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ORIGINAL ARTICLE

Stability of symptom clusters and sentinel symptoms during the first two cycles of adjuvant chemotherapy

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Abstract

Purpose Ascertaining the stability of symptom clusters and identifying sentinel symptoms have been top priorities in symptom cluster research. Identifying sentinel symptoms would help to determine the underlying mechanisms of symptom clusters and facilitate effective symptom management. This study aimed to evaluate the stability of symptom clusters during the 1st and 2nd cycles of adjuvant chemotherapy (CTx) and to identify sentinel symptoms.

Methods This is a secondary data analysis of data from the Paradigm Shift in Chemotherapy-Induced Nausea and Vomiting (PS-CINV) study. Data utilized were from cancer patients who received adjuvant chemotherapy and completed symptom evaluation in the 1st and 2nd cycles ($N = 209$). The severity of 20 symptoms was evaluated on a 0-to-10 numeric rating scale. Principal component and hierarchical cluster analyses identified symptom clusters, and principal variable analysis identified sentinel symptoms.

Results Among 20 symptoms, 13 symptoms formed 4 symptom clusters in the 1st cycle: a physical-psychological (pain, dyspnea, sleep disturbance, anxiety, depression), a gastrointestinal (nausea, loss of appetite, taste change), a fatigue-cognitive (fatigue, difficulty concentrating, drowsiness), and a urosexual (urinary problem, sexual problem) symptom cluster. During the 2nd cycle, stable symptom clusters were identified, with merging of the physical-psychological and fatigue-cognitive symptom clusters, resulting in three clusters. Sentinel symptoms were identified in the following order: anxiety, loss of appetite and fatigue (1st cycle) and loss of appetite, depression, and fatigue (2nd cycle).

Conclusion Symptom clusters demonstrated phase-specific stability. The current study identified a core set of symptoms that form stable symptom clusters during the 1st and 2nd cycles of CTx. Principal variable analysis identified sentinel symptoms which could facilitate efficient symptom management.

Keywords Symptom cluster · Sentinel symptom · Cancer · Chemotherapy

Introduction

Cancer patients often report multiple symptoms and associations between symptoms [1]. Clinical observation of patients' symptom experience has informed researchers about the existence of co-occurring symptoms, called symptom clusters [2]. A symptom cluster is defined as a stable group of two or more interrelated co-occurring symptoms [3]. Top priorities in symptom cluster studies include confirming stable groups of symptoms and identifying sentinel symptoms among symptom clusters [4].

Researchers have tried to identify stable groups of symptoms. However, many symptom cluster studies have often resulted in variable cluster findings [5–9]. The stability of certain group of symptoms over the patient's cancer journey has been demonstrated [9–11]. A few stable symptom clusters have been identified according to a systematic review, i.e., anxiety and depression, nausea and vomiting, nausea and loss of appetite, and fatigue-dyspnea-drowsiness-pain among advanced cancer patients [12]. Dynamic changes in cluster membership before, during, and after completion of chemotherapy (CTx) have been demonstrated through a recent

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longitudinal study which suggested temporal nature of symptom clusters [9]. Experiencing stable symptom clusters, which comprise core symptoms with changes in cluster membership as cancer treatment progresses, is considered reasonable. Symptom cluster stability during the initial treatment phase needs to be further investigated.

Among concurrent symptoms, patients often focus on one or two symptoms of particular significance and mention the occurrence of one symptom to explain other symptoms [1]. Identifying sentinel symptoms would help us to investigate the underlying mechanisms of symptom clusters and thus designate an initial target for efficient symptom management. A limited number of studies have tried to identify sentinel symptoms. Kirkova et al. [13] proposed that the most prevalent symptom is a sentinel symptom; however, this symptom failed to predict the presence or absence of other symptoms in the cluster. A set of symptoms has been evaluated regarding the predictability of pre-determined sentinel symptom of nausea [14–16]. Pain and fatigue are considered key symptoms for classifying patients into latent groups [17].

Principal variables are a subset of the original variables that contain as much information as possible about the original variables [18]. McCabe suggested the concept of "principle variable analysis" and demonstrated theoretical underpinnings for selecting variables and discarding unselected variables [19]. Huh et al. proposed a practical algorithm for selecting variables using the criterion of a minimum trace of partial variances of unselected variables unexplained by selected variables [20]. Principal variable analysis could help to identify sentinel symptoms among symptom clusters using a de novo approach. Sentinel symptoms would in turn help us to investigate underlying mechanisms and facilitate effective symptom management. This study aimed to evaluate the stability of symptom clusters during the 1st and 2nd cycles of adjuvant CTx and to identify sentinel symptoms among clusters of symptoms.

Methods

Design

This is a secondary data analysis of data from the Paradigm Shift in Chemotherapy-Induced Nausea and Vomiting (PS-CINV) study [21].

Sample

Among the chemo-naïve cancer patients who enrolled in the PS-CINV study ($N = 332$), those who completed symptom evaluation in the 1st and 2nd cycles of CTx ($N = 209$) were included in the current study. Patients were excluded if they were receiving concurrent radiotherapy or had health issues that could cause nausea or vomiting (e.g., bowel obstruction) because the primary research outcome of the PS-CINV study was nausea and vomiting (esp. CINV). Patients having difficulties in evaluating symptoms because of cognitive problems or a history of psychiatric problems were also excluded from the study.

Measurements

A 20-symptom list was utilized to understand the overall symptom experience. In an effort to conduct comprehensive but concise symptom assessment, existing symptom assessment tools (MSAS, MDASI, ESAS, CTCAE, FACIT, BSI) and symptom studies were reviewed [22–29]. The review of existing tools demonstrated that short versions included limited number of symptoms, whereas an extensive list of symptoms could end up with a list of symptoms with low prevalence. Authors identified 20 CTx-related symptoms, which were included in more than two instruments. Oncology experts reviewed the 20-symptom list for further inclusion or exclusion. The selected 20 symptoms formed a comprehensive but relatively short list of symptoms. It is of note that the 20-symptom list was inclusive of 12 core symptoms [30], and the lowest symptom prevalence rate was 23.9% in the current study.

Procedure

The study was approved by the institutional review board of the participating hospital (approval number: 4-2014-0700). Participants received detailed information regarding the purpose and details of the study from research nurses. Informed consent was obtained from those who agreed to participate. Patients evaluated the severity of the 20 symptoms after CTx on day 6 of each CTx cycle (the day of CTx infusion was counted as day 1).

Analysis

A de novo approach was applied to identify symptom clusters and sentinel symptoms. Measuring symptoms on a 0-to-10 numeric scale enabled a non-weighted symptom evaluation. The statistical program IBM SPSS 24.0 was used for descriptive statistics, mean, and prevalence comparison. Principal component analysis (PCA) was conducted with promax rotation. Cronbach's alpha value was calculated to evaluate cluster consistency and to identify items to delete to improve consistency of the cluster, with a criterion of Cronbach's alpha close to .70. SAS 9.4 was utilized for hierarchical cluster analysis (HCA) with oblimin rotation with r^2 and an own cluster value of $< .40$ as exclusion criteria. Principal variable analysis was conducted to identify sentinel symptoms. Huh's multipurpose variable selection procedure [20] was applied using

the R program version 3.4.1. Principal variables were selected as a subset of p input variables to contain as much information as possible about the original 13 symptom variables that formed symptom clusters in the 1st and 2nd cycles of CTx. A minimum trace of partial variances of unselected variables unexplained by selected variables was used with a criterion of 0.5 as a cut-off value. For any variable X_j, the unexplained variation of X_k was defined as follows, where x_k was a data vector for the variable X_k:

$$\sum_{k=1}^{p}\left|x_k-\frac{x_j{}'x_k}{x_j{}'x_j}x_j\right|^2, k=1,2,\ldots,p$$

After finding X_j, which minimized this unexplained variation, x_k was replaced by the unexplained residual. If the squared norm of the residual was less than the cut-off value, the variable X_k was deleted, and the dataset was updated. This procedure was repeated until there were no variables left in the dataset.

Results

General characteristics

The mean age of the participating patients ($N = 209$) was 51 years old (SD = 9.80, range: 26 to 73 years). Female patients comprised 64.6% of the patients, and the types of cancer diagnosis included breast cancer (47.8%), stomach cancer (19.6%), colorectal cancer (17.7%), and lung cancer (14.8%). Most of the patients had a stage 1–3 cancer diagnosis, and 99% of them had an ECOG status of 0 (only two patients had an ECOG status of 1) (Table 1).

Symptom experience

Fatigue was the most prevalent symptom in the 1st cycle, followed by loss of appetite and nausea. The mean symptom severity was the highest for loss of appetite, followed by fatigue and nausea. In the 2nd cycle, fatigue again was the most prevalent symptom, followed by taste change, loss of appetite, nausea, and drowsiness (prevalence rate > 85%). The mean symptom severity was the highest for fatigue, followed by alopecia and loss of appetite. There were significant increases between the two cycles of CTx in terms of the prevalence of oral mucositis, taste change, sexual problem, skin and nail change, alopecia, and neuropathy. A significant increase in severity was observed in the symptoms of oral mucositis, sexual problems, skin and nail changes, alopecia, and neuropathy. Although there was no difference in the symptom prevalence of constipation between the two cycles of CTx, a significant decrease in constipation severity was observed in the 2nd cycle (Table 2).

Table 1 General characteristics ($N = 209$)

	M ± SD/*n* (%)
Age	51.18 ± 9.80
Gender	
Male	74 (35.4)
Female	135 (64.6)
Cancer type	
Breast	100 (47.8)
Stomach	41 (19.6)
Colorectal	37 (17.7)
Lung	31 (14.8)
Stage[a]	
0	1 (0.5)
1	50 (23.9)
2	78 (37.3)
3	73 (34.9)
4	7 (3.3)
ECOG[b]	
0	207 (99.0)
1	2 (1.0)
Chemotherapy regimen	
AC	97 (46.4)
AC + F	1 (0.5)
Carboplatin + Vinorelbine	1 (0.5)
Cisplatin + F	1 (0.5)
Cisplatin + Vinorelbine	30 (14.4)
Cisplatin + TS-1	2 (1.0)
CMF	2 (1.0)
FOLFOX	33 (35.4)
Oxaliplatin + Capecitabine	42 (20.1)

[a] According to the AJCC cancer staging manual 7th ed.

[b] ECOG status at enrollment (before the start of chemotherapy)

AC anthracycline and cyclophosphamide, *F* 5-fluorouracil, *CMF* carboplatin + methotrexate + 5-fluorouracil, *FOLFOX* folinic acid (Leucovorin calcium) + 5-Fluorouracil + Oxaliplatin

Symptom clusters and key symptoms

In the first cycle, PCA and HCA identified identical 4 symptom clusters with 13 symptoms. The identified symptom clusters were (1) a physical-psychological symptom cluster: pain, dyspnea, sleep disturbance, anxiety, and depression; (2) a gastrointestinal symptom cluster: nausea, appetite loss, and taste change; (3) a fatigue-cognitive symptom cluster: fatigue, difficulty concentrating, and drowsiness; and (4) a urosexual symptom cluster: urinary problems and sexual problems (Table 3 and Fig. 1a). Seven symptoms (constipation, neuropathy, vomiting, diarrhea, skin and nail changes, mucositis, and alopecia) were excluded from the identified symptom clusters based on the Cronbach's alpha value of symptom cluster and change after item deletion. The identified 4 symptom clusters explained 73.81 and 72.4% of

Table 2 Symptoms in the 1st and 2nd cycles of chemotherapy ($N = 209$)

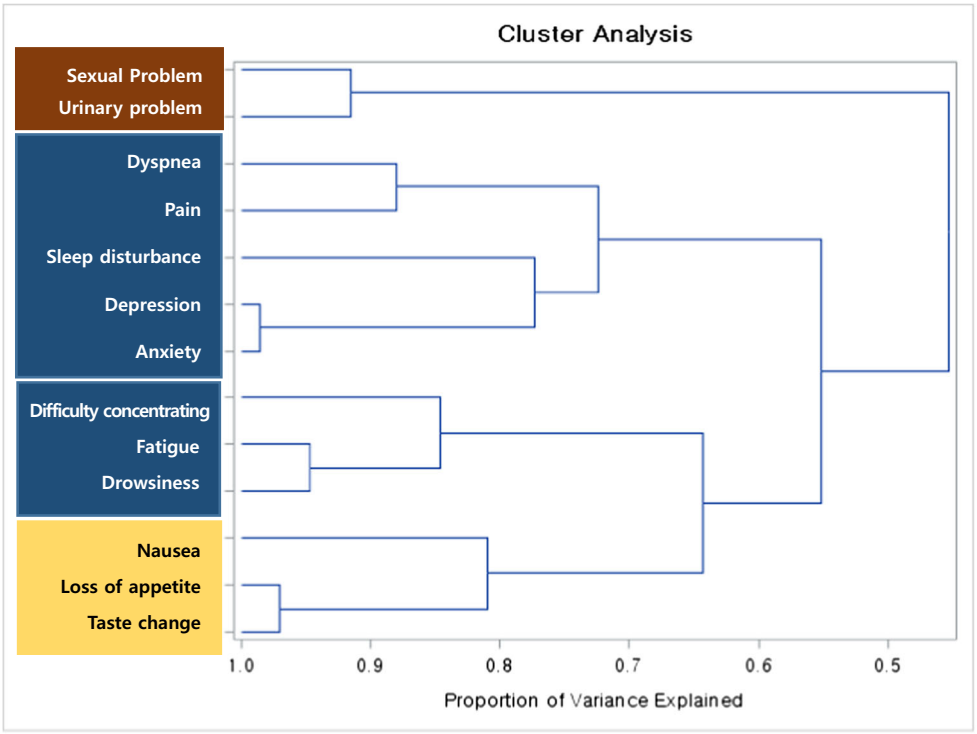
	1st cycle				2nd cycle				McNemar test p value	Wilcoxon signed rank test p value
	Prevalence (%)	Mean	SD	Median	Prevalence (%)	Mean	SD	Median		
Difficulty concentrating	162 (77.5)	3.36	2.81	3.00	168 (80.4)	3.40	2.66	3.00	.451	.662
Drowsiness	174 (83.3)	3.93	2.92	3.50	180 (86.1)	3.99	2.76	4.00	.429	.904
Fatigue	190 (90.9)	4.87	2.87	5.00	199 (95.2)	4.97	2.74	5.00	.064[a]	.829
Sleep disturbance	153 (73.2)	3.76	3.35	3.00	165 (78.9)	3.67	2.90	3.00	.097	.706
Anxiety	134 (64.1)	2.58	2.81	2.00	136 (65.1)	2.48	2.64	2.00	.897	.716
Depression	126 (60.3)	2.33	2.66	1.00	134 (64.1)	2.46	2.58	2.00	.312	.418
Pain	134 (64.1)	2.70	3.01	2.00	136 (65.1)	2.58	2.71	2.00	.890	.835
Dyspnea	115 (55.0)	2.02	2.63	1.00	125 (59.8)	2.30	2.73	1.00	.229	.099
Mucositis	78 (37.3)	1.22	2.26	0.00	106 (50.7)	1.84	2.53	1.00	.001	< .001
Taste change	166 (79.4)	4.31	3.48	4.00	180 (86.1)	4.53	3.33	4.00	.030	.256
Loss of appetite	178 (85.2)	5.00	3.51	5.00	180 (86.1)	4.78	3.28	5.00	.860	.414
Nausea	176 (84.2)	4.41	3.34	4.00	180 (86.1)	4.39	3.18	4.00	.556	.962
Vomiting	78 (37.3)	1.39	2.51	0.00	83 (39.7)	1.46	2.46	0.00	.614	.331
Constipation	125 (59.8)	3.33	3.60	2.00	134 (64.1)	2.66	2.94	2.00	.336	.012
Diarrhea	67 (32.1)	1.37	2.58	0.00	82 (39.2)	1.37	2.38	0.00	.078	.711
Urinary problem	66 (31.6)	1.30	2.54	0.00	74 (35.4)	1.24	2.29	0.00	.358	.940
Sexual problem	50 (23.9)	1.07	2.49	0.00	70 (33.5)	1.51	2.75	0.00	.011	.009
Skin and nail change	52 (24.9)	0.77	1.87	0.00	105 (50.2)	2.02	2.77	1.00	< .001	< .001
Alopecia	66 (31.6)	0.91	2.08	0.00	161 (77.0)	4.87	4.03	5.00	< .001	< .001
Neuropathy	111 (53.1)	2.13	2.77	1.00	148 (70.8)	3.14	3.03	2.00	< .001	< .001

[a] Binomial distribution used

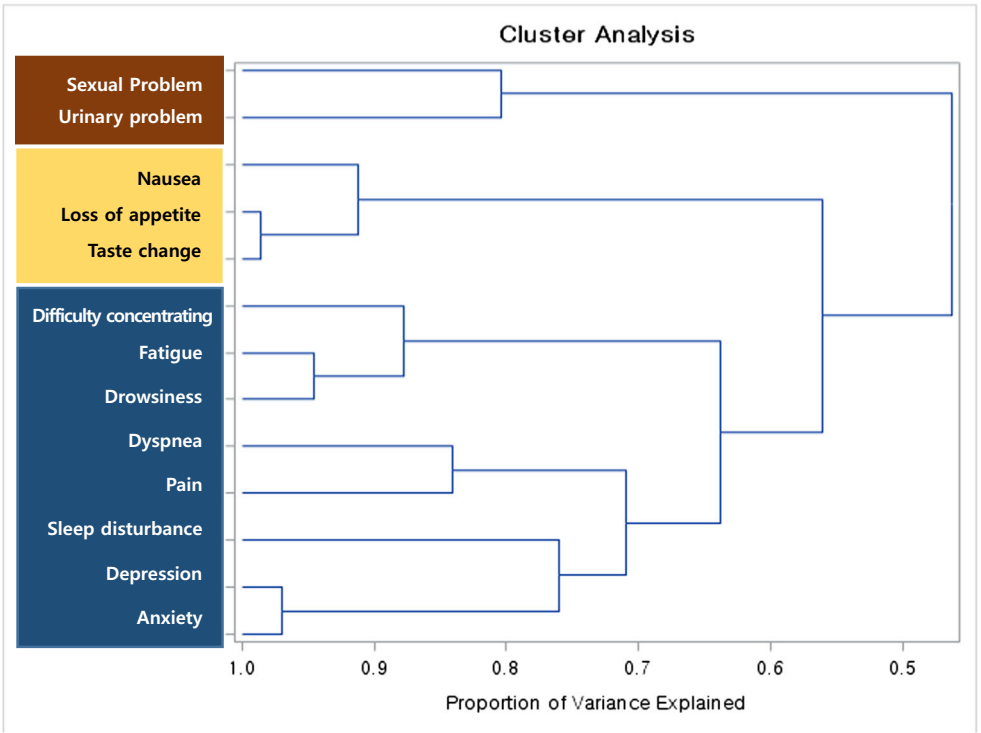
the variance between the 13 symptoms by PCA and HCA, respectively. The principal variable analysis identified sentinel symptoms which contain as much information as possible about the 13 symptoms that formed symptom clusters in the 1st cycle of CTx in the following order: anxiety, loss of appetite, and fatigue. The percentage of variation explained by the selected

Table 3 Symptom clusters in the 1st cycle

	Component				Cronbach's α	R^2 with		1-R**2 Ratio
	1	2	3	4		own cluster	next cluster	
Pain	0.86	0.08	− 0.17	− 0.04	0.86	0.61	0.18	0.48
Anxiety	0.83	− 0.07	0.15	0.00		0.79	0.29	0.29
Dyspnea	0.79	0.02	− 0.17	0.08		0.51	0.14	0.57
depression	0.76	− 0.17	0.26	0.03		0.71	0.31	0.42
Sleep disturbance	0.69	0.21	0.02	− 0.11		0.62	0.27	0.52
Loss of appetite	− 0.06	0.96	− 0.02	0.06	0.86	0.85	0.20	0.19
Taste change	0.05	0.89	− 0.03	0.02		0.82	0.25	0.24
Nausea	0.09	0.65	0.19	− 0.04		0.67	0.27	0.46
Drowsiness	− 0.15	− 0.05	0.97	0.03	0.83	0.74	0.17	0.31
Fatigue	− 0.02	0.17	0.84	− 0.08		0.81	0.30	0.27
Difficulty concentrating	0.17	− 0.02	0.69	0.08		0.69	0.31	0.45
Sexual problem	− 0.15	0.04	0.08	0.92	0.74	0.80	0.06	0.22
Urinary problem	0.19	0.01	− 0.07	0.83		0.80	0.16	0.24



a First Cycle



b Second Cycle

Fig. 1 Symptom cluster dendrogram

variables was 31.3% solely for anxiety, 48.4% for anxiety and loss of appetite, and 59.8% for all three symptoms (anxiety, loss of appetite, and fatigue).

In the second cycle, HCA identified 3 symptom clusters from the identical 13 symptoms identified in the 1st cycle (nausea was a candidate for item deletion with an increase in

Cronbach's alpha; however, the Cronbach's alpha value of the cluster was .88, so nausea was retained in the cluster). The 3 symptom clusters explained 63.8% of the variance between the 13 symptoms. PCA recommended somewhat different cluster solution (inclusion of oral mucositis and neuropathy in the physical-psychological symptom cluster, and constipation, diarrhea, and skin and nail changes in the urosexual symptom cluster) which explained 62.46% of the variance of the 18 symptoms evaluated. Three symptom clusters identified by HCA were selected as final symptom clusters in the second cycle, because 3 symptom clusters comprising 13 symptoms were identical in the PCA and HCA. A dendrogram demonstrated the existence of three symptom clusters from merging of the physical-psychological cluster and fatigue-cognitive symptom cluster into one cluster (Table 4 and Fig. 1b). Principle variable analysis identified sentinel symptoms of the second cycle of CTx in the following order: loss of appetite, depression, and fatigue. The percentage of variation explained by the selected variables was 28.1% solely for loss of appetite alone, 47.2% for loss of appetite and depression, and 62% for all three symptoms (loss of appetite, depression, and fatigue).

Discussion

Stability of symptom clusters

This study demonstrated the stability of symptom clusters maintained in the first two cycles of CTx, which could be of utmost interest for patients starting CTx. Core symptoms that comprised each symptom cluster in both CTx cycles, regardless of analytic technique, supported the stability of symptom clusters in the initial phase. The symptom clusters identified in the current study correspond with three of four of the most common symptom groupings identified through a systematic review of symptom clusters among patients with advanced cancer [12]: anxiety-depression, nausea-appetite loss, and fatigue-dyspnea-drowsiness-pain. A study by Kim et al. [10] on symptom clusters from before and 48 h after the 2nd and 3rd cycles of CTx (which is considered as the initial phase of CTx) also identified depressive mood, insomnia, pain, fatigue, and cognitive disturbance as a single cluster, which corresponds with the symptom cluster findings for the 2nd cycle of CTx in the present study. In a study by Albusoul et al. [9] on breast cancer patients' symptom clusters in their 3rd cycle of CTx, nausea and appetite loss clustered together, and anxiety and depression formed a cluster with symptoms of fatigue, pain, sleep disturbance, and concentration, along with appearance and bowel pattern. Thomas et al. [31] measured symptoms over a year (at baseline and 3, 6, and 12 months) in newly diagnosed cancer patients and conducted a factor analysis of all time points together. Similar cluster membership was identified in that study: anxiety and depression (psychological cluster) and pain, fatigue and sleep (somatic cluster). The current study suggests 'physical-psychological symptom cluster' which is composed of dyspnea, pain, sleep disturbance, depression, and anxiety in the 1st cycle of CTx. It is considered that dyspnea, pain, and sleep disturbance have a closer relationship with psychological symptoms than other physical symptoms which are not part of the physical-psychological symptom cluster.

The stable quality and temporal nature of symptom clusters co-exist. Longitudinal symptom cluster studies have

Table 4 Symptom clusters in the 2nd cycle

	Component			Cronbach's α	R^2 with		1-R**2 Ratio
	1	2	3		own cluster	next cluster	
Pain	0.61	0.06	0.17	0.88	0.51	0.24	0.65
Anxiety	0.76	0.12	−0.06		0.67	0.32	0.48
Dyspnea	0.75	−0.28	0.30		0.43	0.14	0.66
Depression	0.90	−0.04	−0.09		0.67	0.25	0.43
Sleep disturbance	0.51	0.23	0.01		0.46	0.23	0.70
Drowsiness	0.77	−0.07	−0.09		0.46	0.15	0.64
Fatigue	0.67	0.24	−0.09		0.64	0.36	0.56
Difficulty concentrating	0.61	0.19	0.01		0.57	0.29	0.62
Loss of appetite	−0.09	0.98	0.05		0.88	0.32	0.18
Taste change	−0.02	0.90	0.05	0.87	0.81	0.34	0.29
Nausea	0.25	0.65	−0.02		0.69	0.39	0.51
Sexual problem	−0.04	0.01	0.87	0.67	0.76	0.08	0.26
Urinary problem	−0.03	0.10	0.83		0.76	0.11	0.27

supported the temporal nature of symptom clusters: symptom clusters before, during, and after CTx demonstrated dynamic changes in the number and type of symptoms [9, 32]. A systematic review of studies by Dong et al. also reported that symptom clusters were not stable over time in most cases [12]. The emergence of new symptoms with progression of CTx treatment contributes to the temporality of the symptom cluster. Accumulative side effects with repeated cycles of CTx have been reported as apparent starting from the 3rd cycle of CTx [32]. The current study partly supported the temporality of symptom clusters, with a change in cluster membership identified by PCA starting from the 2nd cycle; for example, oral mucositis and neuropathy became part of the physical-psychological symptom cluster. Changes in symptom cluster membership with the emergence of new symptoms as well as the disappearance of previous symptoms with long-term survivorship have also been demonstrated by Molassiotis et al. [33], Esser et al. [11], and Skerman, Yates, and Battistutta [34], who proposed core or defining symptoms for each symptom cluster. Over time, the addition or omission of symptoms other than core symptoms occurred during the patients' cancer journey. Consistent sets of concurrent symptoms not only signify a common cause but also demonstrate the stability of the symptom cluster. It is meaningful that a core set of symptoms during initial phase of CTx formed a stable symptom cluster in the 1st and 2nd cycles in the current study. The phase-specific stability of the symptom cluster (such as in the initial phase of CTx or after completion of CTx, i.e., in the long-term survivorship phase) needs to be acknowledged, and the core set of symptoms that form stable symptom clusters needs to be recognized. The current study's results support the idea of a core set of symptoms that form stable symptom clusters at specific phases of the cancer journey.

Sentinel symptoms

Principal variable analysis was employed to identify sentinel symptoms. The principal variable analysis algorithm enabled the selection of symptoms with the criterion of a minimum trace of partial variances of unselected symptoms unexplained by selected symptoms, thus best representing unselected symptoms. It is noteworthy that the selected principal variable corresponded with the most influential symptom identified in the HCA, with the smallest 1-R**2 ratio for each symptom cluster. Principal variable analysis could be utilized to identify sentinel symptoms in a de novo approach. Previous efforts in identifying sentinel symptoms have been unsatisfactory. High symptom prevalence and severity are not satisfactory criteria [13]. Certain symptoms (i.e., nausea) have been hypothesized as sentinel symptoms, and their relationships with other related symptoms were evaluated through correlation and regression analysis [16], as was the predictability of other symptoms related to certain symptoms through random forest modeling [14]. Among the symptoms of pain, fatigue, sleep disturbance and depression, pain and fatigue were considered as key symptoms for classifying patients into latent groups [17]. As nausea, pain, and fatigue were predefined symptoms of interest, an exploratory approach to identify sentinel symptoms needs to be conducted. Other approaches include the analysis of temporal relationships between symptoms, which may also support the existence of sentinel symptoms. Although not generalizable to all time points, fatigue has frequently predicted subsequent depression, insomnia, and pain, whereas anxiety predicted insomnia [35]. Multilevel modeling of symptom clusters over three consecutive measurements over 5 years among HSCT patients identified fatigue as the most severe and representative symptom [11]. In the current study, fatigue was identified as the third sentinel symptom in both cycles of CTx. Because this study was focused on symptoms at the initial phase of CTx, the level of fatigue could have been relatively low.

It is interesting that although the occurrence and severity of symptoms were not significantly different in the 1st and 2nd CTx cycles, the sentinel symptom identified in the 1st cycle was anxiety and depression in the 2nd cycle. An overall decrease in high anxiety with treatment progression might explain the findings [36, 37]. In comparison, depression has demonstrated greater variation over time (increasing, increasing and decreasing, or just decreasing) [32, 36, 37]. The importance of emotional symptom management at the start of CTx is not only emphasized; it is understood that initial psychological support needs to be more focused on anxiety. With the progression of treatment, clinicians need to keep an eye on the development and severity of depression. It is also noteworthy that a high level of correlation exists between the two symptoms.

In the present study, other sentinel symptoms included loss of appetite and fatigue. As this study invested patients' symptom experience at the initial two cycles of CTx, appetite was selected as a sentinel symptom before fatigue. In the 2nd cycle, loss of appetite became the first sentinel symptom identified. Appetite loss is a well-acknowledged side effect of CTx. However, few evidence-based interventions, which include oral nutritional intervention and use of progestin, exist [38]. As appetite loss forms a cluster with taste change and nausea, targeting a treatable symptom in the cluster, such as nausea, would be a strategic approach in managing this symptom cluster. Fatigue is one of the most common symptoms experienced by cancer patients, with a reported prevalence ranging from 25 to 99% [39]. Studies have demonstrated that incorporating exercise during cancer treatment is a feasible and effective method for managing fatigue

[40–42]. Further studies are warranted to determine whether interventions targeting sentinel symptoms would effectively manage symptom clusters.

Strengths of the current study include identifying stable symptom clusters and sentinel symptoms during the initial phase of CTx. In addition, the assessment was conducted on day 6 of CTx, which enabled less biased recall of the symptom experience. Furthermore, various statistical analysis techniques were employed, and reliable results were identified. However, this study was limited because it involved data collection from a single site. Although the 20-symptom list was inclusive of 12 core symptoms [30], utilizing invalidated 20-symptom list to identify symptom clusters might have contributed to cluster solution. Symptoms included in the identified symptom clusters need to be understood in consideration of the type of chemotherapy patients received. For example, the severity of CINV could be dependent on the emetogenicity of CTx. Neuropathy is problematic in certain types of CTx.

Conclusion

Symptom clusters demonstrated phase-specific stability. The current study identified a core set of symptoms that form stable symptom clusters during the 1st and 2nd cycles of CTx. Principal variable analysis identified sentinel symptoms which could facilitate efficient symptom management.

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Compliance with ethical standards

The study was approved by the institutional review board of the participating hospital (approval number: 4-2014-0700). Participants received detailed information regarding the purpose and details of the study from research nurses. Informed consent was obtained from those who agreed to participate.

Conflict of interest The authors declare that they have no conflicts of interest.

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