Original Article

Symptom Cluster Trajectories During Chemotherapy in Breast Cancer Outpatients

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Abstract

Context. Breast cancer patients often experience multiple symptoms and substantial discomfort. Some symptoms may occur simultaneously and throughout the duration of chemotherapy treatment.

Objectives. The aim of this study was to investigate symptom severity and symptom cluster trajectories during chemotherapy in outpatients with breast cancer in Taiwan.

Methods. This prospective, longitudinal, repeated measures study administered a standardized questionnaire (M. D. Anderson Symptom Inventory Taiwan version) to 103 breast cancer patients during each day of the third 21-day cycle of chemotherapy. Latent class growth analysis was performed to examine symptom cluster trajectories.

Results. Three symptom clusters were identified within the first 14 days of the 21-day chemotherapy cycle: the neurocognition cluster (pain, shortness of breath, vomiting, memory problems, and numbness/tingling) with a trajectory of \( Y = 2.09 - 0.11 \) (days), the emotion-nausea cluster (nausea, disturbed sleep, distress/upset, drowsiness, and sadness) with a trajectory of \( Y = 3.57 - 0.20 \) (days), and the fatigue-anorexia cluster (fatigue, lack of appetite, and dry mouth) with a trajectory of \( Y = 4.22 - 0.21 \) (days). The “fatigue-anorexia cluster” and “emotion-nausea cluster” peaked at moderate levels on chemotherapy days 3–5, and then gradually decreased to mild levels within the first 14 days of the 21-day chemotherapy cycle.

Conclusion. Distinct symptom clusters were observed during the third cycle of chemotherapy. Systematic and ongoing evaluation of symptom cluster trajectories during cancer treatment is essential. Healthcare providers can use these findings to enhance communication with their breast cancer patients and to prioritize symptoms that require attention and intervention.

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Key Words
Symptom cluster, trajectories, breast cancer, chemotherapy

Introduction

Breast cancer is the most common cancer in women in the U.S., and was ranked the highest of all cancer types in terms of overall incidence during 2008–2011 in Taiwan. Adjuvant chemotherapy is an effective treatment for breast cancer, and is now a routinely used cost-saving strategy for treating breast cancer in outpatient settings. Breast cancer patients often experience multiple symptoms and substantial
discomfort, especially during the third chemotherapy cycle. Most symptom studies have used cross-sectional designs to measure symptoms at a single time point. However, because some studies suggest that symptoms may change over time, the use of longitudinal study designs that measure symptoms at multiple time points has increased. Symptom trajectories during chemotherapy have received some attention in the literature, but most studies have focused on changes in individual symptoms such as depression, fatigue, sleep disturbance, and pain. However, some symptoms may occur simultaneously and throughout the duration of chemotherapy treatment. Therefore, the purpose of this study was to investigate symptom severity and symptom cluster trajectories during chemotherapy in breast cancer outpatients in Taiwan.

Ideally, symptoms should be assessed in clusters rather than individually because symptoms in some clusters have synergistic effects on morbidity, mortality, prognosis, and quality of life. Aktas defined a symptom cluster as two or more related symptoms that co-occur as a stable group relatively independently of other symptom clusters. A symptom cluster can cause a vicious cycle in which unrelieved, worsening symptoms increase disease complications, worsen functional/physical status, and increase financial and emotional burdens on the patient. Symptom clusters can also cause patients to discontinue or delay treatment. Therefore, a symptom cluster may have a greater health impact compared with its individual symptoms.

Three different conceptual approaches have been applied in cross-sectional studies of symptom clusters: 1) using factor or cluster analysis to group symptoms, 2) using predetermined symptoms to group symptoms, and 3) using cluster analysis to group individuals. However, few cross-sectional studies have provided direct evidence of the relationships among symptoms. Longitudinal study designs and relevant statistical methods such as growth modeling, growth curve analysis, or growth mixture analysis are needed to test complex models of symptom clusters and to identify patterns of symptom clusters. Previous studies of symptom clusters have focused on specific symptoms and predetermined symptom clusters such as pain, fatigue, sleep disturbance, and depression, which are the most prevalent and distressing symptoms according to clinical and statistical data for breast cancer populations. However, studies that focus only on predetermined symptoms may overlook other important symptoms or symptom clusters. Therefore, evaluating all symptoms simultaneously is essential. A literature review reveals wide variation in the composition of symptom clusters. Most studies in the breast cancer literature have focused on aspects such as treatments, measurement time points, statistical methods, and assessment instruments.

Some studies have investigated the trajectories of symptoms or symptom clusters in patients with lung cancer or other cancer types at several time points during treatment or post-treatment. However, studies of breast cancer symptom clusters during chemotherapy treatment have rarely analyzed symptoms longitudinally and over multiple time points, and no studies have explored daily changes in breast cancer symptom cluster trajectories during a single chemotherapy cycle. Increasing the number of time points for symptom measurement improves accuracy in predicting symptom cluster trajectories. Therefore, the research questions in this study were the following. What are the most severe symptoms during a chemotherapy cycle? What symptom clusters have been identified? What are the trajectories of these symptom clusters? To answer those questions, this prospective longitudinal study used daily measurements to investigate symptom severity in a Taiwan population of breast cancer patients during their third cycle of a 21-day chemotherapy regimen of cyclophosphamide, epirubicin, and fluorouracil (CEF). The main working hypothesis was that the severity of symptom clusters in the breast cancer patients undergoing chemotherapy during the study period would exhibit one of the three distinct trajectories: 1) obvious fluctuation during chemotherapy followed by a gradual decrease to a certain level, 2) consistent decrease in the magnitude of change in symptom cluster severity over time, and 3) intermittent change (no clear pattern).

Methods

This prospective longitudinal study used a repeated measures design to analyze a convenience sample of breast cancer outpatients recruited from the cancer center of a large teaching hospital in south Taiwan. This comprehensive 1700-bed cancer center serves 600 outpatients daily. This study was approved by the institutional review board of the participating hospital. Recruitment criteria were 1) age 18 years or older, 2) diagnosis of breast cancer and completion of two cycles of CEF in adjuvant chemotherapy, 3) record of at least two symptoms during the third CEF cycle, and 4) ability to understand written or verbal Chinese. For each patient who met the recruitment criteria, the researcher introduced the study purpose and procedures and obtained written informed consent to participate. Day 1 of the CEF regimen consisted of cyclophosphamide (500–600 mg/m²), epirubicin (75–90 mg/m²), and fluorouracil (500–600 mg/m²). All drugs were administered intravenously every three weeks for six to eight total cycles. Each participant completed the M. D. Anderson Symptom
Inventory (MDASI) in a diary on each day of their third 21-day CEF cycle. The instrument required three to five minutes to complete. Data were collected from July 2010 to May 2012. A symptom cluster was defined as two or more related symptoms occurring simultaneously as a stable group relatively independently of other symptom clusters.

**Measures**

At baseline, the participants completed the Demographic Profile-Baseline form and a medical information form. The MDASI was then completed for 21 consecutive days in a daily diary. The 19-item Taiwan version of the MDASI (MDASI-T) used in this study included two subscales: a symptom severity subscale (13 items: fatigue, sleep disturbance, pain, drowsiness, poor appetite, nausea, vomiting, shortness of breath, numbness, memory problems, dry mouth, distress, and sadness) and a life interference subscale. Each item was rated using an 11-point scale from 0 (no interference with daily life activities) to 10 (complete interference with daily life activities), and the mean scores were recorded. Because the focus of this study was symptom severity change, the life interference subscale of the MDASI-T was excluded. Based on the standard criteria applied in the literature and in clinical practice, symptom severity was provisionally categorized as mild (rating of 1–3), moderate (rating of 4–6), or severe (rating of 7–10) when interpreting the results. Overall, the MDASI-T has shown acceptable validity and reliability for identifying and monitoring cancer-related symptoms and treatment in cancer patients in Taiwan. The symptom severity subscale used in this study has also shown high reliability (13 items, Cronbach’s α = 0.88).

**Data Analysis**

The statistical progressions of the study variables at baseline and during follow-up periods were summarized as means ± standard deviations for continuous variables and as proportions for categorical variables. Because symptom clusters can theoretically have several trajectories, latent class growth analysis (LCGA) was used to identify and classify trajectories of change in the severity of the 13 symptoms over time.

The LCGA is a recently developed approach to analyze longitudinal trajectories of change in clinical phenomena. Its purposes are to reveal distinct patterns of homogeneous longitudinal trajectories and to explain individual-level differences at the group level. The LCGA summarizes the heterogeneity (i.e., changes in the severity of individual symptoms over time according to the data) by using a finite set of unique polynomial functions, each of which corresponds to a discrete trajectory. Because the magnitude and direction of change can vary freely across trajectories, a set of model parameters (i.e., intercept and slope) is estimated for each trajectory. A major advantage of LCGA is that it provides an alternative to the “classify-then-analyze” procedure, in which items are first classified into groups by a given method (e.g., cluster analysis using a distance metric), and then the clusters are compared in terms of various measures. In the present study, LCGA was the best method of analyzing inter-symptom differences in intra-symptom changes.

The LCGA was then used to test whether the trajectory models were consistent with our primary working hypothesis. If the quadratic components of these models were not significant, further analyses were performed using constant level or linear trajectories. We also continued testing of simpler or more complex models with decreasing or increasing numbers of trajectories to determine whether a model with less than or more than three trajectories had the best data fit. These processes were repeated until they obtained the best model fit, which was determined by comparing the two performance indexes described below. After selecting the most suitable model, posterior probabilities were calculated. Posterior probabilities reflect the likelihood of each symptom belonging to each trajectory, that is, the probability of each individual symptom belonging to each possible class.

Although the subgroups of interest in an LCGA are usually subgroups of individuals, this study used LCGA to identify subgroups of symptoms. The mean severity of each symptom was calculated by averaging the severity of each symptom in the 103 patients. Hence, average mean symptom severity for 13 symptoms was calculated for each day of the study. Trajectory parameters were estimated using a full information maximum-likelihood method that is robust for missingness with the following specifications: $Y_{it} = \beta_0 + \beta_1 \times \text{time}_{it} + \beta_2 \times \text{time}_{it}^2$, $i = 1, \ldots, 13$. The $Y_{it}$ is a latent variable representing average severity of the symptom (i) at time (t) given membership in group (g). Time (t) refers to the time point for data collection; $\beta_0$, $\beta_1$, and $\beta_2$ are the coefficients associated with the intercept, linear, and quadratic rate of change, respectively, in symptom severity scores. For LCGA, the 13 symptoms were grouped into several symptom clusters with similar slopes and adjacent intercepts. Hence, a finite set of unique polynomial functions was obtained for the symptom clusters. The $Y$ axis of the symptom clusters represents the average symptom severity of the symptom clusters (the symptom cluster score; Figs. 1 and 2). The SAS 9.2 software (SAS Institute, Inc., Cary, NC) was used to estimate the model and to calculate two model performance indexes for alternative models: Akaike information criterion and Bayesian
information criterion. Low Akaike information criterion and Bayesian information criterion values are interpreted as a good model fit to the data when an additional latent class is included.

Results

Of the 111 patients who consented to participate, 103 patients completed the study (attrition rate = 7.2%). The age range was 28–69 years (mean...
age 50.5 ± 8.07 years; Table 1). During the third 21-day chemotherapy cycle, symptom severity was mild to moderate. The "most severe" symptoms were identified by averaging the severity of each symptom across all 21 days. Dry mouth was the most severe symptom (2.38 ± 0.66). The next four most severe symptoms were fatigue, lack of appetite, disturbed sleep, and distress/upset (Table 2). Lack of appetite, fatigue, and dry mouth were the three most severe symptoms during week 1; disturbed sleep, dry mouth, and fatigue were the three most severe symptoms during week 2; dry mouth, disturbed sleep, and depression (upset) were the three most severe symptoms during week 3 (Table 3).

Figure 1 presents the severity scores for each symptom cluster on each of the 21 days of the analysis. The LCGA revealed that the trajectories of two symptom clusters within the third 21-day chemotherapy cycle fit the quadratic model: a neurocognition cluster and an emotion-nausea-fatigue-anorexia cluster. The neurocognition cluster included pain, shortness of breath, vomiting, memory problems, and numbness or tingling (the quadratic equation can be written as Y = 2.08 – 0.11 [days] + 0.00241 [day²]; Fig. 1). Over the period examined, the average severity of these symptoms was mild (≤3). The emotion-nausea-fatigue-anorexia cluster included fatigue, nausea, disturbed sleep, distress/upset, lack of appetite, drowsiness, dry mouth, and sadness (the quadratic equation can be written as Y = 3.96 – 0.26 [days] + 0.00658 [day²]; Fig. 1). The average severity of these symptoms decreased from moderate to mild at day 5 (day 4, Y = 3.03; day 5, Y = 2.82; Fig. 1).

The severities of symptom clusters fluctuated widely during days 1–14, but were relatively stable during days 15–21. Therefore, days 1–14 were reanalyzed. The reanalysis yielded three symptom clusters that fit the linear model: a neurocognition cluster, an emotion-nausea cluster, and a fatigue-anorexia cluster. The neurocognition cluster included pain, shortness of breath, vomiting, memory problems, and numbness or tingling (the linear equation can be written as Y = 2.09 – 0.11 [days]; Fig. 2). The average severity of these symptoms was mild over the period examined. The emotion-nausea cluster included nausea, disturbed sleep, distress/upset, drowsiness, and sadness (the linear equation can be written as Y = 3.57 – 0.20 [days]). The average severity of these symptoms decreased from moderate to mild during days 3–5 (day 2, Y = 3.17; day 3, Y = 2.97; day 4, Y = 2.77; day 5, Y = 2.57; Fig. 2). The fatigue-anorexia cluster included fatigue, lack of appetite, and dry mouth (the linear equation can be written as Y = 4.22 – 0.21 [days]). The average severity of these symptoms decreased from moderate to mild at day 5 (day 5, Y = 3.17; day 6, Y = 2.96; Fig. 2).

### Discussion

This study is the first to examine the trajectories of symptom clusters in breast cancer patients during a 21-day cycle of chemotherapy. This study is unique because the symptom clusters included in the LCGA were not predetermined. Rather, multiple symptoms were included in an LCGA analysis to determine how they clustered during the 21-day cycle. Moreover, the longitudinal design of this study could theoretically determine the stability of symptom clusters over time. The LCGA approach not only provides group level data as in conventional analyses, but also reveals high inter-symptom variability within the trajectories.

During the 21-day chemotherapy cycle, average symptom severity ranged from mild to moderate. The five most severe symptoms were dry mouth, fatigue, lack of appetite, disturbed sleep, and distress/upset. The three most severe symptoms (fatigue, lack of appetite, and disturbed sleep) were consistent with those reported in Chen and Lin. Lack of

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**Table 1**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No.</th>
<th>%</th>
</tr>
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<tbody>
<tr>
<td>Age (yrs)</td>
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<td></td>
</tr>
<tr>
<td>≤30</td>
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<tr>
<td>31–40</td>
<td>13</td>
<td>12.6</td>
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<tr>
<td>41–50</td>
<td>36</td>
<td>35.0</td>
</tr>
<tr>
<td>51–60</td>
<td>43</td>
<td>41.7</td>
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<tr>
<td>61–70</td>
<td>10</td>
<td>9.7</td>
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<tr>
<td>Grade 1–6</td>
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<td>11.7</td>
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<tr>
<td>Grade 7–9</td>
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<tr>
<td>High school</td>
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<td>34.0</td>
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<tr>
<td>University/college</td>
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<td>31.1</td>
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<tr>
<td>Graduate school</td>
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<td>2.9</td>
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<tr>
<td>Marital status</td>
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<td>6.8</td>
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<tr>
<td>Married/partnered</td>
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<td>80.6</td>
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<tr>
<td>Separated</td>
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<td>2.9</td>
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<td>Divorced</td>
<td>4</td>
<td>3.9</td>
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<tr>
<td>Widowed</td>
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<td>5.8</td>
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<td>Religion</td>
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<td>19.4</td>
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<tr>
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<td>51.5</td>
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<tr>
<td>Christianity</td>
<td>8</td>
<td>7.7</td>
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<tr>
<td>Taoism</td>
<td>21</td>
<td>20.4</td>
</tr>
<tr>
<td>Other</td>
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<td>1</td>
</tr>
<tr>
<td>Disease stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In situ</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>I</td>
<td>32</td>
<td>31.1</td>
</tr>
<tr>
<td>II</td>
<td>50</td>
<td>48.5</td>
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<td>III</td>
<td>20</td>
<td>19.4</td>
</tr>
<tr>
<td>Type of surgery</td>
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<td></td>
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<tr>
<td>MRM</td>
<td>26</td>
<td>25.2</td>
</tr>
<tr>
<td>BCS/Lumpectomy</td>
<td>58</td>
<td>56.3</td>
</tr>
<tr>
<td>MRM + TRAM</td>
<td>18</td>
<td>17.5</td>
</tr>
<tr>
<td>Missing data</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

BCS = breast conserving surgery; MRM = modified radical mastectomy; TRAM = transverse rectus abdominis myocutaneous flap reconstruction.
appetite decreases chewing activity, which causes a dry mouth. Bone marrow suppression caused by CEF chemotherapy can cause anemia and fatigue. The patients also had high sleep disturbance, which is consistent with an earlier systematic overview of 10 studies of the association between chemotherapy and sleep disturbances. Dry mouth, fatigue, appetite loss, and sleep disturbance cause physical distress and an ensuing vicious cycle between physical distress and emotional distress/upset.

Over the 21-day chemotherapy cycle, some symptoms in each cluster were consistent with those reported in the literature, but some symptoms were not. In Nguyen et al., a review of five studies related to symptom clusters in breast cancer found that the only symptoms that occurred in a cluster were nausea and poor appetite. Similarly, our patients simultaneously experienced nausea and poor appetite in the emotion-nausea-fatigue-anorexia cluster. However, Kim et al. investigated treatment-related symptom clusters in 282 breast cancer patients who had received at least three cycles of chemotherapy, radiotherapy, or concurrent chemoradiation across three time points (time point 1 was before treatment; time point 2 was 48 hours after the second chemotherapy cycle or during the last week of radiotherapy; and time point 3 was 48 hours after the third chemotherapy cycle or 1 month after completion of radiotherapy). In a secondary analysis performed across three time points by factor analysis

Table 2

<table>
<thead>
<tr>
<th>Symptom Items</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Your dry mouth at its worst</td>
<td>1.57</td>
<td>3.45</td>
<td>2.38 (.66)</td>
</tr>
<tr>
<td>Your fatigue (tiredness) at its worst</td>
<td>1.42</td>
<td>4.09</td>
<td>2.37 (.94)</td>
</tr>
<tr>
<td>Your lack of appetite at its worst</td>
<td>1.28</td>
<td>4.34</td>
<td>2.29 (1.04)</td>
</tr>
<tr>
<td>Your disturbed sleep at its worst</td>
<td>1.54</td>
<td>3.05</td>
<td>2.20 (.50)</td>
</tr>
<tr>
<td>Your depression (upset) at its worst</td>
<td>1.42</td>
<td>3.07</td>
<td>2.01 (.56)</td>
</tr>
<tr>
<td>Your sadness at its worst</td>
<td>1.29</td>
<td>3.17</td>
<td>1.96 (.66)</td>
</tr>
<tr>
<td>Your drowsiness (sleepiness) at its worst</td>
<td>1.21</td>
<td>3.53</td>
<td>1.94 (.81)</td>
</tr>
<tr>
<td>Your nausea at its worst</td>
<td>0.60</td>
<td>3.79</td>
<td>1.75 (1.14)</td>
</tr>
<tr>
<td>Your forgetfulness at its worst</td>
<td>1.42</td>
<td>1.73</td>
<td>1.57 (.10)</td>
</tr>
<tr>
<td>Your pain at its worst</td>
<td>0.92</td>
<td>1.83</td>
<td>1.30 (.29)</td>
</tr>
<tr>
<td>Your vomiting at its worst</td>
<td>0.46</td>
<td>2.79</td>
<td>1.24 (.78)</td>
</tr>
<tr>
<td>Your shortness of breath at its worst</td>
<td>0.79</td>
<td>1.89</td>
<td>1.29 (.38)</td>
</tr>
<tr>
<td>Your numbness or tingling at its worst</td>
<td>0.85</td>
<td>1.81</td>
<td>1.15 (.25)</td>
</tr>
</tbody>
</table>

Table 3

<table>
<thead>
<tr>
<th>Symptom Items</th>
<th>Week 1 Mean (SD)</th>
<th>Week 2 Mean (SD)</th>
<th>Week 3 Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Your dry mouth at its worst</td>
<td>3.19 (.34)</td>
<td>2.29 (.19)</td>
<td>1.74 (.13)</td>
</tr>
<tr>
<td>Your fatigue (tiredness) at its worst</td>
<td>3.56 (.56)</td>
<td>2.00 (.26)</td>
<td>1.56 (.09)</td>
</tr>
<tr>
<td>Your lack of appetite at its worst</td>
<td>2.66–4.09</td>
<td>1.59–2.38</td>
<td>1.42–1.70</td>
</tr>
<tr>
<td>Your disturbed sleep at its worst</td>
<td>3.58 (.57)</td>
<td>1.94 (.38)</td>
<td>1.35 (.05)</td>
</tr>
<tr>
<td>Your depression (upset) at its worst</td>
<td>2.69–4.34</td>
<td>1.40–2.46</td>
<td>1.28–1.45</td>
</tr>
<tr>
<td>Your sadness at its worst</td>
<td>2.71 (.35)</td>
<td>2.23 (.26)</td>
<td>1.66 (.08)</td>
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<tr>
<td>Your drowsiness (sleepiness) at its worst</td>
<td>2.18–3.03</td>
<td>1.81–2.51</td>
<td>1.54–1.76</td>
</tr>
<tr>
<td>Your nausea at its worst</td>
<td>2.70 (.37)</td>
<td>1.77 (.20)</td>
<td>1.57 (.08)</td>
</tr>
<tr>
<td>Your forgetfulness at its worst</td>
<td>2.80 (.32)</td>
<td>1.70 (.14)</td>
<td>1.36 (.05)</td>
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<tr>
<td>Your pain at its worst</td>
<td>2.08–3.07</td>
<td>1.42–2.02</td>
<td>1.48–1.68</td>
</tr>
<tr>
<td>Your vomiting at its worst</td>
<td>2.24–3.17</td>
<td>1.45–1.85</td>
<td>1.29–1.42</td>
</tr>
<tr>
<td>Your shortness of breath at its worst</td>
<td>2.97 (.49)</td>
<td>1.55 (.17)</td>
<td>1.29 (.06)</td>
</tr>
<tr>
<td>Your numbness or tingling at its worst</td>
<td>2.14–3.53</td>
<td>1.28–1.81</td>
<td>1.21–1.39</td>
</tr>
<tr>
<td>Your shortness of breath at its worst</td>
<td>3.18 (.56)</td>
<td>1.30 (.33)</td>
<td>0.71 (.09)</td>
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<tr>
<td>Your numbness or tingling at its worst</td>
<td>3.14–3.79</td>
<td>0.85–1.69</td>
<td>0.60–0.83</td>
</tr>
<tr>
<td>Your forgetfulness at its worst</td>
<td>1.63 (.08)</td>
<td>1.61 (.09)</td>
<td>1.48 (.05)</td>
</tr>
<tr>
<td>Your pain at its worst</td>
<td>1.49–1.73</td>
<td>1.46–1.70</td>
<td>1.42–1.58</td>
</tr>
<tr>
<td>Your vomiting at its worst</td>
<td>1.17–1.83</td>
<td>1.12–1.42</td>
<td>0.92–1.10</td>
</tr>
<tr>
<td>Your shortness of breath at its worst</td>
<td>2.29 (.50)</td>
<td>0.98 (.16)</td>
<td>0.52 (.05)</td>
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<tr>
<td>Your numbness or tingling at its worst</td>
<td>1.41–2.79</td>
<td>0.74–1.21</td>
<td>0.46–0.60</td>
</tr>
<tr>
<td>Your shortness of breath at its worst</td>
<td>1.67 (.23)</td>
<td>1.08 (.13)</td>
<td>0.85 (.06)</td>
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<tr>
<td>Your numbness or tingling at its worst</td>
<td>1.39 (.24)</td>
<td>1.10 (.06)</td>
<td>0.91 (.04)</td>
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</tbody>
</table>
approach, Kim et al.\textsuperscript{34} identified an upper gastrointestinal cluster (nausea, vomiting, decreased appetite) and a psychoneurological symptom cluster from 20 symptoms measured by the General Fatigue Scale, Profile of Mood States-short form, Pittsburgh Sleep Quality Index, and by the Side Effect Checklist. Interestingly, nausea and vomiting were grouped into two different clusters instead of a single cluster in our study. One explanation is that, because the symptom clusters were obtained by a statistical method, symptoms in some clusters may have had different pathophysiological causes or shared a common etiology. In addition, the participants received a dose of prophylactic anti-emetic premedication (Solu-Medrol\textsuperscript{[methyl prednisolone]} 40 mg\textsuperscript{2} Vial IV/Vena [diphenhydramine] 30 mg\textsuperscript{1} Amp IV/Setoral [ramosetron] 0.3 mg\textsuperscript{2} Amp IV) 30 minutes before CEF chemotherapy, which reduced the severity of vomiting. Although nausea and vomiting may be associated with the same physiologic reaction, the use of anti-emetic premedication in this study suggests that the nausea likely resulted from subjective feelings involving higher brain regions\textsuperscript{35} related to emotion control.

As in our study, an earlier study by Kim et al.\textsuperscript{34} reported that depressed mood, fatigue, and insomnia were clustered together, but were not the only three symptoms in the psychoneurological symptom cluster. Another Taiwan study used the 13-item M. D. Anderson Symptom Inventory to investigate 151 outpatients with various cancers.\textsuperscript{36} The emotion-nausea-fatigue-anorexia cluster used in our 21-day analysis is the same as the first and third factors in Chen and Tseng,\textsuperscript{36} the clusters are labeled differently.

Analysis of the trajectories of symptom clusters defined by the LCGA revealed the fatigue-anorexia cluster, the emotion-nausea cluster, and the neurocognition cluster within the first 14 days of the 21-day chemotherapy cycle. Our labels for these clusters were similar to those used in Bender et al.,\textsuperscript{37} who performed an exploratory secondary analysis of 88 patients who had received surgery and adjuvant chemotherapy for breast cancer (stages I–III). Four assessment instruments and a hierarchical cluster analysis revealed three symptom clusters (perceived cognitive impairment, mood problems, and fatigue), which is consistent with the present results. In the present study, the fatigue-anorexia cluster and emotion-nausea cluster also peaked at moderate levels on chemotherapy days 3–5, and then gradually decreased to mild levels within the first 14 days of the 21-day chemotherapy cycle. These results are consistent with those reported in several earlier studies of the trajectories of individual symptoms in patients undergoing chemotherapy. Studies of breast cancer patients undergoing chemotherapy show that symptom severity is highest on the first two or three days after chemotherapy.\textsuperscript{38,39}

The fatigue-anorexia cluster may include lack of appetite and dry mouth because proinflammatory cytokines inhibit cortisol production, which decreases appetite, and thus decreases intake of food and water. Proinflammatory cytokines also increase fatigue and decrease production of adenosine triphosphate, which is needed for skeletal muscle activity.\textsuperscript{40} In addition, because chewing is the most efficient way to stimulate salivary flow,\textsuperscript{41} patients with low food intake are expected to exhibit dry mouth symptoms due to decreased chewing activity. Farhangfar et al.\textsuperscript{42} reported that dry mouth and appetite loss are significantly associated with reduced dietary intake, which may then cause dehydration. Dehydration also decreases circulatory volume and causes weakness, dizziness, and fatigue\textsuperscript{43} while fatigue often coincides with loss of appetite.

The emotion-nausea cluster included nausea, disturbed sleep, distress/upset, drowsiness, and sadness. Nausea may affect subjective feelings as well as sleep quality. Because nausea involves higher brain regions\textsuperscript{35} related to emotion control, nausea can also cause emotional distress. Cancer-related symptoms; treatment-related side effects; and negative environmental and lifestyle factors, emotional status, and mood can cause distress and sleep disturbance, which can then cause drowsiness. Disturbed sleep can also cause a deleterious feedback loop that increases the severity of other symptoms such as nausea and sadness.

The neurocognition cluster included pain, shortness of breath, vomiting, memory problems, and numbness or tingling. Patients in the present study reported that several symptoms occurred concurrently or sequentially. For example, uncontrollable or frequent vomiting in the neurocognition cluster can cause shortness of breath and pain sensations. A possible explanation is that the vomiting center is located in the medulla oblongata, which is related to breathing function and brainstem responses.\textsuperscript{14} Continuous rhythmic contractions of the diaphragm, abdominal wall, and thoracic muscles can also precipitate muscle and chest pain. Moreover, vomiting can cause the airways to close and decrease respiration,\textsuperscript{14} which may then cause a shortness of breath sensation.

Although further studies are needed, these preliminary results have several implications for clinical practice. First, the trajectories of symptom clusters observed in this study indicate that during the first two weeks of each chemotherapy cycle, healthcare providers can use a checklist to identify high-risk patients for the fatigue-anorexia symptom cluster and for the emotion-nausea symptom cluster. Healthcare
providers can also use these data to educate patients in symptom clusters before they begin chemotherapy and to advise patients on general strategies for managing their symptoms.\textsuperscript{45} Patients can also be routinely screened for these symptoms throughout the chemotherapy process. Laboratory evaluations can then focus on the onset and severity of specific current symptoms, and patients with multiple symptoms can be scheduled for further assessment and examinations. Patients with mild symptom clusters may only require clinical observation and education in symptom management, whereas patients with moderate symptom clusters may require local noninvasive interventions or comprehensive bundled care for simultaneous treatment of several symptoms. For example, components of bundled care could include exercise and nutrition counseling, behavior modification interventions (e.g., counseling, social support, cognitive therapy, and biofeedback), mind-body interventions (e.g., massage, music therapy, relaxation, tai chi and qi gong), alternative medicine (e.g., stimulation of the Tsu San-li and Neiguan acupuncture points), or energy conservation.\textsuperscript{45–47} Second, further studies are needed to characterize patients who experience the most severe symptom clusters such as the fatigue-anorexia cluster and the emotion-nausea cluster that were empirically identified in this study. The identification of subgroups of patients who have similar symptom clusters would improve stratification of risk for these clusters in chemotherapy patients. Symptom management interventions targeted specifically at high-risk groups would then improve patient outcomes. Third, comprehensive assessment tools are needed to facilitate the symptom cluster assessment process.

\textbf{Study Limitations}

This study has several limitations. First, the presence of two or more symptoms in the third chemotherapy cycle did not indicate that the symptom clusters are consistent across prior or subsequent treatment cycles. Further studies are needed to monitor each treatment cycle and to identify patterns of symptom clusters that emerge during chemotherapy. Second, the MDASI only evaluates 13 symptoms. This measure may not have captured other possibly more important symptoms. Third, the sample was recruited from a single medical center, which limits the potential generalizability of the results. Thus, the results should be replicated in larger samples of breast cancer patients from various hospitals. Last, our study tends to have more married patients and different ethnicities may be associated with the severity of symptoms.\textsuperscript{15} We did not control those characteristics of patients which was a limitation of the study.

\textbf{Conclusions}

Healthcare providers can apply the results of this study to enhance communication with their patients and to increase the effectiveness of multidisciplinary teams in various aspects of care. These findings can also assist healthcare providers in prioritizing interventions for symptoms that require immediate attention. An improved understanding of symptom cluster trajectories in breast cancer patients undergoing chemotherapy can help to identify high-risk patients and can assist health professionals in developing and improving reference guidelines for optimizing the type of nursing care and timing of nursing care for breast cancer patients.

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\textbf{References}

11. Miaskowski C, Aouizerat BE, Dodd M, Cooper B. Conceptual issues in symptom clusters research and their


