Asia-Pacific Journal of Oncology Nursing 11 (2024) 100343

Contents lists available at ScienceDirect

Asia-Pacific Journal of Oncology Nursing

journal homepage: www.apjon.org

Original Article

Symptom clusters in breast cancer survivors with and without type 2 diabetes over the cancer trajectory

Susan Storey [a,*], Xiao Luo [b], Jie Ren [c], Kun Huang [d], Diane Von Ah [e]

[a] Indiana University School of Nursing, Indianapolis, IN, USA
[b] Department of Management Science and Information Systems, School of Business, Oklahoma State University, OK, USA
[c] Department of Biostatistics and Health Data Science, Indiana University School of Medicine Indianapolis, IN, USA
[d] Department of Biostatistics and Health Data Science, Indiana University School of Medicine; Regenstrief Institute, Indianapolis, IN, USA
[e] College of Nursing, Cancer Research, Center for Healthy Aging, Self-Management and Complex Care, The Ohio State University, Columbus, OH, USA

ARTICLE INFO

Keywords:
Breast cancer survivors
Type 2 diabetes
Symptom clusters
Natural language processing
Cancer trajectory
Electronic health record

ABSTRACT

Objective: This study aimed to investigate symptoms and symptom clusters in breast cancer survivors (BCS) with and without type 2 diabetes across three crucial periods during the cancer trajectory (0-6 months, 12-18 months, and 24-30 months) post-initial chemotherapy.
Methods: Eight common symptoms in both BCS and individuals with diabetes were identified through natural language processing of electronic health records from January 2007 to December 2018. Exploratory factor analysis was employed to discern symptom clusters, evaluating their stability, consistency, and clinical relevance.
Results: Among the 4601 BCS in the study, 20% (n = 905) had a diabetes diagnosis. Gastrointestinal symptoms and fatigue were prevalent in both groups. While BCS in both groups exhibited an equal number of clusters, the composition of these clusters differed. Symptom clusters varied over time between BCS with and without diabetes. BCS with diabetes demonstrated less stability (repeated clusters) and consistency (same individual symptoms comprising clusters) than their counterparts without diabetes. This suggests that BCS with diabetes may experience distinct symptom clusters at pivotal points in the cancer treatment trajectory.
Conclusions: Healthcare providers must be attentive to BCS with diabetes throughout the cancer trajectory, considering intensified and/or unique profiles of symptoms and symptom clusters. Interdisciplinary cancer survivorship models are essential for effective diabetes management in BCS. Implementing a comprehensive diabetes management program throughout the cancer trajectory could alleviate symptoms and symptom clusters, ultimately enhancing health outcomes and potentially reducing healthcare resource utilization.

Introduction

Advances in prevention, screening, and treatment for breast cancer have improved overall survivor rates for breast cancer survivors (BCSs). As cancer survival rates increase, the potential for living with other comorbid conditions also increases.[1,2] Approximately 78% of BCS have at least one comorbid condition.[2] Type 2 diabetes is a common comorbid condition among BCS.[2] In our previous studies, we found that up to 16% of BCS also had a diagnosis of diabetes.[3] As BCS live longer, understanding the influence of comorbid conditions is of foremost importance for those living with the conditions and for the healthcare team providing care to these survivors.

Independently, BCS and people with diabetes experience similar symptoms, including gastrointestinal issues, fatigue, peripheral neuropathy, anxiety, depression, sleep disturbance, and decrements in physical function and cognition.[4–9] These symptoms rarely occur in isolation, as they are often interrelated and likely to co-occur, known as symptom clusters.[10] These interrelated symptoms can influence and/or intensify other symptoms.[11] Among cancer patients, symptom clusters have been associated with poorer health outcomes and quality of life.[12–17] Despite the increased number of studies investigating symptom clusters in cancer survivors, studies examining the influence of comorbid conditions, such as diabetes and breast cancer, on symptom clusters are lacking. Breast cancer and diabetes each initiate inflammatory responses that generate

* *Corresponding author.*
E-mail address: sustorey@iu.edu (S. Storey).

https://doi.org/10.1016/j.apjon.2023.100343
Received 10 May 2023; Accepted 10 November 2023

physiologic processes such as oxidative stress and the overexpression of proinflammatory cytokines which may contribute to the onset of symptoms/symptom clusters.[8,18,19] Therefore, it is plausible that the presence of comorbid diabetes may potentiate the symptoms/symptom clusters of BCS. As the projections for diabetes worldwide are predicted to increase to 783 million people by 2045,[20] it is imperative that healthcare providers understand the role of diabetes on the symptoms/symptom clusters among BCS over time.

To our knowledge, no longitudinal studies have examined symptoms/symptom clusters in BCS with diabetes from initiation of chemotherapy through cessation of treatment into early survivorship. Therefore, the purpose of this study was to utilize data from the electronic health record (EHR) to examine individual symptoms and symptom clusters in BCS with diabetes compared to BCS without diabetes at three key periods over the cancer trajectory from initial chemotherapy into early survivorship. Specific aims were to (1) determine the prevalence of individual symptoms, (2) identify the individual symptoms that makeup symptom clusters, and (3) compare symptom clusters between BCS with/without diabetes at three key periods. Understanding and characterizing symptoms/symptom clusters specific to BCS with diabetes are crucial to guide clinical practice. Findings from this study will offer pertinent information to healthcare teams providing care for BCS with diabetes.

Methods

Study design, setting, and sample

This retrospective cohort study used EHRs from a large statewide health repository from the Regenstrief Institute that included clinical health data from 5 health systems in central Indiana.[21] Eligibility criteria included women at baseline who (1) had a non-metastatic diagnosis of breast cancer (stage I–III) per statewide cancer registry data and International Classification of Diseases (ICD) codes; (2) received chemotherapy either alone or in combination with other adjuvant therapy (surgery and/or radiation); (3) had a breast cancer diagnosis with and without diabetes (type 2) (prior to cancer diagnosis) per ICD codes and medication lists for anti-diabetes medications; (4) were adults age $\geq$ 21 years, although breast cancer risk increases with age, younger BCS were included as symptom profiles may differ by age;[7,22] (5) had clinical notes in the EHRs. Exclusion criteria were (1) other diagnoses of cancer, except basal or squamous skin cancer; (2) metastatic breast cancer; (3) receiving subsequent chemotherapy after the initial chemotherapy for their cancer diagnosis. Data from January 2007 through December 2018 were extracted from the EHRs. A total of 4601 BCS were identified through the statewide cancer registry and ICD codes. The university's Institutional Review Board approved this study.

Symptom data

Seven common symptoms (gastrointestinal, fatigue, peripheral neuropathy, anxiety, depression, sleep, and cognitive function) were selected a priori as identified by other researchers in BCS and people with diabetes.[7,23,24] Symptom data were identified and extracted from the clinical notes in the EHR. A set of commonly used symptom phrases for each of the seven symptoms was used as seed symptom expressions. For example, “anorexia”, “poor appetite”, “not hungry”, “no or decreased appetite”, “constipation”, “bloating”, “diarrhea”, “cramping”, “nausea”, “vomiting”, “difficulty swallowing” are seed symptoms for GI. Then, a natural language processing model was developed to identify synonyms of the seed symptoms written in the clinical notes. The natural language processing model[25] first uses Unified Medical Language System MetaMap[26] to extract phrases, then the natural language processing model utilized a semantic clustering step to identify the synonyms from the extracted phrases. After applying the natural language processing model, we identified additional symptom phrases relevant to those seed symptoms to capture various symptom expressions written in the clinical notes.[25] For example, identified synonym expressions for gastrointestinal issues included bloating symptoms, bloated feeling, gas bloating, constipating, diarrhea, reduced appetite, decreased appetite, nausea/vomiting, morning vomiting, recurrent vomiting, intermittent vomiting, constipated, intractable vomiting, diarrhea vomiting, nauseated, persistent vomiting, nausea, emesis, nausea sickness, nauseous, and so on. See Appendix 1 for more information on the natural language processing model. After applying the NLP model on symptom extraction, we randomly selected 1693 sentences from the clinical notes with symptoms for validation. Two annotators labeled the data. The Cohen's kappa value was calculated to measure inter-rater reliability. The Cohen's kappa value between the two annotators is 0.89. Conflicts were resolved using a consensus vote from a third annotator. The NLP model gained an acceptable performance of F1 0.82 on this sampled dataset. Since there is a large number of clinical notes, the processing time for all clinical notes is around 96 h (using a PC with 8 GB memory and 1.6 GHz Intel Core Processor) including applying Unified Medical Language System for the initial phrase extraction. For this study, because of the large number of individual descriptive terms for gastrointestinal symptoms in the clinical notes of the EHR, symptoms were combined into the gastrointestinal symptom category and included the four most common symptoms (nausea, vomiting, diarrhea, and constipation) among BCS and people with diabetes based on previous literature.[24,27]

Data collection

Demographic (age, body mass index, gender, and race) and medical (comorbidities and cancer stage) characteristics were extracted from the EHRs. A modified Charlson Comorbidity Index (excluding diabetes and breast cancer) was used to account for comorbidities.

Symptom data were collected at three key periods in the cancer treatment trajectory post-initial chemotherapy: 0–6 months (T1), 12–18 months (T2), and 24–30 months (T3). These periods were chosen because symptom clusters are typically related to treatment and/or disease and may vary over time. Symptoms and symptom clusters are more acute in the days following initial chemotherapy treatments,[28,29] with symptoms typically decreasing over time. However, symptom clusters may wax and wane over time and, in many cases, linger for years post-treatment.[30] Therefore, it is important to examine the symptoms and symptom clusters at key periods across the cancer trajectory to get an accurate reflection of the experience.

Three periods over the cancer trajectory were chosen as they represent distinct phases of the cancer care continuum. The three key periods were (1) Time 1 (T1; 0–6 months) represents when chemotherapy is initiated and at which time acute symptoms are first noticed (i.e., the post-initial chemotherapy period); (2) Time 2 (T2; 12–18 months) represents when the treatment regimens are continuing and/or ending and BCS begin experiencing the cumulative effects of treatment on symptom clusters (i.e., the completion and immediate post-treatment period); (3) Time 3 (T3; 24–30 months) represents early survivorship, when BCS may experience lingering symptoms well-beyond treatment cessation (i.e., post-treatment and early survivorship period).

Symptom occurrence was noted at each time frame in the absence of standard symptom severity measures in the EHR. If patients had multiple notes in a time period, the number of occurrences of each symptom was calculated as the number of encounter notes that have the symptom mentioned. It is worth noting that if the same symptom is mentioned multiple times in the same note, it only counts once for that encounter note. It was not required for a patient to have symptoms in all three time periods to be included in the study. That means a patient might have symptoms in one or two time periods.

Data analysis

Symptom data were available for 1034 BCS with diabetes and 4523 BCS without diabetes. To control for potential confounders, we employed

propensity score matching (PSM) to form matched subgroups of BCS with and without diabetes.[31] PSM was conducted using R package "MatchIt" with nearest-neighbor 1-to-1 matching.[32] Propensity scores were derived from a logistic regression model with age, Charlson Comorbidity Index, race, and stage as covariates. Through PSM, 1034 BCS without diabetes were chosen to match the group of BCS with diabetes. Baseline demographic characteristics and clinical outcomes of matched subjects were summarized using mean and standard deviation for continuous variables and frequency and percent for categorical variables. Differences were compared between BCS with and without diabetes using ANOVA and Chi-square tests. A value of $P < 0.05$ was deemed significant. To investigate symptom cluster structures among the BCS with and without diabetes at each time point (T1, T2, and T3), we applied exploratory factor analysis for the frequency of symptoms that occurred using the R package "psych". The minimum residual solutions were calculated based on unweighted least squares with the Promax oblique rotation. This approach was chosen based on the hypotheses that symptoms cluster together possibly sharing underlying mechanisms.[33,34] The exploratory factor analysis included six symptoms (gastrointestinal, fatigue, peripheral neuropathy, anxiety, depression, and sleep). Due to the low number of cognitive symptoms reported in the dataset (< 0.1%), they were not included in the analysis. Cronbach's alpha was used to evaluate the internal consistency reliability of each cluster, deeming values above 0.6 as acceptable.[35] The results of exploratory factor analysis for one through three factors were examined for each period. Several criteria guided the determination of factor numbers, recognizing the absence of a gold standard. These criteria included parallel analysis, very simple structure, minimum average partial criterion, and Bayesian information criterion.[36,37] In cases where these criteria did not concur, we selected the factor solution that led to the most favorable factor structure, the best clinical interpretation and aligned with previous symptom cluster studies. Additional criteria used to select the factor numbers included a minimum of two or more symptoms per factor, with factor loadings $\geq$ 0.3,[38] as well as similarity of symptom clusters as identified in the literature other non-diabetes BCS populations. Symptom clusters were categorized by symptoms with the highest to lowest factor loadings.[38,39] Symptom clusters were observed for stability (whether the same cluster appeared over time) and consistency (if the specific symptoms within the cluster remained over time).[40–42] Cross-loading of factors (a symptom that occurs in more than one cluster during the same period) was accepted as it may inform future exploration of mechanistic linkages across symptom clusters.[38,42] All statistical analyses were conducted with R v4.1.2.

Results

Cohort characteristics

Table 1 provides the demographic and medical characteristics of BCS in the study cohort ($n = 1034$ for each cohort). Most of the sample was white and had stage II breast cancer. Statistically significant differences were noted between BCS with and without diabetes, specifically, BCS with diabetes had higher body mass index.

Symptom prevalence

Table 2 displays the prevalence of individual symptoms by diabetes status at each period. Across all three periods, the most prevalent symptoms in BCS with and without diabetes were gastrointestinal, fatigue, peripheral neuropathy, and anxiety.

Symptom clusters

Time 1 (T1): 0–6 months

Table 3 presents the symptom clusters within the post-initial chemotherapy period (T1) among BCS with and without diabetes.

Table 1
Breast cancer survivor cohort characteristics ($N = 2068$).

Variable	With diabetes ($n = 1034$)	Without diabetes ($n = 1034$)	*P* value
Age (years), mean (SD)	59.55 (10.68)	60.16 (11.59)	0.219
BMI (kg/m^2), mean (SD)	33.89 (8.25)	31.23 (17.71)	**0.005**
CCI, mean (SD)	1.79 (2.80)	1.59 (2.68)	0.103
Race			
Black	178 (17.2%)	154 (14.9%)	0.313
White	849 (82.1%)	876 (84.7%)	
Other	6 (0.6%)	4 (0.4%)	
Unknown	1 (0.1%)	0 (0.0%)	
Stage			
I	315 (30.5%)	328 (31.7%)	0.712
II	509 (49.2%)	509 (49.2%)	
III	210 (20.3%)	197 (19.1%)	

BMI, body mass index; CCI, Charlson Comorbidity Index.

Cronbach's alpha for the clusters in both the with and without diabetes groups ranged from 0.651 to 0.845. At T1, we found two primary symptom clusters for BCS with diabetes and two symptom clusters for BCS without diabetes. In the BCS with diabetes, cluster 1 (highest to lowest factor loadings) includes *fatigue-gastrointestinal-peripheral neuropathy symptoms*. Cluster 2 consists of *anxiety-depression* symptoms. For BCS without diabetes, cluster 1 includes *fatigue-peripheral neuropathy-gastrointestinal* symptoms. Cluster 2 consists of *anxiety-depression-sleep* symptoms. In this time period, BCS with and without diabetes had the same number of symptoms clusters ($n = 2$). However, the number of individual symptoms reported between the groups was different (5 vs. 6) with the BCS without diabetes reporting more.

Time 2 (T2): 12–18 months

Table 4 shows the symptom clusters during the completion of treatment and immediate post-treatment period (T2) by diabetes status. Cronbach's alpha for the clusters in the with and without diabetes groups ranged from 0.723 to 0.854. At T2, two symptom clusters were identified for BCS with diabetes and one symptom clusters among BCS without diabetes during this period. Among BCS with diabetes, Cluster 1 (highest to lowest factor loadings) includes *anxiety-depression-sleep-gastrointestinal symptoms.* Cluster 2 consists of *fatigue-peripheral neuropathy-gastrointestinal* symptoms. For BCS without diabetes, Cluster 1 consists of fatigue-*peripheral neuropathy-anxiety-gastrointestinal symptoms.* Cluster 2 consists of *anxiety-depression-sleep symptoms.* During this time period, BCS with diabetes had more symptom clusters (2 vs. 1) and more individual symptoms (7 vs. 4) that made up the clusters than BCS without diabetes.

Time 3 (T3): 24–30 months

Table 5 displays symptom clusters by diabetes status at T3 (post-treatment and early survivorship period). Cronbach's alpha for the clusters in the with and without diabetes groups ranged from 0.671 to 0.840. At T3, only one symptom cluster was identified in BCS with diabetes and two symptom clusters in BCS without diabetes. In BCS with diabetes, Cluster 1 includes (highest to lowest factor loadings) *fatigue-gastrointestinal-peripheral neuropathy-anxiety* symptoms. In BCS without diabetes, cluster 1 is a symptom cluster that consisted of *fatigue-gastrointestinal-peripheral neuropathy* symptoms. Cluster 2 is a symptom cluster of *anxiety-depression-sleep* symptoms. In this time period (T3), BCS with diabetes had fewer symptom clusters (1 vs. 2) and less individual symptoms (4 vs. 6) than BCS without diabetes.

Based on the exploratory factor analysis results over the three periods, we identified two symptom clusters at T1 for both groups, and differing numbers of symptom clusters at T2 and T3 between BCS with and without diabetes. The number and composition of symptom loadings within the clusters varied some between BCS with and without diabetes.

Table 2
Prevalence of individual symptoms by diabetes status at each period.

Symptom	With diabetes			Without diabetes		
	T1 (n = 905)	T2 (n = 683)	T3 (n = 526)	T1 (n = 852)	T2 (n = 643)	T3 (n = 538)
GI	590 (65.2%)	288 (42.2%)	223 (42.4%)	455 (53.4%)	233 (36.2%)	206 (38.3%)
Fatigue	523 (57.8%)	251 (36.7%)	169 (32.1%)	439 (51.5%)	181 (28.1%)	134 (24.9%)
PN	296 (32.7%)	140 (20.5%)	104 (19.8%)	189 (22.2%)	102 (15.9%)	69 (12.8%)
Anxiety	299 (33.0%)	159 (23.3%)	102 (19.4%)	216 (25.4%)	103 (16.0%)	88 (16.4%)
Depression	268 (29.6%)	156 (22.8%)	119 (22.6%)	177 (20.8%)	93 (14.5%)	90 (16.7%)
Sleep	115 (12.7%)	52 (7.6%)	32 (6.1%)	75 (8.8%)	26 (4.0%)	24 (4.5%)

GI, gastrointestinal; PN, peripheral neuropathy.
Time 1: 0–6 months post-initial chemotherapy.
Time 2: 12–18 months post-initial chemotherapy.
Time 3: 24–30 months post-initial chemotherapy.

Discussion

This study used clinical data from EHRs to comprehensively examine the symptoms and symptom clusters of BCS with and without diabetes over three key periods in the cancer trajectory. Using this large dataset, we identified 19% of BCS with a diagnosis of diabetes, which exceeds our previous findings[3] and is well above the national estimates of 11% in the general population.[43] These findings also support that of other cancer researchers, who have found diabetes to be a common comorbid condition among BCS.[18,44]

Individual symptom prevalence

In each period, we noted that gastrointestinal symptoms followed by fatigue were the most prevalently documented individual symptoms in BCS with and without diabetes. Gastrointestinal symptoms are common in people with diabetes and may be related to glycemic control and/or complications associated with gastric motility dysfunction,[45,46] which could, in turn, contribute to fatigue. Among all BCS, researchers have noted that fatigue is the most common symptom reported during active cancer treatment, extending well beyond treatment cessation.[7,47–49] Fatigue is also a highly prevalent symptom among women with diabetes,[50] and its cooccurrence with breast cancer presence has been shown to notably increase the risk for fatigue.[7] It is plausible that gastrointestinal symptoms (nausea, vomiting, diarrhea, and constipation) and decrements in nutritional status associated with diabetes, cancer treatments, and/or the cancer diagnosis may also contribute to fatigue in BCS. Thus, careful attention by providers regarding gastrointestinal symptoms which can impact the nutritional status of BCS over the treatment trajectory is warranted.

We noted that one symptom cross-loaded (or was present in more than one cluster in a single period) in BCS with diabetes. Gastrointestinal symptoms, cross-loaded at T2, and was present in both the *anxiety-depression-sleep-gastrointestinal* and the *fatigue-peripheral neuropathy-gastrointestinal* clusters. The presence of cross-loadings in the clusters may indicate that these symptoms are pervasive and interconnected with the overall symptom burden and suggest that better management of these symptoms may attenuate other symptoms. Although cross-loading has been identified as important for exploring linkages between symptoms,[33,42] studies of symptom clusters have failed to discuss this in their findings or examine potential mechanistic linkages. More research is warranted to explore possible biological linkages between the symptoms in symptom clusters that cross-load as this may assist in identifying BCS at-risk for higher symptom/symptoms cluster profiles.

Importantly, we found BCS with diabetes experienced the majority of symptoms at T1 and T2 (n = 7) and fewest symptoms at T3 (n = 4). Suggesting that individual symptoms in BCS with diabetes may be exacerbated during the active treatment period when acute symptoms are prominent and into early cessation of treatment when cumulative effects of treatment are noted. These findings differ from our previous study that found BCS with diabetes reported more symptoms than BCS without diabetes 3–8 years post-treatment.[7] However, that study did not look at key time periods in the cancer trajectory which may have contributed to the disparate findings. Future prospective studies should examine the symptoms and symptom cluster experience of BCS with and without diabetes throughout the cancer trajectory to confirm these findings and facilitate the development of specific time-tailored strategies to better manage symptoms.

Symptom clusters

Based on the EHR data retrieval, we noted important findings regarding symptom clusters of BCS with and without diabetes. First, we noted that overall, the symptom clusters of BCS with and without diabetes in this study were similar to those found in previous literature with BCS.[46] Second, we found BCS with and without diabetes typically had two symptom clusters except for T3 when BCS with diabetes had one symptom cluster; and at T1 when BCS without diabetes had one symptom cluster. The higher number of symptom clusters at T1 and T2 compared

Table 3
Symptom clusters by diabetes status at 0–6 months post-initial chemotherapy (Time 1).

Time 1	With diabetes (n = 905)		Without diabetes (n = 852)	
Symptom	Cluster 1[a]	Cluster 2[a]	Cluster 1[a]	
GI	0.861	–	0.715	–
Fatigue	0.874	–	0.859	–
PN	0.648	–	0.724	–
Anxiety	–	1.117	–	0.735
Depression	–	0.337	–	0.689
Sleep	–	–	–	0.314
Cronbach's α	0.845	0.651	0.814	0.644

GI, gastrointestinal; PN, peripheral neuropathy.
[a] Symptom clusters characterized by highest loading factor.

Table 4
Symptom clusters by diabetes status at 12–18 months post-initial chemotherapy (Time 2).

Time 2	With diabetes (n = 683)		Without diabetes (n = 643)	
Symptom	Cluster 1[a]	Cluster 2[a]	Cluster 1[a]	Cluster 2[a]
GI	0.325	0.428	0.657	–
Fatigue	–	0.915	0.922	–
PN	–	0.593	0.814	–
Anxiety	1.109	–	0.741	–
Depression	0.395	–	–	–
Sleep	0.370	–	–	–
Cronbach's α	0.723	0.735	0.854	–

GI, gastrointestinal; PN, peripheral neuropathy.
[a] Symptom clusters characterized by highest loading factor.

Table 5
Symptom clusters by diabetes status at 24–30 months post-initial chemotherapy (Time 3).

Time 3	With diabetes (n = 526)		Without diabetes (n = 538)	
Symptom	Cluster 1[a]	Cluster 2[a]	Cluster 1[a]	Cluster 2[a]
GI	0.843	–	0.753	–
Fatigue	0.962	–	1.023	–
PN	0.581	–	0.637	–
Anxiety	0.573	–	–	0.920
Depression		–	–	0.537
Sleep		–	–	0.500
Cronbach's α	0.818	–	0.840	0.671

GI, gastrointestinal; PN, peripheral neuropathy.
[a] Symptom clusters characterized by highest loading factor.

to T3 among BCS with diabetes, may be indicative of the profound impact cancer treatment has on the development of co-occurring symptoms (symptom clusters) earlier in the treatment trajectory. Lastly, we noticed differences in the stability (clusters repeated over time) of the types of symptom clusters at each period and over the trajectory for BCS with diabetes compared to BCS without diabetes. Among BCS with diabetes, we found one stable (clusters repeated over time) symptom cluster and consistency (symptoms within the cluster remained over time) in the fatigue, peripheral neuropathy and gastrointestinal symptoms at T1 and T2. While the three symptoms were the same at T1 and T2, the factor loadings differed within the cluster. Specifically, fatigue was the highest loading factor at both times, but gastrointestinal and peripheral neuropathy loaded differently. At T3, the symptom of anxiety also loaded on the cluster. For BCS without diabetes, two stable and consistent symptom clusters were found at T1 and T3. Specifically, fatigue, peripheral neuropathy, and gastrointestinal symptoms were noted. While the three symptoms were the same at T1 and T3, the factor loadings differed within the cluster. The second symptom cluster included anxiety, depression, and sleep symptoms for which the factor loadings remained the consistent at T1 and T3. Other researchers have noted the dynamic characteristics of symptom clusters over time in BCS.[15,51,52] The stability and consistency in the types of symptom clusters found in our study may be a result of the small number of symptoms in the analysis or may have been influenced by the complex contribution of diabetes to the symptom clusters experienced by BCS. Our findings suggest that BCS with diabetes may experience unique symptoms within the symptom clusters over the cancer trajectory. More research with a larger number of symptoms is needed to ascertain the influence of diabetes on the symptom clusters of BCS with diabetes.

Our findings on the types of symptom clusters differ somewhat from those found in a recent systematic review of symptom cluster studies (n = 32) among BCS.[51] In their review, the researchers noted that the most reported symptom clusters in BCS included a fatigue/sleep disturbance cluster, a psychological (depression-anxiety) cluster, and a gastroi ntestinal (nausea, lack of appetite, diarrhea) cluster. However, the studies in that review did not compare symptom clusters between BCS with and without diabetes.[51] Thus, our findings suggest that the type of symptom clusters may vary over time for BCS with and without diabetes, underscoring the need for more research in this area.

In two studies that examined symptom clusters of people with diabetes without cancer, the researchers identified symptom clusters that included fatigue, peripheral neuropathy, gastrointestinal, and cognitive symptoms, along with other symptoms commonly associated with diabetes such as polyuria, polydipsia, dry skin, and sexual dysfunction among others.[9,24] Combined findings from these studies indicate that BCS with diabetes may experience unique symptom clusters and greater symptom burden than BCS without diabetes. Understanding the types of symptom clusters over time and the differences between BCS with and without comorbid diabetes is crucial to guide clinical practice. Overall, there is a paucity of research examining the role of diabetes in symptom clusters of BCS. In an exploratory study, researchers examined subgroups of heterogeneous cancer survivors with diabetes (n = 43) during chemotherapy administration for severity and patterns of preselected symptoms (pain, fatigue, change in appetite, nausea, and vomiting).[53] The researchers found two distinct subgroups based on severity. In subgroup 1, people with cancer with diabetes experienced mild symptoms (no pain, mild fatigue, change in appetite, and nausea) at baseline, which remained mild over the study period. In subgroup 2, people with cancer with diabetes experienced mild symptom severity progressing to moderate symptom severity, with marked increases in fatigue, nausea, numbness, and tingling.[53] However, the study did not examine symptom clusters and included a small sample size, of which only twelve (29%) were BCS, limiting generalizability. The study also included people with type 1 diabetes, which is a distinctly different disease that may have influenced their findings.[53] Lastly, the study was conducted over an 8-week period and captured the most acute symptoms but did not account for symptoms that may occur over time and into survivorship.[53]

Symptom clusters can also be influenced by cancer treatment across the cancer trajectory. In a study of BCS (n = 77) over a 24-month period,[54] researchers noted that, compared to later time points, most of the variability in symptom clusters occurred within the first 6 months post-initiation of chemotherapy. These authors purport that symptom clusters are more intense during active treatment and abate over time.[54] Similarly, in our study, we found that BCS with diabetes had more symptoms and symptom clusters at T1 and T2 (n = 2), whereas BCS without diabetes had more symptoms and symptom clusters at T1 and T3.

The findings from this study suggest that BCS may experience significant symptom clusters during chemotherapy, immediately post-treatment, and well into survivorship. Prospective studies examining the symptom clusters of BCS with diabetes over time are warranted, as they may facilitate the development of interventions to mitigate symptoms and symptom clusters over key time periods in the cancer trajectory.

Having breast cancer and diabetes concurrently and managing both diagnoses over the long-term may contribute to symptom clusters. Among heterogeneous cancer patients with diabetes, researchers have found that cancer and its treatment had a negative effect on diabetes self-management activities.[5,53,55] It is conceivable that difficulty with diabetes self-management activities may perpetuate and/or exacerbate the symptoms and symptom clusters experienced by BCS during key periods of the cancer trajectory. Specifically, perturbations in glycemic control from chemotherapy regimens and/or other diabetic complications may intensify inflammatory responses[8,18] which may influence symptom clusters. More research is warranted to explore glycemic control and inflammatory responses as potential etiologies of the symptom clusters among BCS with diabetes.

In summary, our study examined the symptom clusters of BCS with diabetes, which, to our knowledge, has not been previously reported. We found that the number and type of individual symptoms and symptom clusters differed among of BCS with diabetes compared to BCS without diabetes over the three time periods. These findings suggest that BCS with diabetes may experience additional and/or unique symptom clusters at key periods in the cancer treatment trajectory. Prospective research studies are needed to confirm these findings.

Strengths and limitations

Our study had several strengths. First, using EHRs to examine symptoms and symptom clusters in a large cohort of BCS is innovative, and, to our knowledge, EHRs have not been widely utilized to identify symptoms/symptom clusters in a large longitudinal sample of BCS. Second, utilizing EHRs may have minimized the burden on BCS as well as mitigated the costs associated with conducting a longitudinal study of this size. The use of propensity scoring to match samples of BCS with and without diabetes is a strength of our study. We used one-to-one matching

to select a subgroup of BCS without diabetes that had similar propensity scores as BCS with diabetes to estimate the impact of diabetes on the symptom/symptom clusters, which reduced the potential influence from of confounding variables increasing the rigor of our analysis and interpretation. Lastly, this study provided a foundation for developing prospective studies that can use standardized measures of symptoms and symptom clusters in BCS with diabetes at key times during the cancer trajectory.

Our study also had several limitations. The descriptive, retrospective study design precluded the ability to establish causality. Although we used ICD codes and medication lists to identify BCS with diabetes, some BCS may have been prediabetic or undiagnosed and not captured in our dataset. Estimates suggest that 352 million people live with prediabetes, and 240 million live with undiagnosed diabetes worldwide.[20] Therefore, it is imperative that identifying diabetes in addition to initial and ongoing screening for diabetes, be a standard of care throughout breast cancer treatment and well into survivorship. Our study was limited by the number of pre-selected symptoms, future studies should examine symptom clusters using a larger number of symptoms. In this study, we did not account for laboratory blood glucose measures of diabetes control, the effects of different types and dosing of chemotherapy regimens, other types of cancer treatment, and/or disease progression. Prospective studies should include these variables as they may influence the type and number of symptom clusters. Lastly, the symptom data used in this study were extracted from the clinical notes as occurrence of symptoms due to the lack of availability of standardized symptom severity measurement tools in the EHR clinical notes. Although EHR data may not capture all symptoms or the severity of symptoms, it most likely captures the most salient and problematic symptoms experienced and reported in real time by BCS to their providers. The types and dynamic nature of the symptoms and symptom clusters identified in this study elucidate the importance of assessing BCS with diabetes throughout the cancer trajectory. Despite these limitations, the findings from this study have implications for clinical practice and future research. Larger prospective research studies are needed to determine if BCS with diabetes experience distinct and/or a greater number of symptoms and/or symptom clusters over the treatment trajectory as well as the role of lifestyle and social factors on them.

Conclusions

Given that BCS are living longer, and the prevalence of diabetes is estimated to increase exponentially by 2045, healthcare providers will continue to be challenged with managing diabetes in BCS. Therefore, it is imperative that healthcare providers recognize and continually assess BCS with diabetes across the cancer trajectory for intensified and/or unique profiles of symptoms and symptom clusters. Interdisciplinary cancer survivorship models are needed to facilitate the management of diabetes in BCS. Implementation of a comprehensive diabetes management program over the cancer trajectory could mitigate symptoms and symptom clusters, ultimately improving health outcomes and potentially reducing the utilization of healthcare resources.

CRediT authorship contribution statement

Storey, S: Conceptualization, Methodology, Data curation, Writing-original draft preparation, Supervision, Writing review & editing, Funding acquisition. **Luo, X:** Methodology, Data curation, Software, Validation, Writing-original draft preparation. **Ren, J:** Data curation, Formal analysis, Visualization, Writing-original draft preparation. **Huang, K:** Conceptualization, Resources. **Von Ah, D:** Conceptualization, Writing-review & editing. All authors had full access to all the data in the study, and the corresponding author had final responsibility for the decision to submit for publication. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Declaration of competing interest

The authors declare not conflict of interest.

Funding

This study was funded by an RE01 grant from the Oncology Nursing Foundation (PI Storey). The funding source had not role in the design, execution, analysis, interpretation of data or decision to submit the results.

Ethics statement

This study was approved by the Institutional Review Board of Indiana University-Purdue University, Indianapolis, IN.

Declaration of Generative AI and AI-assisted technologies in the writing process

No AI tools/services were used during the preparation of this work.>

Appendix

Appendix 1 to this article can be found online at https://doi.org/10.1016/j.apjon.2023.100343.

References

1. Rowley WR, Bezold C, Arikan Y, Byrne E, Krohe S. Diabetes 2030: insights from yesterday, today, and future trends. *Popul Health Manag.* 2017;20(1):6–12. https://doi.org/10.1089/.pop.2015.0181.
2. Fu MR, Axelrod D, Guth AA, et al. Comorbidities and quality of life among breast cancer survivors: a prospective study. *J Personalized Med.* 2015;5(3):229–242. https://doi.org/10.3390/.jpm5030229.
3. Storey S, Zhang Z, Luo X, et al. Differences in health-related outcomes and health care resource utilization in breast cancer survivors with and without type 2 diabetes. *J Patient Cent Res Rev.* 2022;9(1):15–23. https://doi.org/10.17294/2330-0698.1862.
4. Hershey DS, Pierce SJ. Examining patterns of multivariate, longitudinal symptom experiences among older adults with type 2 diabetes and cancer via cluster analysis. *Eur J Oncol Nurs.* 2015;19(6):716–723. https://doi.org/10.1016/j.ejon.2015.05.006.
5. Hershey DS, Tipton J, Given B, Davis E. Perceived impact of cancer treatment on diabetes self-management. *Diabetes Educat.* 2012;38(6):779–790. https://doi.org/10.1177/0145721712458835.
6. Evangelista AL, Santos EM. Cluster of symptoms in women with breast cancer treated with curative intent. *Support Care Cancer.* 2012;20(7):1499–1506. https://doi.org/10.1007/.s00520-011-1238-1.
7. Storey S, Cohee A, Gathirua-Mwangi WG, et al. Impact of diabetes on the symptoms of breast cancer survivors. *Oncol Nurs Forum.* 2019;46(4):473–484. https://doi.org/10.1188/.19.ONF.473-484.
8. Hammer M, Storey S, Hershey DS, et al. Hyperglycemia and cancer: a state-of-the-science review. *Oncol Nurs Forum.* 2019;46(4):459–472. https://doi.org/10.1188/19.ONF.459-472.
9. Brady V, Whisenant M, Wang X, et al. Characterization of symptoms and symptom clusters for type 2diabetes using a large nationwide electronic health record database. *Diabetes Spectr.* 2022;35(2):159–170. https://doi.org/10.2337/ds21-0064.
10. Kim HJ, McGuire DB, Tulman L, Barsevick AM. Symptom clusters: concept analysis and clinical implications for cancer nursing. *Cancer Nurs.* 2005;28(4):270–284. https://doi.org/10.1097/00002820-200507000-00005.
11. Nguyen J, Cramarossa G, Bruner D, et al. A literature review of symptom clusters in patients with breast cancer. *Expert Rev Pharmacoecon Outcomes Res.* 2011;11(5):533–539. https://doi.org/10.1586/erp.11.55.
12. Kim HJ, Barsevick AM, Beck SL, Dudley W. Clinical subgroups of a psychoneurologic symptom cluster in women receiving treatment for breast cancer: a secondary analysis. *Oncol Nurs Forum.* 2012;39(1):E20–E30. https://doi.org/10.1188/12.ONF.E20-E30.
13. Dodd MJ, Cho MH, Cooper BA, Miaskowski C. The effect of symptom clusters on functional status and quality of life in women with breast cancer. *Eur J Oncol Nurs.* 2010;14(2):101–110. https://doi.org/10.1016/j.ejon.2009.09.005.
14. Doong SH, Dhruva A, Dunn LB, et al. Associations between cytokine genes and a symptom cluster of pain, fatigue, sleep disturbance, and depression in patients prior to breast cancer surgery. *Biol Res Nurs.* 2015;17(3):237–247. https://doi.org/10.1177/1099800414550394.
15. Berger AM, Kumar G, LeVan TD, Meza JL. Symptom clusters and quality of life over 1 year in breast cancer patients receiving adjuvant chemotherapy. *Asia Pac J Oncol Nurs.* 2020;7(2):134–140. https://doi.org/10.4103/apjon.apjon_57_19.
16. Ganesh V, Drost L, Chiu N, et al. Symptom clusters using the Brief Pain Inventory in patients with breast cancer. *Ann Palliat Med.* 2017;6(suppl 2):S170–S176. https://doi.org/10.21037/apm.2017.09.05.

17. Miaskowski C, Barsevick A, Berger A, et al. Advancing symptom science through symptom cluster research: expert panel proceedings and recommendations. *J Natl Cancer Inst*. 2017;109(4):djw253. https://doi.org/10.1093/jnci/djw253.
18. Ferroni P, Riondino S, Buonomo O, Palmirotta R, Guadagni F, Roselli M. Type 2 diabetes and breast cancer: the interplay between impaired glucose metabolism and oxidant stress. *Oxid Med Cell Longev*. 2015;2015:183928. https://doi.org/10.1155/2015/183928.
19. Giovannucci E, Harlan DM, Archer MC, et al. Diabetes and cancer: a consensus report. *CA Cancer J Clin*. 2010;60(4):207–221. https://doi.org/10.3322/caac.20078.
20. International Diabetes Federation. *Diabetes Facts & Figures*; 2021. https://idf.org/aboutdiabetes/what-is-diabetes/facts-figures.html. Accessed August 31, 2022.
21. McDonald CJ, Overhage JM, Tierney WM, et al. The Regenstrief medical record system: a quarter century experience. *Int J Med Inf*. 1999;54(3):225–253. https://doi.org/10.1016/s1386-5056(99)00009-x.
22. Storey S, Cohee A, Von Ah D, et al. Presence and distress of chemotherapy-induced peripheral neuropathy symptoms in upper extremities of younger and older breast cancer survivors. *JPCRR*. 2020;7(4):295–303. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7644124/.
23. Hammer J, Howell S, Bytzer P, Horowitz M, Talley NJ. Symptom clustering in subjects with and without diabetes mellitus: a population-based study of 15,000 Australian adults. *Am J Gastroenterol*. 2003;98(2):391–398.
24. García AA, Bose E, Zuñiga JA, Zhang W. Mexican Americans' diabetes symptom prevalence, burden, and clusters. *Appl Nurs Res*. 2019;46:37–42. https://doi.org/10.1016/j.apnr.2019.02.002.
25. Luo X, Storey S, Gandhi P, Zhang Z, Metzger M, Huang K. Analyzing the symptoms in colorectal and breast cancer patients with or without type 2 diabetes using EHR data. *Health Inf J*. 2021;27(1):14604582211000785. https://doi.org/10.1177/14604582211000785.
26. Aronson AR, Lang FM. An overview of MetaMap: historical perspective and recent advances. *J Am Med Inf Assoc*. 2010;17(3):229–236. https://doi.org/10.1136/jamia.2009.002733.
27. Han CJ, Yang GS, Syrjala K. Symptom experiences in colorectal cancer survivors after cancer treatments: a systematic review and meta-analysis. *Cancer Nurs*. 2020;43(3):E132–E158. https://doi.org/10.1097/NCC.0000000000000785.
28. Pettersson G, Berterö C, Unosson M, Börjeson S. Symptom prevalence, frequency, severity, and distress during chemotherapy for patients with colorectal cancer. *Support Care Cancer*. 2014;22(5):1171–1179. https://doi.org/10.1007/s00520-013-2069-z.
29. Giesinger JM, Wintner LM, Zabernigg A, et al. Assessing quality of life on the day of chemotherapy administration underestimates patients' true symptom burden. *BMC Cancer*. 2014;14:758. https://doi.org/10.1186/1471-2407-14-758.
30. Haidinger R, Bauerfeind I. Long-term side effects of adjuvant therapy in primary breast cancer patients: results of a web-based survey. *Breast Care*. 2019;14(2):111–116. https://doi.org/10.1159/000497233.
31. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika*. 1983;70(1):41–55. https://doi.org/10.2307/2335942.
32. Ho D, Imai K, King G, Stuart E. Matching as nonparametric preprocessing for reducing model dependence in parametric causal inference. *Polit Anal*. 2007;15(3):199–236. https://doi.org/10.1093/pan/mpl013.
33. Miaskowski C, Dodd M, Lee K. Symptom clusters: the new frontier in symptom management research. *J Natl Cancer Inst Monogr*. 2004;32:17–21. https://doi.org/10.1093/jncimonographs/lgh023.
34. Miaskowski C, Aouizerat BE, Dodd M, Cooper B. Conceptual issues in symptom clusters research and their implications for quality-of-life assessment in patients with cancer. *J Natl Cancer Inst Monogr*. 2007;37:39–46. https://doi.org/10.1093/jncimonographs/lgm003.
35. Oh JH, Thor M, Olsson C, et al. A factor analysis approach for clustering patient reported outcomes. *Methods Inf Med*. 2016 Oct 17;55(5):431–439. https://doi.org/10.3414/ME16-01-0035. Epub 2016 Sep 2. PMID: 27588322; PMCID: PMC5518610.
36. Watkins MW. Exploratory factor analysis: a guide to best practice. *J Black Psychol*. 2018;44(3):219–246. https://doi.org/10.1177/0095798418771807.
37. Courtney Matthew GR. Determining the number of factors to retain in EFA: using the SPSS R-menu v2 0 to make more judicious estimations. *Practical Assess Res Eval*. 2019;18. https://doi.org/10.7275/9cf5-2m72. Article 8.
38. Pozzar RA, Hammer MJ, Cooper BA, et al. Symptom clusters in patients with gynecologic cancer receiving chemotherapy. *Oncol Nurs Forum*. 2021;48(4):441–452. https://doi.org/10.1188/21.ONF.441-452.
39. Matzka M, Köck-Hódi S, Jahn P, Mayer H. Relationship among symptom clusters, quality of life, and treatment-specific optimism in patients with cancer. *Support Care Cancer*. 2018;26(8):2685–2693. https://doi.org/10.1007/s00520-018-4102-8.
40. Harris CS, Kober KM, Cooper B, et al. Symptom clusters in outpatients with cancer using different dimensions of the symptom experience. *Support Care Cancer*. 2022;30(8):6889–6899. https://doi.org/10.1007/s00520-022-07125-z.
41. Harris CS, Dodd M, Kober KM, et al. Advances in conceptual and methodological issues in symptom cluster research: a 20-year perspective. *ANS Adv Nurs Sci*. 2022;45(4):309–322. https://doi.org/10.1097/ANS.0000000000000423.
42. Ward Sullivan C, Leutwyler H, Dunn LB, Miaskowski C. A review of the literature on symptom clusters in studies that included oncology patients receiving primary or adjuvant chemotherapy. *J Clin Nurs*. 2018;27(3-4):516–545. https://doi.org/10.1111/jocn.14057.
43. Centers for Disease Control and Prevention. *National Diabetes Statistics Report*; 2022. https://www.cdc.gov/diabetes/data/statistics-report/index.html. Accessed September 12, 2022.
44. Lega IC, Austin PC, Fischer HD, et al. The impact of diabetes on breast cancer treatments and outcomes: a population-based study. *Diabetes Care*. 2018;41(4):755–761. https://doi.org/10.2337/dc17-2012.
45. Boronikolos GC, Menge BA, Schenker N, et al. Upper gastrointestinal motility and symptoms in individuals with diabetes, prediabetes and normal glucose tolerance. *Diabetologia*. 2015;58(6):1175–1182. https://doi.org/10.1007/s00125-015-3538-3.
46. Du YT, Rayner CK, Jones KL, Talley NJ, Horowitz M. Gastrointestinal symptoms in diabetes: prevalence, assessment, pathogenesis, and management. *Diabetes Care*. 2018;41(3):627–637. https://doi.org/10.2337/dc17-1536.
47. Bower JE, Ganz PA, Desmond KA, et al. Fatigue in long-term breast carcinoma survivors: a longitudinal investigation. *Cancer*. 2006;106(4):751–758. https://doi.org/10.1002/cncr.21671.
48. Biering K, Frydenberg M, Pappot H, Hjollund NH. The long-term course of fatigue following breast cancer diagnosis. *J Patient Rep Outcomes*. 2020;4(1):37. https://doi.org/10.1186/s41687-020-00187-9.
49. Ruiz-Casado A, Álvarez-Bustos A, de Pedro CG, Méndez-Otero M, Romero-Elías M. Cancer-related fatigue in breast cancer survivors: a review. *Clin Breast Cancer*. 2021;21(1):10–25. https://doi.org/10.1016/j.clbc.2020.07.011.
50. Fritschi C, Bronas UG, Park CG, Collins EG, Quinn L. Early declines in physical function among aging adults with type 2 diabetes. *J Diabet Complicat*. 2017;31(2):347–352. https://doi.org/10.1016/j.jdiacomp.2016.06.022.
51. So WKW, Law BMH, Ng MSN, et al. Symptom clusters experienced by breast cancer patients at various treatment stages: a systematic review. *Cancer Med*. 2021;10(8):2531–2565. https://doi.org/10.1002/cam4.3794.
52. Sullivan CW, Leutwyler H, Dunn LB, et al. Stability of symptom clusters in patients with breast cancer receiving chemotherapy. *J Pain Symptom Manag*. 2018;55(1):39–55. https://pubmed.ncbi.nlm.nih.gov/28838866/.
53. Hershey DS, Given B, Given C, Corser W, von Eye A. Predictors of diabetes self-management in older adults receiving chemotherapy. *Cancer Nurs*. 2014;37(2):97–105. https://doi.org/10.1097/NCC.0b013e3182888b14.
54. Starkweather A, Kelly DL, Thacker L, Wright ML, Jackson-Cook CK, Lyon DE. Relationships among psychoneurological symptoms and levels of C-reactive protein over 2 years in women with early-stage breast cancer. *Support Care Cancer*. 2017;25(1):167–176. https://doi.org/10.1007/s00520-016-3400-2.
55. Terao N. A qualitative study of blood glucose and side effect self-management among patients with type 2 diabetes undergoing chemotherapy for cancer. *Asia Pac J Oncol Nurs*. 2022;10(2):100172. https://doi.org/10.1016/j.apjon.2022.100172.