Higher Levels of Stress and Neuropsychological Symptoms Are Associated With a High Nausea Profile in Patients With Cancer Receiving Chemotherapy

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OBJECTIVES: To evaluate differences in the severity of global, cancer-specific, and cumulative life stress, resilience, and common neuropsychological symptoms among four subgroups of patients with distinct chemotherapy-induced nausea (CIN) profiles.

SAMPLE & SETTING: Adult patients with cancer (N = 1,343) receiving chemotherapy.

METHODS & VARIABLES: Patients completed stress, resilience, and neuropsychological symptom severity measures. The Memorial Symptom Assessment Scale was used to assess CIN occurrence six times over two cycles of chemotherapy. Parametric and nonparametric statistics were used to evaluate differences among subgroups of patients with distinct CIN profiles.

RESULTS: The high class had significantly higher levels of global, cancer-specific, and cumulative life stress; significantly higher levels of depression, anxiety, sleep disturbance, morning and evening fatigue, and pain; and lower levels of morning and evening energy and cognitive dysfunction.

IMPLICATIONS FOR NURSING: Clinicians need to evaluate CIN occurrence across each cycle of chemotherapy and assess patients for various types of stress and common neuropsychological symptoms.

KEYWORDS cancer; chemotherapy; nausea; stress; symptoms

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Despite advances in evidence-based antiemetic regimens, 30%–60% of patients with cancer report unrelieved chemotherapy-induced nausea (CIN) (Röhrl et al., 2019). This large range in prevalence rates suggests a significant amount of interindividual variability in this symptom. Given that the known risk factors for CIN do not explain all its interindividual variability, additional risk factors warrant evaluation (Singh et al., 2018). For example, a cancer diagnosis and associated treatments and fear of recurrence are stressful experiences for most patients (Mazor et al., 2019). Equally important, an individual's level of resilience can affect their response to these events (García-León et al., 2019; Oppegaard, Harris, Shin, Paul, Cooper, Levine, et al., 2021). However, research on associations between CIN and stress and resilience is limited.

Although patients with cancer can experience several types of stress (e.g., global stress, cancer-specific stress, cumulative life stress) (Langford et al., 2020), except for two previous studies (Singh et al., 2018; Singh, Paul, et al., 2020), the evidence to support an association between CIN and stress has been inferred from intervention studies that evaluated the efficacy of a variety of stress reduction techniques. For example, findings from one systematic review suggested that progressive muscle relaxation, a stress-reducing intervention, decreases CIN and vomiting in patients with breast cancer (Kapogiannis et al., 2018). Additional, albeit inconclusive, evidence was reported in two exercise intervention studies (Haller et al., 2021; Johnsson et al., 2019). In the first study, which evaluated the

effects of a single session of endurance or resistance training in women with breast cancer within the first week of chemotherapy (Johnsson et al., 2019), only general stress levels decreased in the endurance group, whereas general stress and CIN decreased in the resistance group over time. In the second pilot study (Haller et al., 2021), the effects of an integrative mind–body–medicine group program on stress and CIN in women with breast cancer were evaluated. Although global stress scores, evaluated using the Perceived Stress Scale (PSS), decreased over time, CIN scores increased.

In the current authors' first study, which evaluated risk factors for the occurrence of CIN in patients prior to their second or third cycle of chemotherapy, patients with CIN reported higher levels of global stress (assessed using the PSS) and cancer-specific stress (assessed using the Impact of Event Scale–Revised [IES-R]) in the univariable analyses (Singh et al., 2018). Of note, in the multivariable analysis, each one-point increase in PSS scores was associated with a 3% increase in the odds of belonging to the CIN group. In the authors' second study, which used hierarchical linear modeling to evaluate which demographic, clinical, stress, and symptom characteristics were associated with initial levels and the trajectories of CIN severity (Singh, Paul, et al., 2020), higher levels of intrusive thoughts (assessed using the IES-R) were associated with higher CIN severity scores at enrollment. Across various studies (Haller et al., 2021; Johnsson et al., 2019; Kapogiannis et al., 2018; Singh et al., 2018; Singh, Paul, et al., 2020), direct and indirect evidence supports the hypothesis that positive associations exist between CIN occurrence and/or severity and stress. However, none of these studies evaluated for associations among CIN occurrence and all three types of stress (global, cancer-specific, and cumulative life stress) in the same sample of patients.

Resilience is an individual's ability to handle adversity (Campbell-Sills & Stein, 2007). In the only cross-sectional study identified, which used the Connor-Davidson Resilience Scale to assess resilience in patients with breast cancer (Ristevska-Dimitrovska et al., 2015), lower levels of resilience were associated with higher CIN and vomiting severity scores. However, the conclusions that can be drawn from this study are limited because CIN and vomiting were assessed together as a single item on the European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire–Core 30.

Regarding associations between CIN and neuropsychological symptoms, findings from a limited number of studies suggest that higher levels of sleep disturbance (Crane et al., 2020; Hockenberry et al., 2017; Singh et al., 2018; Singh, Paul, et al., 2020), depression (Crane et al., 2020; Hockenberry et al., 2017; Singh et al., 2018; Singh, Paul, et al., 2020), fatigue (Crane et al., 2020; Hockenberry et al., 2017; Singh et al., 2018; Singh, Paul, et al., 2020), and anxiety (Singh et al., 2018; Whisenant et al., 2019) are associated with higher occurrence rates for and/or severity of CIN. In addition, pain (Fink et al., 2020; Kwekkeboom et al., 2018) and cognitive dysfunction (Bajic et al., 2018; Whisenant et al., 2019) may co-occur with CIN. Although these studies provide preliminary evidence of positive associations among CIN and a number of neuropsychological symptoms, none of these studies evaluated for differences in the severity of these symptoms in patients with distinct CIN profiles.

Using latent class analysis (LCA), Singh et al. (2023) identified subgroups of patients (N = 1,343) with four distinct CIN occurrence profiles (none [N = 548, 41%], increasing–decreasing [N = 289, 22%], decreasing [N = 119, 9%], and high [N = 387, 29%]) (see Supplemental Figure 1). In addition, differences in demographic and clinical characteristics and co-occurring common gastrointestinal symptoms among these profiles were described. Given the need to identify additional risk factors for unrelieved CIN, this article builds on the findings of Singh et al. (2023) and evaluates differences in the severity of global, cancer-specific, and cumulative life stress, as well as resilience and common neuropsychological symptoms, among four subgroups of patients with distinct CIN occurrence profiles.

Methods

Conceptual Framework

The theory of symptom management served as the theoretical framework for the entire study, which was funded by the National Cancer Institute (Weiss et al., in press). Specifically, the symptom experience domain and person characteristics were the foci for this analysis.

Patients and Settings

As previously described (Singh et al., 2023), eligible patients were aged 18 years or older; had a diagnosis of breast, gastrointestinal, gynecologic, or lung cancer; had received chemotherapy within the past four weeks; were scheduled to receive at least two additional cycles of chemotherapy; were able to read, write, and understand English; and provided written

informed consent. Patients were recruited from two comprehensive cancer centers, one Veterans Affairs hospital, and four community-based oncology programs.

Study Procedures

The study was approved by the institutional review board at the University of California and each of the study sites. Of 2,234 patients approached, 1,343 consented to participate and provided evaluable data on the occurrence of CIN for this analysis. Patients' refusal to participate was primarily because of being overwhelmed with their cancer treatment. Eligible patients were approached on the infusion unit during their first or second cycle of chemotherapy to discuss participation in the study. Patients completed the CIN occurrence item on the Memorial Symptom Assessment Scale (MSAS) (Portenoy et al., 1994) six times in their homes during their next two cycles of chemotherapy. Assessments 1 and 4 were completed prior to chemotherapy administration, assessments 2 and 5 were completed about one week after chemotherapy administration, and assessments 3 and 6 were completed about two weeks after chemotherapy administration. All other questionnaires were completed at enrollment prior to the patient's second or third cycle of chemotherapy.

Instruments

Demographic and clinical characteristics: Patients completed a demographic questionnaire, the Karnofsky Performance Status (KPS) scale (Karnofsky, 1977), the Self-Administered Comorbidity Questionnaire (Sangha et al., 2003), and a smoking history questionnaire. Disease and treatment information was obtained from patients' medical records.

Assessment of CIN occurrence: The occurrence of CIN was measured using the nausea item from the MSAS at each of the six assessments. The MSAS is a valid and reliable symptom assessment instrument for patients with cancer that evaluates the occurrence, severity, frequency, and distress of 32 common symptoms (Portenoy et al., 1994).

Stress and resilience measures: The 14-item PSS was used as a measure of global perceived stress according to the degree that life circumstances are appraised as stressful during the course of the previous week (Cohen et al., 1983). Total PSS scores range from 0 to 56. In this study, the Cronbach's alpha was 0.85.

The 22-item IES-R was used to measure cancer-related distress (Horowitz et al., 1979). Patients rated each item based on how distressing each potential difficulty was for them during the past week "with respect to their cancer and its treatment." Levels of intrusion, avoidance, and hyperarousal as perceived by the patient are evaluated using three subscales. Sum scores of 24 or greater indicate clinically meaningful post-traumatic symptomatology, and scores of 33 or greater indicate probable post-traumatic stress disorder (PTSD) (Creamer et al., 2003). In this study, the Cronbach's alpha for total IES-R score was 0.92.

The 30-item Life Stressor Checklist–Revised is an index of lifetime trauma exposure (e.g., death of a loved one, a sexual assault) (Wolfe & Kimerling, 1997). Total scores are obtained by summing the total number of events endorsed. If patients endorsed an event, they were asked to indicate how much that stressor affected their life during the past year. These responses were averaged to yield a mean "affected" score. In addition, a PTSD sum score was created based on the number of positively endorsed items (of 21) that reflect the *Diagnostic and Statistical Manual of Mental Disorders* (fourth edition) PTSD Criteria A for having experienced a traumatic event.

The 10-item Connor-Davidson Resilience Scale evaluates a patient's personal ability to handle adversity (e.g., "I am able to adapt when changes occur") (Campbell-Sills & Stein, 2007). Total scores range from 0 to 40, with higher scores indicating higher self-perceived resilience. The normative adult mean score in the United States is 31.8 (SD = 5.4) (Campbell-Sills et al., 2009). In this study, the Cronbach's alpha was 0.9.

Assessment of neuropsychological symptoms: An evaluation of other common symptoms was performed using valid and reliable instruments. These symptoms and their respective measures were as follows: depressive symptoms using the Center for Epidemiological Studies–Depression scale (Radloff, 1977), trait and state anxiety using the Spielberger State-Trait Anxiety Inventory (Spielberger et al., 1983), cognitive function using the Attentional Function Index (Cimprich et al., 2005), sleep disturbance using the General Sleep Disturbance Scale (Lee, 1992), morning and evening fatigue and energy using the Lee Fatigue Scale (Lee et al., 1991), and pain using the Brief Pain Inventory (Daut et al., 1983).

Data Analyses

Descriptive statistics and frequency distributions were generated for sample characteristics at enrollment using IBM SPSS Statistics, version 27.0. As previously described (Singh et al., 2023),

unconditional LCA was used to identify distinct profiles of CIN occurrence that characterized unobserved subgroups of patients (i.e., latent classes) during the six assessments. Prior to performing the LCA, patients who responded "no" to the nausea item on the MSAS for five or six assessments (i.e., these patients did not experience nausea across the two cycles of chemotherapy) were identified and labeled as the "none" class (N = 548). Then, LCA was performed using data from the remaining 795 patients.

Estimation was carried out with full information maximum likelihood with standard errors and a chi-square test that was robust to non-normality and nonindependence of observations ("estimator = MLR") using a logit link because the items are binary. Model fit was evaluated to identify the solution that best characterized the observed latent class structure with the Bayesian Information Criterion, Vuong–Lo–Mendell–Rubin likelihood ratio test, entropy, and latent class percentages that were large enough to be reliable (i.e., likely to replicate in new samples) (Muthén & Muthén, 1998–2017). Missing data were accommodated with the use of the Expectation-Maximization algorithm (Muthén & Shedden, 1999). Mixture models, like LCA, are known to produce solutions at local maxima. Therefore, the models for this study were fit with from 800 to 2,400 random starts. This approach ensured that the estimated model was replicated many times and was not because of a local maximum. Estimation was done using Mplus, version 8.2.

Parametric and nonparametric tests were used to evaluate differences among the latent classes in stress, resilience, and neuropsychological symptom scores at enrollment. Statistical significance was set at $p < 0.05$. Post hoc contrasts were done using a Bonferroni-corrected p value of < 0.008 (0.05/6 possible pairwise contrasts).

Results

LCA

As previously reported (Singh et al., 2023), 548 patients (41%) who had one or fewer occurrences of CIN over the six assessments were labeled as the none class. A three-class solution was selected for the remaining 795 patients whose data were entered into the LCA. For the increasing–decreasing class (N = 289, 22%), the CIN occurrence rate increased from the first to the second assessment, decreased at the third assessment, and increased again at the fourth and fifth assessments before decreasing at the sixth assessment. For the decreasing class (N = 119, 9%), the occurrence rate for CIN increased slightly from the first to the second assessment, then gradually decreased over the remaining four assessments. For the high class (N = 387, 29%), the occurrence rates for CIN remained consistently high over the six assessments.

Demographic and Clinical Characteristics

As previously described (Singh et al., 2023), compared to the none class, the high class was significantly younger, more likely to have a lower annual household income, and more likely to have childcare responsibilities (see Supplemental Table 1). In addition, these patients had lower KPS scores and higher Self-Administered Comorbidity Questionnaire scores; were more likely to self-report diagnoses of ulcer/stomach disease, anemia or blood disease, or depression; and were more likely to have received only chemotherapy, chemotherapy on a 14-day cycle, and a highly emetogenic chemotherapy regimen. Compared to the increasing–decreasing class, patients in the high class had lower KPS scores, were less likely to exercise on a regular basis, and were more likely to have gastrointestinal cancer and less likely to have gynecologic cancer.

Compared to the none class, the increasing–decreasing class was younger and more likely to be female. In addition, they had higher MAX2 scores and lower KPS scores, were more likely to self-report a diagnosis of depression, and were less likely to receive a minimal/low emetogenic chemotherapy regimen. Compared to the none class, patients in the decreasing class had lower KPS scores.

Stress and Resilience Scores

Compared to the none class, the other three classes had higher PSS scores (see Table 1). The increasing–decreasing and high classes had higher IES-R intrusion subscale and total scores compared to the none class. The high class had higher IES-R avoidance and hyperarousal subscale scores, as well as higher Life Stressor Checklist–Revised affected sum, PTSD, and total scores compared to the none class. No differences were found among the classes in Connor-Davidson Resilience Scale scores.

Neuropsychological Symptom Scores

Compared to the none class, the other three classes reported significantly higher levels of depression, trait anxiety, sleep disturbance, and morning and evening fatigue (see Table 2). The increasing–decreasing and high classes reported higher levels of state anxiety and

lower levels of attentional function compared to the none class. Compared to the none class, the high class reported lower levels of morning and evening energy and a higher number of pain locations. Compared to the increasing–decreasing and decreasing classes, the high class reported higher levels of depression, sleep disturbance, and morning fatigue. Compared to the other three classes, a higher percentage of patients in the high class reported the occurrence of cancer and noncancer pain, as well as greater worst pain intensity and pain interference scores.

Discussion

The current study, which builds on the authors' previous findings (Singh et al., 2023), is the first to identify associations among stress, resilience, and neuropsychological symptoms in patients with distinct CIN occurrence profiles. Because the researchers' previous study provided in-depth explanations for the associations between the distinct CIN profiles and various demographic and clinical characteristics, this discussion focuses on the common and distinct risk factors across the CIN occurrence profiles related to stress, resilience, and neuropsychological symptoms (see Table 3).

Stress Characteristics and Worse CIN Profiles

This study is the first to evaluate associations between CIN occurrence and three distinct types of stress. In terms of global stress, it is notable that compared to the none class, the other three classes had significantly higher but comparable PSS scores. Although a clinically meaningful cutoff score is not available for the PSS, the scores for the three highest

TABLE 1. Differences in Stress and Resilience Scores Among Nausea Latent Classes

	None (0) (N = 548)		Increasing–Decreasing (1) (N = 289)		Decreasing (2) (N = 119)		High (3) (N = 387)			
Measure	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD	Statistic	p
CDRS total score	30.59	6.3	30.11	6.29	29.3	6.67	29.58	6.44	F = 2.42	< 0.065
IES-R avoidance subscale	0.86	0.62	0.95	0.69	1	0.69	1.05	0.72	F = 6.04, PWC = 0 < 3	< 0.001
IES-R hyperarousal subscale	0.5	0.55	0.69	0.69	0.65	0.7	0.84	0.72	F = 20.75, PWC = 0 and 1 < 3; 2 < 3	< 0.001
IES-R intrusion subscale	0.75	0.62	0.93	0.74	0.92	0.72	1.1	0.75	F = 18.17, PWC = 0 < 1 and 3; 1 < 3	< 0.001
IES-R total score	15.88	11.13	19.16	13.74	19.19	13.36	22.4	14.18	F = 18.42, PWC = 0 < 1 and 3; 1 < 3	< 0.001
LSC-R affected sum	10.11	9.56	12.58	11.83	10.92	10.48	13.86	11.34	F = 7.33, PWC = 0 < 1 and 3	< 0.001
LSC-R PTSD sum	2.69	2.86	3.27	3.07	2.57	2.38	3.64	3.35	F = 6.93, PWC = 0 and 2 < 3	< 0.001
LSC-R total score	5.49	3.62	6.2	3.88	5.64	3.72	6.86	4.33	F = 7.3, PWC = 0 and 2 < 3	< 0.001
PSS score	16.71	7.71	18.96	8.61	19.04	7.83	20.45	8.11	F = 16.32, PWC = 0 < 1, 2, and 3	< 0.001

CDRS—Connor-Davidson Resilience Scale; IES-R—Impact of Event Scale–Revised; LSC-R—Life Stressor Checklist–Revised; PSS—Perceived Stress Scale; PTSD—post-traumatic stress disorder; PWC—pairwise comparison

Note. Total scores on the CDRS range from 0 to 40, with higher scores indicating higher self-perceived resilience. A total score on the IES-R of 24 or greater indicates clinically meaningful post-traumatic symptomatology. LSC-R affected sum scores range from 0 to 150, LSC-R PTSD sum scores range from 0 to 21, and LSC-R total scores range from 0 to 30, with higher scores on all scales indicating a greater impact of the stressor on patients during the past year. PSS scores range from 0 to 56, with higher scores indicating greater global perceived stress.

TABLE 2. Differences in Neuropsychological Symptom Severity Scores Among Nausea Latent Classes

	None (0) (N = 548)		Increasing–Decreasing (1) (N = 289)		Decreasing (2) (N = 119)		High (3) (N = 387)			
Measure	**$\bar{X}$**	**SD**	**$\bar{X}$**	**SD**	**$\bar{X}$**	**SD**	**$\bar{X}$**	**SD**	**Statistic**	**p**
Attentional Function Index	6.8	1.7	6.3	1.8	6.4	1.7	5.9	1.8	F = 16.77, PWC = 0 > 1 and 3; 1 > 3	< 0.001
CES-D scale	10.3	8.5	13.2	9.8	12.9	9.8	16.1	10.1	F = 27.81, PWC = 0 < 1, 2, and 3; 1 and 2 < 3	< 0.001
Evening energy	3.8	2	3.4	1.9	3.5	2.2	3.3	2	F = 4.38, PWC = 0 > 3	0.004
Evening fatigue	4.8	2.2	5.5	2	5.4	2.3	5.9	2	F = 21.06, PWC = 0 < 1, 2, and 3	< 0.001
Morning energy	4.6	2.3	4.4	2.1	4.5	2.2	4.1	2.2	F = 4.97, PWC = 0 > 3	0.002
Morning fatigue	2.5	2.1	3.2	2.2	3.2	2.3	3.9	2.3	F = 26.35, PWC = 0 < 1, 2, and 3; 1 and 2 < 3	< 0.001
General Sleep Disturbance Scale	46.7	19.5	52	19.7	52.9	18.3	60.7	19.5	F = 37.49, PWC = 0 < 1, 2, and 3; 1 and 2 < 3	< 0.001
State Anxiety Inventory	31.2	11.2	34.1	12.6	34.1	12.9	37.4	12.8	F = 19.39, PWC = 0 < 1 and 3; 1 < 3	< 0.001
Trait Anxiety Inventory	32.9	9.7	35.3	10.7	35.7	10.5	37.9	10.7	F = 17.21, PWC = 0 < 1, 2, and 3; 1 < 3	< 0.001
For patients with pain (N = 957)										
Number of pain locations	7.2	7.2	8.6	7.1	7.8	8	9.1	8.3	F = 3.49, PWC = 0 < 3	0.015
Pain interference	2.6	2.4	2.9	2.4	2.9	2.3	3.9	2.6	F = 15.61, PWC = 0, 1, and 2 < 3	< 0.001
Worst pain intensity	5.8	2.5	5.9	2.4	5.7	2.7	6.6	2.6	F = 5.41, PWC = 0, 1, and 2 < 3	0.001
Measure	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**Statistic**	**p**
Type of pain									$\chi^2 = 50.11$	< 0.001
Cancer and noncancer pain	141	26	82	29	27	24	150	40	PWC = 0, 1, and 2 < 3	–
No pain	182	34	64	23	26	23	88	23	PWC = 0 > 1 and 3	–
Only cancer pain	119	18	99	35	36	32	93	25	PWC = 0 < 1 and 3	–

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TABLE 2. Differences in Neuropsychological Symptom Severity Scores Among Nausea Latent Classes *(Continued)*

	None (0) (N = 548)		Increasing–Decreasing (1) (N = 289)		Decreasing (2) (N = 119)		High (3) (N = 387)			
Measure	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**Statistic**	**p**
Type of pain *(continued)*										
Only noncancer pain	98	22	38	13	25	22	49	13	PWC not significant	–

CES-D—Center for Epidemiological Studies–Depression; PWC—pairwise comparison
Note. On the Attentional Function Index, scores range from 0 to 10, with scores less than 5 indicating low cognitive functioning, scores from 5 to 7.5 indicating moderate cognitive functioning, and scores greater than 7.5 indicating high cognitive functioning. On the CES-D, scores range from 0 to 60, with scores of 16 or greater indicating clinical significance. On the Lee Fatigue Scale, scores range from 0 to 10, with evening energy scores of 3.5 or lower, evening fatigue scores of 5.6 or greater, morning energy scores of 6.2 or lower, and morning fatigue scores of 3.2 or greater indicating clinical significance. On the General Sleep Disturbance Scale, scores range from 0 to 147, with scores of 43 or greater indicating clinical significance. On the Spielberger State-Trait Anxiety Inventory, scores range from 20 to 80, with state anxiety scores of 31.8 or greater and trait anxiety scores of 32.2 or greater indicating clinical significance.
Note. The n values per characteristic may not add up to the total N because some participants did not answer every question.
Note. Because of rounding, percentages may not total 100.

CIN classes are comparable to scores reported by men and women one month after a myocardial infarction (Xu et al., 2015). Because global stress activates the hypothalamic–pituitary–adrenal axis (Chu et al., 2023) and the three highest CIN classes had similar levels of global stress, additional research is warranted on the threshold of stress that contributes to the occurrence of CIN.

Regarding cancer-specific stress, although all IES-R subscale and total scores were higher in the high class, only the intrusion and IES-R total scores were higher in the increasing–decreasing class compared to the none class. Although the IES-R total score for the high class approached the cutoff for post-traumatic symptomatology, 40% of these patients exceeded this cutoff and 20% met the criteria for PTSD. This rate of PTSD is higher than the 6.1%–9.2% reported for the general population of the United States (Sareen, 2022). In addition, the high class's IES-R total score is similar to that of a sample of postpartum women with severe nausea (Kjeldgaard et al., 2019). Clinicians need to assess for cancer-related stress and PTSD in patients receiving chemotherapy. Cognitive behavioral therapies, mindfulness-based approaches, and telehealth interventions may reduce stress and PTSD symptoms, as well as CIN occurrence and severity (Beerse et al., 2020; Boyd et al., 2018).

In terms of cumulative life stress, compared to the none class, the high class reported higher levels of cumulative exposure to and effects of stressful life events. In addition, compared to the none class, Life Stressor Checklist–Revised affected scores were higher in the increasing–decreasing class. This association between cumulative life stress and CIN may be partially explained by an increase in allostatic load. Allostatic load is defined as the cumulative burden of chronic stress and life events that can result in overwhelming physiologic changes (Guidi et al., 2021). Stress can initiate changes in the autonomic nervous system and/or hypothalamic–pituitary–adrenal axis that result in increases in inflammatory responses (Shields & Slavich, 2017). This hypothesis is supported by reported associations between increases in allostatic load and more severe nausea in patients with migraines (Blumenfeld et al., 2021).

Neuropsychological Symptoms and Worse CIN Profiles

Compared to the none class, the other three classes reported higher severity scores for 5 of 10 neuropsychological symptoms (depression, trait anxiety, sleep disturbance, morning fatigue, and evening fatigue). This finding is not surprising given that previous studies reported on the co-occurrence of these symptoms with CIN in patients with ovarian (Donovan et al., 2016), breast (Crane et al., 2020; Jung et al., 2016; Kwekkeboom et al., 2018; Peoples et al., 2017; Whisenant et al., 2019), gastrointestinal (Hong et al., 2020; Kwekkeboom et al., 2018), and lung (Kwekkeboom et al., 2018) cancers. Of note, for the

three highest CIN classes, scores for trait anxiety, sleep disturbance, and fatigue (morning and evening) exceeded these symptoms' clinically meaningful cutoff scores. In addition, for the high class, Center for Epidemiological Studies–Depression scale scores exceeded the clinically meaningful cutoff. Similar to stress, the co-occurrence of common neuropsychological symptoms in the three highest CIN classes suggests common biologic mechanisms (Kim et al., 2012).

For example, evidence suggests that common neuropsychological symptoms associated with the administration of chemotherapy may be related to increases in levels of proinflammatory cytokines (Bajic et al., 2018; Bower, 2019; Kim et al., 2012; Miller et al., 2013; Vichaya et al., 2015) and/or alterations in the microbiome–gut–brain axis (Bajic et al., 2018; Jordan et al., 2018; Singh, Dhruva, et al., 2020). Postchemotherapy increases in levels of proinflammatory cytokines may exert direct effects (e.g., cross

TABLE 3. Neuropsychological Symptom and Stress Characteristics Associated With Membership in Nausea Latent Classes Compared to the None Class

Characteristics	Increasing–Decreasing	Decreasing	High
Neuropsychological symptoms			
Higher depression	●	●	●
Higher state anxiety	●		●
Higher trait anxiety	●	●	●
Lower attentional function	●		●
Higher sleep disturbance	●	●	●
Lower evening energy			●
Higher evening fatigue	●	●	●
Lower morning energy			●
Higher morning fatigue	●	●	●
Higher number of pain locations			●
Higher pain interference			●
Higher worst pain intensity			●
Stress			
Higher IES-R avoidance score			●
Higher IES-R hyperarousal score			●
Higher IES-R intrusion score			●
Higher IES-R total score	●		●
Higher LSC-R affected score	●		●
Higher LSC-R post-traumatic stress disorder score			●
Higher LSC-R total score			●
Higher Perceived Stress Scale score	●	●	●

IES-R—Impact of Event Scale–Revised; LSC-R—Life Stressor Checklist–Revised

the blood–brain barrier) and/or indirect effects (e.g., vagal stimulation) within the brain that result in the perception of CIN, as well as various neuropsychological symptoms (Bajic et al., 2018; Bower, 2019; Kim et al., 2012). Additional evidence to support this hypothesis comes from studies that identified associations between the occurrence of CIN and perturbations in a number of inflammatory (Singh et al., 2021) and gut–brain axis (Singh, Dhruva, et al., 2020) pathways.

Changes in gut microbiome ecology after chemotherapy may alter bidirectional signaling in the microbiome–gut–brain axis (Jordan et al., 2018). In addition to CIN (Singh, Dhruva, et al., 2020), emerging evidence suggests that changes in the gut microbiome are associated with a number of neuropsychological symptoms (Jordan et al., 2018). For example, in studies of patients with major depressive disorder (Jiang et al., 2015) and fatigue (Nagy-Szakal et al., 2017), decreases in the abundance of a short-chain fatty acid synthesizing microbiome, *Faecalibacterium spp*., was associated with depression and fatigue. In addition, sleep disturbance was associated with a decrease in abundance of *Streptococcus spp*. (Jackson et al., 2015). Future studies can investigate for associations among CIN and psychoneurological symptoms and changes in gut microbiome diversity, composition, and metabolites. Given that findings from preclinical studies suggest that prebiotic- and probiotic-induced changes in the gut may alleviate depression and anxiety (Liu et al., 2015), these interventions warrant investigation in patients with cancer.

Compared to the none class, the increasing–decreasing and high classes reported lower Attentional Function Index scores, which suggests a moderate level of cognitive impairment. Although cognitive impairment was shown to be part of a neuropsychological symptom cluster (Hormozi et al., 2019), the current study is the first to identify an association with CIN. Increases in the levels of proinflammatory cytokines may explain this association (Kim et al., 2012). For example, in a preclinical study (Briones & Woods, 2014), administration of a highly emetogenic chemotherapy regimen that increased levels of interleukin-1 beta and tumor necrosis factor-alpha in the corpus callosum of rats was associated with decreases in cognitive function. In addition, in a study with the same sample (Oppegaard, Harris, Shin, Paul, Cooper, Chan, et al., 2021), two of the perturbed pathways associated with cognitive dysfunction were associated with CIN occurrence (e.g., cytokine–cytokine receptor interaction pathway and mitogen-activated protein kinase signaling pathway) (Singh et al., 2021).

KNOWLEDGE TRANSLATION

- Higher levels of global stress, cancer-specific stress, and cumulative life stress were reported by patients with higher occurrence rates for nausea across two cycles of chemotherapy.
- Patients with higher occurrence rates for chemotherapy-induced nausea had clinically meaningful levels of depression, anxiety, sleep disturbance, fatigue, and pain.
- Higher occurrence rates for chemotherapy-induced nausea were associated with reporting clinically meaningful decrements in energy and cognitive function.

Finally, compared to the none class, the high class was more likely to report decrements in morning and evening energy, as well as higher rates of cancer and noncancer pain, an average of nine pain locations, pain intensity scores in the moderate to severe range, and moderate levels of pain interference. In addition, patients in the high class reported the highest levels of comorbidity. The cumulative effects of these factors undoubtedly contribute to decrements in morning and evening energy levels.

Limitations

Despite several novel findings, certain limitations warrant consideration. First, stress and resilience were evaluated only at enrollment. To demonstrate causal relationships, future studies need to evaluate for changes in CIN, stress, and resilience over time. Second, several risk factors for CIN, such as occurrence of CIN in the first cycle (Molassiotis et al., 2014), motion sickness (Naito et al., 2020), and morning sickness (Naito et al., 2020), were not evaluated. Future studies need to evaluate these risk factors as well as the dose and duration of antiemetics taken at home. Third, because the majority of patients were female and White, future studies need to include a more diverse sample to increase generalizability of the results. Lastly, future studies need to evaluate dose and duration of self-care measures (e.g., ginger, cannabis) that patients take to alleviate symptoms at home.

Implications for Nursing and Conclusion

This study identified a number of stress characteristics and neuropsychological symptoms associated with worse CIN profiles. With 1,343 (59.2%) patients reporting CIN, this symptom continues to be a significant clinical problem. To manage this distressing symptom, clinicians need to continuously assess

patients for CIN, stress, and co-occurring symptoms. For patients in the high class, an evaluation of their level of adherence to their antiemetic regimen and the need for changes in their prescription(s) warrant careful consideration. In addition, based on the risk factors identified in this study, appropriate interventions may include the following: mental health referral/counseling services for depression and anxiety; dietary interventions (Najafi et al., 2019); guided imagery and progressive muscle relaxation for attentional function, fatigue, and energy (Charalambous et al., 2016); and mindfulness- and exercise-based interventions to reduce stress and improve sleep (Beerse et al., 2020; Boyd et al., 2018). Equally important, clinicians can determine whether patients require changes in their pharmacologic interventions to decrease specific symptoms (e.g., changes in analgesic prescriptions). Finally, clinicians can monitor patients' level of adherence to and the efficacy of various pharmacologic and nonpharmacologic symptom management interventions and recommend alternative strategies if warranted.

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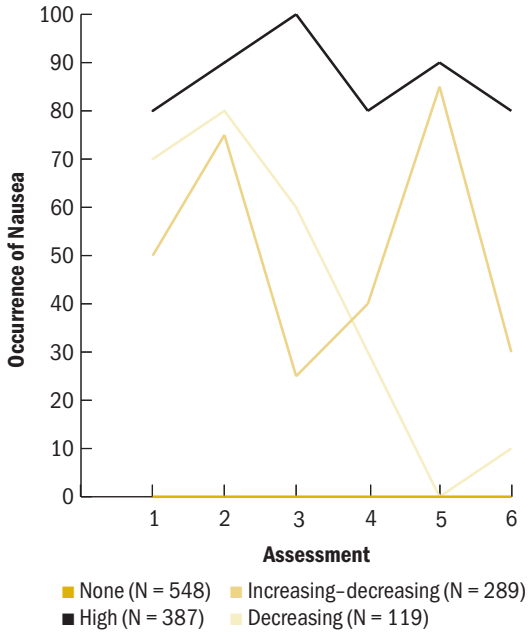
SUPPLEMENTAL FIGURE 1. Chemotherapy-Induced Nausea Trajectories for Patients in Each of the Latent Classes



SUPPLEMENTAL TABLE 1. Differences in Demographic and Clinical Characteristics Among the Nausea Latent Classes

	None (0) (N = 548)		Increasing–Decreasing (1) (N = 289)		Decreasing (2) (N = 119)		High (3) (N = 387)		
Characteristic	**$\bar{X}$**	**SD**	**$\bar{X}$**	**SD**	**$\bar{X}$**	**SD**	**$\bar{X}$**	**SD**	**Statistics**
Age (years)	60	12.1	54.6	12.4	58.1	12.5	54.9	11.8	F = 18.75, p < 0.001, PWC = 0 > 1 and 3; 2 > 1
AUDIT score	3.1	2.3	2.9	2.5	2.9	3.1	2.9	2.5	F = 0.36, p = 0.781
Body mass index (kg/m^2)	26.2	5.5	25.6	5.5	26.3	5.8	26.6	6.1	F = 2.01, p = 0.111
Education (years)	16.3	3.1	16.4	2.9	16	2.7	16	3.1	F = 1.43, p = 0.232
KPS score	83.1	11.9	80.5	12.1	78.5	12	75.7	12.6	F = 27.23, p < 0.001
MAX2 score	0.17	0.09	0.18	0.08	0.18	0.08	0.18	0.07	F = 4.16, p = 0.006
Number of comorbid conditions	2.4	1.4	2.3	1.3	2.4	1.5	2.6	1.5	F = 2.87, p = 0.036
Number of metastatic sites with lymph node involvement[a]	1.3	1.3	1.2	1.2	1.1	1.1	1.2	1.2	F = 1.52, p = 0.207
Number of metastatic sites without lymph node involvement	0.9	1.1	0.7	1	0.7	0.9	0.7	1	F = 2.96, p = 0.031
Number of prior cancer treatments	1.7	1.6	1.5	1.4	1.9	1.7	1.5	1.5	F = 2.9, p = 0.034
SCQ score	5.2	3	5.2	2.9	5.8	3.5	6	3.5	F = 4.9, p = 0.002
Time since diagnosis (years)	2.2	4.3	1.7	3.4	2.3	4.4	1.7	3.4	KW, p = 0.134
Demographic Characteristic	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**Statistics**
Annual household income ($)									KW, p = 0.005, PWC = 0 > 3
Less than 30,000 (reference)	67	14	43	17	23	22	88	25	
30,000–70,000	102	21	54	21	26	25	72	20	
70,001–100,000	91	19	42	16	20	19	50	14	
More than 100,000	222	46	120	46	37	35	144	41	
Exercise status									χ^2 = 11.2, p = 0.011 PWC = 1 > 3
Exercises regularly	381	70	220	78	82	71	246	66	
Gender									χ^2 =17.88, p < 0.001
Female	399	73	247	86	96	81	302	78	
Male	149	27	42	15	23	19	85	23	
Living, marital, and employment status									
Married or partnered	363	67	186	65	69	59	236	62	χ^2 = 4.57, p = 0.206
Currently employed	197	36	110	39	34	29	125	33	χ^2 = 4.74, p = 0.192
Lives alone	104	19	59	21	35	30	86	23	χ^2 = 6.58, p = 0.087
Race and ethnicity									χ^2 =17.78, p = 0.038
Asian or Pacific Islander	67	12	39	14	14	12	48	13	
Black	45	8	16	6	14	12	20	5	
Hispanic, mixed ethnic background, or other	50	9	34	12	5	4	53	14	
White	379	70	198	69	83	72	261	68	

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SUPPLEMENTAL TABLE 1. Differences in Demographic and Clinical Characteristics Among the Nausea Latent Classes *(Continued)*

	None (0) (N = 548)		Increasing–Decreasing (1) (N = 289)		Decreasing (2) (N = 119)		High (3) (N = 387)		
Demographic Characteristic	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**Statistics**
Responsibilities									
Child care	96	18	64	23	22	19	108	29	$\chi^2 = 15.59$, p = 0.001, PWC = 0 < 3
Elder care	38	8	18	7	9	8	32	9	$\chi^2 = 1.38$, p = 0.711
Smoking status									$\chi^2 = 7.66$, p = 0.054
Has a past or current history of smoking	202	38	82	29	47	40	136	36	
Clinical Characteristic	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**Statistics**
Cancer diagnosis									$\chi^2 = 21$, p = 0.013
Breast	215	39	121	42	52	44	152	39	Not significant
Gastrointestinal	171	31	70	24	35	29	136	35	PWC = 1 < 3
Gynecologic	92	17	70	24	15	13	56	15	PWC = 1 > 3
Lung	70	13	28	10	17	14	43	11	Not significant
Comorbid condition									
High blood pressure	179	33	74	26	41	35	112	29	$\chi^2 = 5.78$, p = 0.123
Back pain	130	24	69	24	34	29	113	29	$\chi^2 = 4.61$, p = 0.203
Depression	77	14	63	22	18	15	99	26	$\chi^2 = 22.11$, p < 0.001, PWC = 0 < 1 and 3
Osteoarthritis	76	14	32	11	14	12	42	11	$\chi^2 = 2.44$, p = 0.486
Lung disease	72	13	22	8	13	11	46	12	$\chi^2 = 5.87$, p = 0.118
Anemia or blood disease	50	9	39	14	16	13	59	15	$\chi^2 = 8.81$, p = 0.032, PWC = 0 < 3
Diabetes	44	8	18	6	17	14	43	11	$\chi^2 = 9.42$, p = 0.024
Heart disease	38	7	10	4	5	4	24	6	$\chi^2 = 4.9$, p = 0.179
Liver disease	37	7	16	6	8	7	26	7	$\chi^2 = 0.54$, p = 0.91
Rheumatoid arthritis	23	4	8	3	1	1	11	3	$\chi^2 = 4.23$, p = 0.238
Ulcer or stomach disease	19	4	12	4	3	3	31	8	$\chi^2 = 12.37$, p = 0.006, PWC = 0 < 3
Kidney disease	3	1	9	3	–	–	7	2	$\chi^2 = 11.08$, p = 0.011
CT regimen									$\chi^2 = 20.13$, p = 0.003
Only CT	347	66	205	71	82	70	288	76	PWC = 0 < 3
CT and targeted therapy	157	30	78	27	32	27	87	23	Not significant
Only targeted therapy	26	5	5	2	4	3	4	1	PWC = 0 > 3
CT regimen emetogenicity									KW = 25.23, p < 0.001, PWC = 0 < 1 and 3
Minimal or low	132	24	38	13	26	22	63	17	
Moderate	330	61	190	66	69	59	221	58	
High	79	15	59	21	23	20	97	26	

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SUPPLEMENTAL TABLE 1. Differences in Demographic and Clinical Characteristics Among the Nausea Latent Classes *(Continued)*

Clinical Characteristic	None (0) (N = 548) n	None (0) (N = 548) %	Increasing–Decreasing (1) (N = 289) n	Increasing–Decreasing (1) (N = 289) %	Decreasing (2) (N = 119) n	Decreasing (2) (N = 119) %	High (3) (N = 387) n	High (3) (N = 387) %	Statistics
Antiemetic regimen									$\chi^2 = 29.33$, p = 0.001
Serotonin receptor antagonist and steroid	246	47	139	49	59	50	174	47	Not significant
Steroid or serotonin receptor antagonist alone	123	23	59	21	23	20	60	16	Not significant
NK1 receptor antagonist and 2 other antiemetics	104	20	71	25	31	27	115	31	Not significant
None	53	10	95	33	57	48	202	53	PWC = 0 > 1
Cycle length									KW = 29.73, p < 0.001, PWC = 0 and 1 < 3, 1 > 2
14-day cycle	204	38	95	33	57	48	202	53	
21-day cycle	289	54	173	60	55	47	154	40	
28-day cycle	47	9	19	7	6	5	25	7	
Metastatic site									$\chi^2 = 13.42$, p = 0.145
No metastasis	170	32	95	33	37	31	126	33	
Metastatic disease in lymph nodes and other sites	146	27	64	22	23	20	91	24	
Metastatic disease only in other sites	125	23	56	20	26	22	73	19	
Lymph node metastasis only	96	18	71	25	32	27	93	24	
Prior cancer treatment									$\chi^2 = 19.86$, p = 0.019
Only surgery, CT, or RT	219	41	132	47	37	32	161	43	Not significant
Surgery and CT, or surgery and RT, or CT and RT	112	21	56	20	32	27	59	16	PWC = 2 > 3
Surgery, CT, and RT	70	13	25	9	21	18	56	15	Not significant
No prior treatment	128	24	67	24	27	23	103	27	Not significant

[a]The total number of metastatic sites evaluated was 9.
AUDIT—Alcohol Use Disorders Identification Test; CT—chemotherapy; KPS—Karnofsky Performance Status; KW— Kruskal–Wallis; NK1—neurokinin-1; PWC—pairwise comparison; RT—radiation therapy; SCQ—Self-Administered Comorbidity Questionnaire
Note. Scores on the KPS range from 30 ("I feel severely disabled and need to be hospitalized") to 100 ("I feel normal; I have no complaints or symptoms"). Scores on the SCQ range from 0 to 39, with higher scores indicating a higher comorbidity burden.
Note. The n values per characteristic may not add up to the total N because some participants did not answer every question.
Note. Because of rounding, percentages may not total 100.