	611	41
50–64	514	34
65 or older	375	25
Race[a]		
White	715	48
Asian	367	24
Black	288	19
Other	128	9
Ethnicity		
Non-Hispanic	1,205	80
Hispanic	295	20
Marital status[a]		
Married or cohabiting	883	59
Divorced, separated, or widowed	446	30
Never married	156	10
Education level[a]		
Less than high school degree	185	12
High school degree	258	17
Some college	493	33
Undergraduate degree or greater	547	36
Employment status[a,b]		
Working	843	56
Not working	638	43
Annual income ($)[a]		
Less than 40,000	526	35
40,000 or greater	729	49
Cancer stage[a]		
I	693	46
II	557	37
III	154	10
IV	32	2
Cancer treatment history[c]		
Surgery	1,379	93
Chemotherapy	891	60
Radiation therapy	875	59

[a]Does not total 1,500 because of missing data

[b] Not working includes retired, disabled, or unemployed; working includes employed, homemaker, or student.

[c] Participants could choose multiple responses.

TABLE 2.

Model Fit Information for LCPA Models Fit to Breast Cancer Survivor Data

Class	Number of Parameters	AIC	BIC	Entropy	VLMR[a]	BLRT[a]
2	13	42,453.566	42,522.638	0.882	p < 0.001	p < 0.001
3	18	41,989.507	42,085.145	0.823	p < 0.001	p < 0.001
4[b]	23	41,724.69	41,846.894	0.861	p = 0.0056	p < 0.001
5	28	41,580.397	41,729.167	0.861	p = 0.1403	p < 0.001

[a]Chi-square statistic for the VLMR and the BLRT; when nonsignificant ($p < 0.05$), the VLMR and BLRT test provide evidence that a K-1–class model fits the data better than a K-class model.

[b]Four-class model was selected based on its having a smaller BIC than the three-class model and nonsignificant VLMR in the five-class model.

AIC—Akaike information criterion; BIC—Bayesian information criterion; BLRT—bootstrapped likelihood ratio test; LCPA—latent class profile analysis; VLMR—Vuong–Lo–Mendell–Rubin likelihood ratio test

TABLE 3.

Differences in Severity of Symptoms Among the Latent Classes Using the Four-Class Solution (N = 1,500)

	Class 1 (n = 864)		Class 2 (n = 282)		Class 3 (n = 161)		Class 4 (n = 193)		
Variable	$\overline{X}$	**SD**	$\overline{X}$	**SD**	$\overline{X}$	**SD**	$\overline{X}$	**SD**	**p**
Pain	43.77	4.31	60.35	5.26	46.1	4.9	65.99	5.89	< 0.001
Fatigue	44.39	6.48	55.36	8.09	53.4	8.32	64.32	6.98	< 0.001
Sleep disturbance	45.45	7.93	52.79	8.49	55.96	8.37	61.42	8.33	< 0.001
Depression	44.1	3.68	49.8	5.96	59.26	6.16	68.96	6.75	< 0.001

class 1—symptoms within normal limits; class 2—pain with fatigue and sleep disturbance; class 3—depression with fatigue and sleep disturbance; class 4—all high symptom burden

Note. Clinically relevant symptom thresholds include pain: less than 50 is normal, 50–59 is mild, 60–69 is moderate, and 70 or greater is severe; fatigue and sleep disturbance: less than 50 is normal, 50–54 is mild, 55–74 is moderate, and 75 or greater is severe; and depression: less than 55 is normal, 55–64 is mild, 65–74 is moderate, and 75 or greater is severe.

TABLE 4.

Results of Multinomial Logistic Regression: Predicting Symptom Clusters

Predictor	β	Standard Error	Odds Ratio	95% CI
Class 2 versus class 1				
Age at diagnosis (years)				
21–64	0.75	0.25	2.12	[1.29,3.49]**
65 or older[a]	-	-	-	-
Employment status				
Not working	0.52	0.21	1.69	[1.13,2.52]*
Working[a]	-	-	-	-
Cancer treatment				
Chemotherapy	0.88	0.2	2.41	[1.63,3.55]***
Number of comorbidities	0.56	0.09	1.74	[1.47,2.07]***
Class 3 versus class 1				
Age at diagnosis				
21–64	0.84	0.32	2.31	[1.23,4.32]**
65 or[a]	-	-	-	-
Education level				
Less than high school degree	0.61	0.43	1.85	[0.79,4.32]
High school degree	0.45	0.35	1.56	[0.78,3.11]
Some college	0.69	0.26	1.98	[1.19,3.29]**
Undergraduate degree or greater[a]	-	-	-	-
Employment status				
Not working	0.49	0.25	1.98	[1.2,3.29]**
Working[a]				
Class 4 versus class 1				
Age at diagnosis (years)				
21–64	1.64	0.33	5.17	[2.73,9.78]***

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Predictor	β	Standard Error	Odds Ratio	95% CI
65 or older[a]	-	-	-	-
Education level				
Less than high school degree	1.06	0.4	2.89	[1.31,6.36]**
High school degree	0.78	0.36	2.18	[1.11,4.41]*
Some college	0.9	0.29	2.46	[1.4,4.32]**
Undergraduate degree or greater[a]	-	-	-	-
Employment status				
Not working	1.08	0.24	2.96	[1.85,4.73]***
Working[a]	-	-	-	-
Cancer treatment				
Chemotherapy	0.99	0.25	2.69	[1.66,4.38]***
Number of comorbidities	0.63	0.1	1.88	[1.54,2.29]***

* p < 0.05;

** p < 0.01;

*** p < 0.001

[a]Reference category

CI—confidence interval; class 1—symptoms within normal limits; class 2—pain with fatigue and sleep disturbance; class 3—depression with fatigue and sleep disturbance; class 4—all high symptom burden

Note. Class 1 was used as the reference group.

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