Brief Report

Distress-Based Gastrointestinal Symptom Clusters and Impact on Symptom Interference and Quality of Life in Patients with a Hematologic Malignancy Receiving Chemotherapy

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Abstract

Background/Significance. People with cancer can experience co-occurring related symptoms, labeled symptom clusters. Gastrointestinal (GI) symptoms are common side effects of chemotherapy, but little research has investigated GI symptom clusters. A further gap in symptom cluster research is the lack of studies reporting symptom clusters based on symptom distress ratings.

Purpose. To identify distress-based GI symptom clusters and to investigate their relationship to symptom interference with daily life and quality of life (QoL).

Subjects. About 105 adults with hematologic malignancy receiving chemotherapy.

Methods. On Day 1 of a cycle of chemotherapy, participants completed a modified version of the Memorial Symptom Assessment Scale assessing 30 clinically relevant symptoms, the M.D. Anderson Symptom Inventory Symptom Interference with Daily Life subscale, and the Fox Simple Quality of Life Scale. Exploratory factor analysis was used to identify distress-based symptom clusters. Symptom clusters with ≥50% GI symptoms were labeled GI symptom clusters. Linear mixed modeling explored relationships between GI symptom clusters and symptom interference with daily life and QoL.

Results. Of the six distress-based symptom clusters found, the bloating cluster and appetite cluster were identified as GI symptom clusters. Both the bloating cluster and the appetite cluster were significantly related to symptom interference with daily life, but only the appetite cluster was significantly related to QoL.

Conclusions. This research demonstrates the existence of distress-based GI symptom clusters and their relationship to symptom interference and QoL. Future work should explore predictors of distress-based symptom clusters and interventions to manage them. J Pain Symptom Manage 2017;53:751−758.

Key Words
Hematologic malignancy, gastrointestinal, symptom cluster, symptom distress, symptom interference, quality of life

Introduction

Patients with cancer can experience co-occurring inter-related symptoms defined as symptom clusters.[1,2] Symptom cluster research has been emerging as a novel way to conceptualize co-occurring symptoms, but some limitations remain.

Most symptom cluster research focuses on symptom severity to the exclusion of other symptom dimensions. Symptom theories, such as the Symptom Experience Model[3] and the Theory of Unpleasant Symptoms,[4] describe the importance of multiple symptom dimensions. For patients with cancer, even

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a symptom with mild severity can be highly distressing as the presence of certain symptoms may indicate disease progression or the need to delay treatment. It is important to acknowledge that the symptom dimensions provide discrete information and impact patient outcomes differently. To our knowledge, only two studies have explored symptom clusters based on the dimension of symptom distress.[5,6]

Symptom cluster research also underrepresents gastrointestinal (GI) symptoms. Chemotherapy is associated with as many as 19 GI symptoms, yet no cancer symptom assessment contains all 19 GI symptoms.[7] The underassessment of GI symptoms may contribute to an underidentification of GI symptom clusters (i.e., a symptom cluster where ≥50% of the component symptoms are GI symptoms). A review of symptom cluster research revealed that the only GI symptom cluster consistently identified is that of nausea and vomiting, with or without lack of appetite, and nearly all the studies identifying this GI symptom cluster used the M.D. Anderson Symptom Inventory (MDASI) to assess symptoms.[7] The M.D. Anderson Symptom Instrument (MDASI) contains four GI symptoms.

Purpose

The presence of distress-based GI symptom and their impact on symptom interference with daily life and quality of life (QoL) is unknown. The purpose of this research is to address gaps in symptom cluster literature by describing GI symptom clusters based on symptom distress, using a GI comprehensive symptom assessment, and exploring how distress-based GI symptom clusters impact symptom interference with daily life and QoL.

Method

Design and Sample

This research is part of a larger institutional review board-approved study investigating symptom clusters and patient-related outcomes in patients with a hematologic malignancy receiving chemotherapy. Participants were adults with a hematologic malignancy, able to read and write in English, receiving at least their third cycle of chemotherapy, and had not received radiation therapy in the last six months. A more detailed report of participant inclusion criteria is reported elsewhere.[8] Patients with a hematologic malignancy were selected because these patients are rarely included in cancer symptom studies or are lumped together with solid tumor diagnoses.

Instruments

Participants self-reported demographics, including age, gender, ethnicity, race, education, partner status, and income. Participants' medical records were reviewed to record diagnosis, chemotherapy regimen dose (e.g., standard dose or reduced dose), emetogenicity rating of chemotherapy regimen, and cycle number of chemotherapy.

Distress-based symptom clusters were derived from symptom distress ratings assessed through a modified version of the Memorial Symptom Assessment Scale (MSAS).[9] In the original MSAS, participants are asked to review a 32-item list of symptoms and indicate if a symptom was present in the last week. For each symptom present, distress is rated on a 0−4 scale, from not at all to very much. The original MSAS has well documented reliability and validity among the oncology population ($\alpha = 0.83-0.88$).[9,10] In the previous work, we focused on comprehensively assessing GI symptoms, modifying the original 32-item MSAS to add nine more GI symptoms identified through the literature and by cancer symptom experts.[7] In this work, we chose to focus on symptoms that meet criteria to be considered clinically relevant as these symptoms are at highest need for intervention. Cherwin and Kwekkeboom[8] operationalized a clinically relevant symptom as a symptom that has prevalence greater than 15% and has a moderate to severe rating in at least one symptom dimension (i.e., duration, severity, or distress). Based on this definition, symptom data from the modified 41-item MSAS were reduced to 30 items by removing symptoms that did not meet the criteria to be considered clinically relevant (Table 1).[8] Symptom data from the 30 clinically relevant items were included for analysis.

Symptom interference with daily life was assessed using the Symptom Interference Subscale of the MDASI.[11] Participants are asked to rate how much their symptoms interfered with six aspects of daily life in the last week on a scale from 0 (did not interfere) to 10 (interfered completely). The Symptom Interference Subscale has been shown to be reliable among cancer populations ($\alpha = 0.91$).[11]

QoL was assessed using the Fox Simple Quality of Life Scale (FSQoLS).[12] The FSQoLS contains 25 items concerning enjoyment of life, feelings of well-being, and life satisfaction. Participants are asked to consider how they felt in the past week and rate agreement with the items from one (strongly disagree) to five (strongly agree). The FSQoLS demonstrated significant convergent validity with other measures of QoL ($r = 0.80-0.91$) and has high internal consistency in people with cancer ($\alpha = 0.93$).[12]

Procedure

Beginning on Day 1 of a cycle of chemotherapy, participants completed the demographic questionnaire, the modified MSAS, the MDASI Symptom Interference Subscale, and the FSQoLS. Participants also completed

Table 1
Items on Modified 41-Item MSAS and Clinically Relevant Symptom Items

Modified MSAS	Clinically Relevant Symptom Items
Anticipatory nausea	
Anticipatory vomiting	
Difficulty concentrating	X
Pain	X
Dry mouth	X
Appetite loss	X
Cough	X
Numbness in hands or feet	X
Feeling nervous	X
Feeling drowsy	X
Lack of energy	X
Heartburn	X
Belching	X
Difficulty sleeping	X
Feeling bloated	X
Problems with urination	
Difficulty swallowing	
Shortness of breath	X
Nausea	X
Vomiting	
Retching	
Feeling sad	X
Feeling full early	X
Diaphoresis	X
Rectal burning	
Worrying	X
Rectal itching	
Problems with sexual interest or activity	
Passing gas	X
Itching of the skin	X
Feeling dizzy	X
Diarrhea	X
Feeling irritable	X
Taste changes	X
Mouth sores	
Weight loss	
Hair loss	X
Constipation	X
Swelling of the arms or legs	X
Image change	X
Changes in skin	X

MSAS = Memorial Symptom Assessment Scale.

questionnaires at weekly intervals over three weeks of ongoing treatment (Days 7, 14, and 21).

Data Analysis

Exploratory factor analysis was used to identify distress-based symptom clusters. Symptom distress ratings at Day 7 from the 30 clinically relevant symptoms were used in the factor analysis. Symptom ratings from Day 7 were chosen as this was the period in which symptom distress scores were the highest and as such, in most need of intervention. Assessing symptoms on the day of chemotherapy administration (Day 1) underestimates patients' therapy-related symptom burden as this is when symptoms are the best.[13]

After the symptom cluster structure was determined, we calculated a composite score for each symptom cluster. The composite score was calculated as an average of distress ratings from all the component symptoms from each symptom cluster at each measurement point (Days 1, 7, 14, and 21). The use of composite scores to represent symptom clusters has been used and validated in symptom cluster research.[14] Each composite score was then categorized as no distress (score of 0, not at all), mild distress (score less than 1, a little bit), and greater than mild distress (score of 1 or greater, somewhat to very much).

To explore the relationship between distress-based symptom clusters and patient-related outcomes, we used linear mixed modeling approach to fit linear mixed models to symptom interference with daily life and QoL scores, with symptom clusters and time (Days 1, 7, 14, and 21) as fixed effects. This approach uses all available data from repeated measurements to provide more precise estimates of effects[15] and handles missing values with likelihood methods under the assumption that the data are missing at random.[16] Specifically, we used SAS procedure MIXED and a compound symmetry covariance structure to account for the within-subject correlation because of repeated measurements. Fit of the models was assessed and compared using Akaike information criterion. A significance level of 0.05 was used for statistical tests. The analyses were adjusted for important covariates using a sequential approach.[17] Factors shown to be related to symptom distress were tested for inclusion in the model as covariates (i.e., age, sex, partner status, emetogenicity of chemotherapy, dose of chemotherapy, chemotherapy cycle length). Interactions of symptom clusters with covariates were examined to determine whether any may act as moderators of the relationships between symptom clusters and patient-related outcomes (Fig. 1). Interactions or covariates by themselves were considered for inclusion in the models based on their significance and Akaike information criterion.

Results

Sample Characteristics

A total of 227 patients were screened, 134 were eligible, and 112 (84%) enrolled in the study and provided signed consent (Fig. 2). Data were available for analysis from 105 participants at Day 1, 97 participants at Day 7 (92%), 94 participants at Day 14 (89%), and 91 participants at Day 21 (86%). Demographic characteristics of the sample are reported in Table 2.

Distress-Based GI Symptom Clusters

Six distress-based symptom clusters were found and explained 53% of the variance. The symptom clusters were named the appetite, bloating, appearance, fatigue, emotions, and worry clusters (Table 3). We

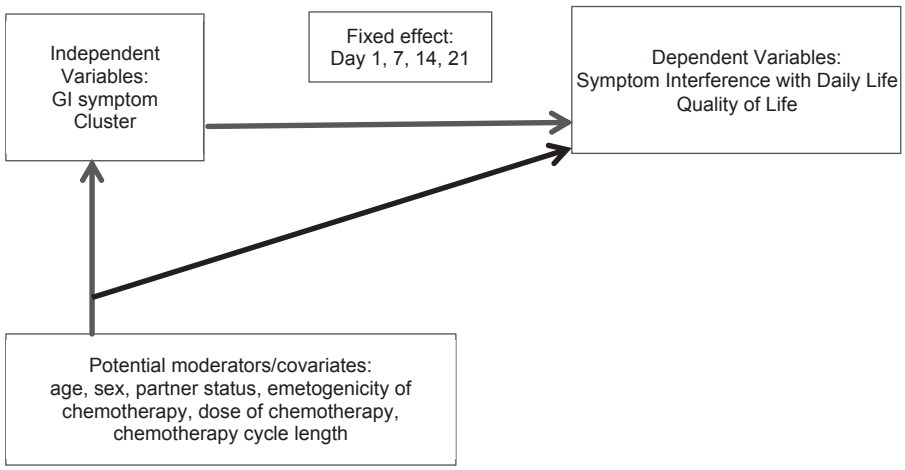

Fig. 1. Model of distress-based gastrointestinal (GI) symptom clusters and symptom interference with daily life and quality of life.

examined the component symptoms in each symptom cluster, and the appetite cluster (lack of appetite, nausea, and taste changes) and the bloating cluster (belching, feeling bloated, and diaphoresis) were identified as GI clusters. All distress-based symptom clusters are presented in Table 3 but are not discussed in detail in this report as the purpose of this analysis was to exclusively describe distress-based GI symptom clusters.

Relationship Between Distress-Based Symptom Clusters and Symptom Interference with Daily Life

The appetite cluster and bloating cluster were both significantly related to symptom interference with daily life (Table 4). With regard to the bloating cluster, those with greater than mild distress ($b = 1.17$, $P < 0.001$) and those with mild distress ($b = 0.63$, $P = 0.004$) reported significantly more symptom interference as compared with those with no distress. For the appetite cluster, the relationship between symptom distress and symptom interference with daily life was moderated by emetogenicity of chemotherapy ($P = 0.04$).

Relationship Between Distress-Based Symptom Clusters and QoL

The bloating cluster was not significantly related to QoL; thus, it was not included in the model (Table 4). The appetite cluster was significantly related to QoL ($P = 0.002$), such that those with greater than mild distress reported significantly lower QoL as compared with those with no distress ($b = -0.16$, $P = 0.002$). The model for QoL also included emetogenicity of chemotherapy ($P = 0.04$), relationship status ($P = 0.05$), and time ($P < 0.001$). Specifically for the appetite cluster, high emetogenicity and no partner status were associated with lower QoL ($P = 0.04$ and 0.05, respectively), and compared with Day 1, QoL was lower on all other days ($P < 0.001$).

Discussion

The first aim of this work was to determine if GI symptom clusters exist within the dimension of symptom distress. Indeed, of the six distress-based symptom clusters identified overall, two were GI symptom clusters. However, the complexity of symptom cluster research lies in discovering how and why symptoms form symptom clusters. Symptoms in a symptom cluster are by definition related.[1,2] However, Lacasse and Beck[18] argued that there may be variability in the way that symptoms in a symptom cluster are related, postulating that component symptoms may share a common cause such as chemotherapy toxicity, whereas others act as moderators of other symptoms, such as pain disturbing sleep.

Chemotherapy toxicity has been shown to cause a number of nutrition symptoms, including nausea, taste changes, and lack of appetite.[19,20] Thus, the component symptoms of the appetite cluster may be related through impact on ability to eat and enjoy food with a potential shared mechanism of chemotherapy toxicity. However, the relationship behind the component symptoms of the bloating cluster appears to be more complex. Chemotherapy is associated with reduced GI motility and constipation,[19,20] which can lead to bloating and belching, but these symptoms are not directly related to diaphoresis. Rather, diaphoresis may be a side effect of symptom management. More than a quarter of the patients in this study were using an opioid medication (Table 2), some of which (i.e., oxycodone and hydrocodone) have been shown to cause constipation and diaphoresis.[21] Thus, the component symptoms of the

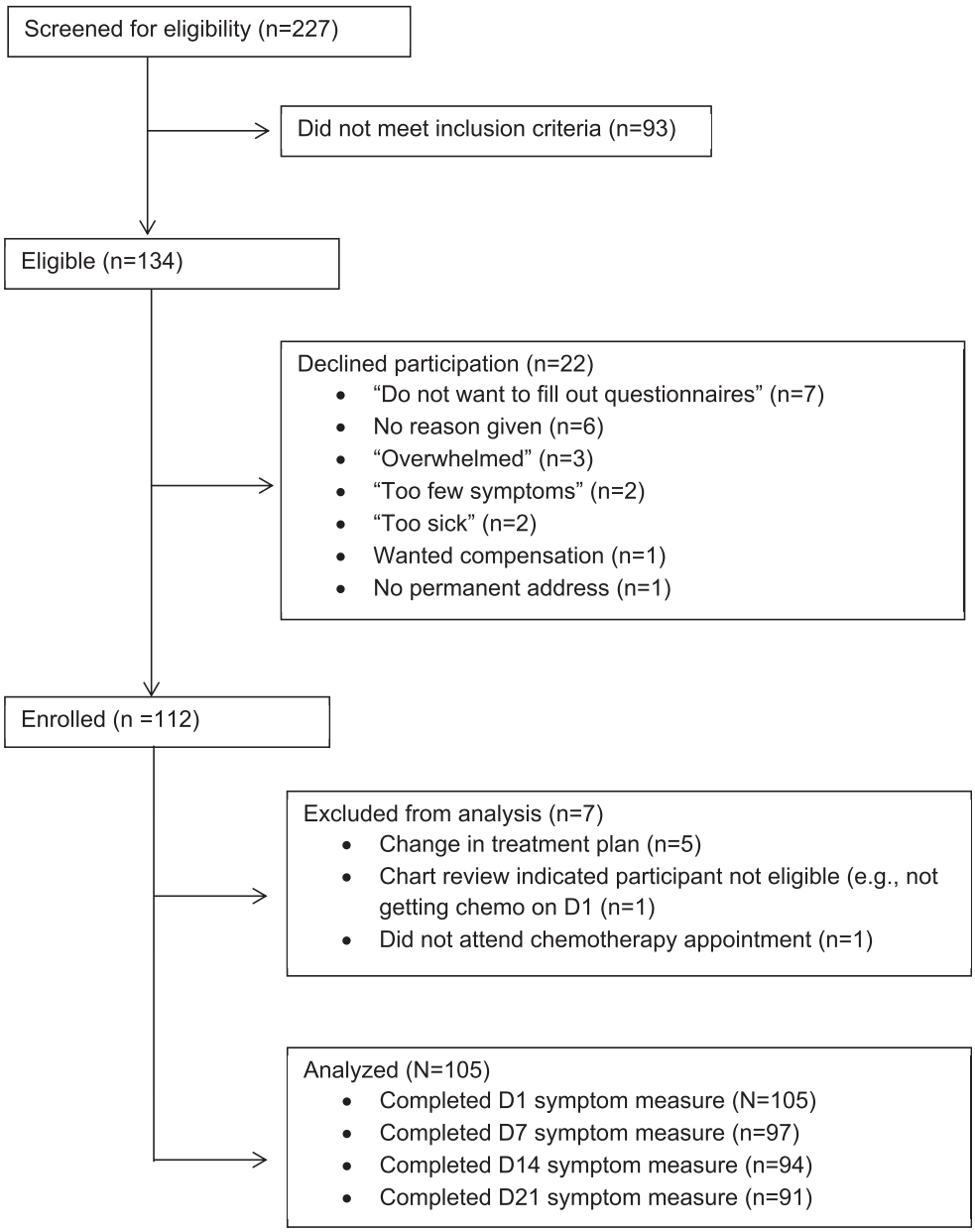

Fig. 2. Consolidated Standards of Reporting Trials (CONSORT) flow diagram. GI = gastrointestinal.

bloating cluster may be related through chemotherapy toxicity resulting in reduced GI motility, pain control efforts resulting in reduced GI motility and diaphoresis, or as yet undescribed mechanisms.

The second goal of this work was to explore the relationship between distress-based GI symptom clusters and symptom interference with daily life and QoL. Indeed, we found that both the appetite cluster and the bloating cluster were related to symptom interference with daily life, and the appetite cluster was significantly related to QoL. However, the relationship between the appetite cluster and symptom interference was moderated by emetogenicity of the chemotherapy.

Research has shown a correlation between severity-based GI symptom clusters and symptom interference with daily life.[6,22] To our knowledge, research done by Suwisith et al[6] is the only work examining how distress-based GI symptom clusters correlate to symptom interference, reporting that they can be a strong predictor of functional status. Findings from our study add evidence that the appetite cluster and bloating cluster also correlate to symptom interference with daily life.

Only the appetite cluster was significantly related to QoL where the bloating cluster was not. The stronger relationship between appetite cluster symptoms and QoL may be because symptoms related to eating

Table 2
Sample Characteristics

Participant Characteristics	*n* (%)
Age (yrs)	
Range	18–86
Mean (SD)	56.7 (15.3)
Sex, *n* (%)	
Male	59 (56.2)
Female	46 (43.8)
Race, *n* (%)	
White	101 (96.2)
Black or African American	1 (1.0)
Asian	1 (1.0)
American Indian or Alaskan Native	1 (1.0)
Missing	1 (1.6)
Ethnicity, *n* (%)	
Non-Hispanic or Latino	100 (95.2)
Hispanic or Latino	1 (1.0)
Missing	4 (3.8)
Education, *n* (%)	
Some high school, diploma, or GED	28 (26.7)
Some college or college degree	52 (49.5)
Some graduate or graduate degree	25 (23.8)
Relationship status, *n* (%)	
Partnered	73 (69.5)
Not partnered	32 (30.5)
Income, *n* (%)	
<$20,000	10 (9.5)
>$20,000	77 (73.4)
Missing	18 (17.1)
Diagnosis, *n* (%)	
Lymphoma	88 (83.8)
Leukemia	11 (10.5)
Leukemia & lymphoma	4 (3.8)
Myelodysplastic syndrome	2 (1.9)
Emetogenicity of chemotherapy, *n* (%)	
Low	3 (2.9)
Moderate	35 (33.3)
High or very high	67 (63.9)
Chemotherapy cycle length, *n* (%)	
Three weeks	60 (57.1)
Four weeks	45 (42.9)
Chemotherapy dose, *n* (%)	
Standard	93 (88.6)
Reduced	12 (11.4)
GI supportive medications	
Range	0–12
Mean (SD)	4.46 (3.06)
Class of GI supportive medications prescribed,[a] *n* (%)	
Antiemetic	78 (74)
Antacid	77 (73)
Stool softener	39 (37)
Opioid pain	29 (28)
Topical analgesic (e.g., topical lidocaine)	8 (8)
Antidiarrheal	4 (4)
Appetite stimulant or GI motility	2 (2)
Oral care (e.g., medicated mouthwash)	2 (2)
Antigas	0 (0)

GED = General Educational Development; GI = gastrointestinal.
[a]Does not sum to 100% as participants could be taking more than one class of medication.

Table 3
Distress-Based Symptom Clusters at Day 7 of Chemotherapy and Factor Loadings

Symptom Cluster	Factor Loadings					
Image cluster						
Image change	0.95					
Skin change	0.50					
Fatigue cluster						
Feeling drowsy		0.82				
Lack of energy		0.72				
Shortness of breath		0.58				
Feeling dizzy		0.45				
Emotions cluster						
Difficulty concentrating			0.61			
Feeling nervous			0.71			
Feeling sad			0.40			
Hair loss			0.40			
Swelling of arms or legs			0.44			
Bloating cluster[a]						
Belching				0.76		
Feeling bloated				0.59		
Diaphoresis				0.62		
Worry cluster						
Worrying					−0.51	
Numbness					−0.56	
Appetite cluster[a]						
Lack of appetite						−0.66
Nausea						−0.60
Taste changes						−0.71
Cronbach alpha	0.70	0.76	0.78	0.69	0.45	0.75
Eigen value	6.42	2.33	2.05	1.89	1.67	1.53
Explained variance, %	21.4	7.8	6.8	6.3	5.6	5.1
Cumulative variance, %	21.4	29.2	36.0	42.3	47.9	53.0

[a]Indicates a gastrointestinal (GI) symptom cluster (i.e., a symptom cluster ≥50% GI symptoms).

and enjoyment of food are more strongly linked to QoL than general discomfort symptoms like bloating or belching. This has been confirmed by a number of studies describing participants' experiences with nausea and taste changes, and a common theme that emerges is how meaningful enjoyment of food can be.[23] Eating disturbances can be very distressing and as such may have a stronger correlation with QoL.

While discussing GI symptom clusters, it is important to note that the only consistently identified GI symptom cluster is that of nausea and vomiting with or without lack of appetite, but we did not replicate this GI symptom cluster in this study. This may be because of the symptoms we included for analysis. For this work, we used symptom data from 30 symptoms identified as being clinically relevant. This made the symptoms included for analysis unique, limiting our ability to compare results with prior studies. However, the identification of clinically relevant symptoms provides evidence for further evaluation of the presence of these symptoms and suggesting potential targets for intervention.

Limitations

This study used a convenience sample of exclusively hematology patients receiving chemotherapy so the results are not representative of the entire cancer chemotherapy population. We also had a relatively small sample size ($n = 97$ at Day 7). Minimal sample size requirements for factor analysis is 100, but more stable factor solutions (i.e., symptom clusters) require a minimal sample size of 200.[24] Although analysis

Table 4
Linear Mixed Models for Symptom Interference with Daily Life and Quality of Life

Model for Symptom Interference	*b*	95% CI	t	$P > \|t\|$	F	$P > F$
Intercept	1.39	0.72, 2.05	4.13	<0.001		
Bloating symptom cluster distress					8.27	<0.001
Greater than mild vs. no distress	1.17	0.56, 1.78	3.77	<0.001		
Mild vs. no distress	0.63	0.20, 1.06	2.88	0.004		
Appetite symptom cluster distress					20.90	<0.001
Greater than mild vs. no distress	1.24	0.38, 2.09	2.84	0.01		
Mild vs. no distress	1.05	0.40, 1.69	3.20	0.002		
Emetogenicity of chemotherapy: high vs. low	0.89	0.06, 1.73	2.11	0.04	7.95	0.01
Appetite symptom cluster distress × emetogenicity					3.14	0.04
Greater than mild (high−low) vs. no distress (high−low)	0.92	−0.13, 1.97	1.72	0.09		
Mild (high−low) vs. no distress (high−low)	−0.40	−1.22, 0.42	−0.95	0.34		
Model for quality of life						
Intercept	4.32	4.10, 4.54	38.89	<0.001		
Appetite symptom cluster distress					6.32	0.002
Greater than mild vs. no distress	−0.16	−0.25, −0.06	−3.18	0.002		
Mild vs. no distress	−0.01	−0.09, 0.06	−0.36	0.72		
Day					8.80	<0.001
Day 7 vs. Day 1	−0.12	−0.19, −0.05	−3.30	0.001		
Day 14 vs. Day 1	−0.17	−0.24, −0.10	−4.83	<0.001		
Day 21 vs. Day 1	−0.13	−0.20, −0.06	−3.68	<0.001		
Emetogenicity of chemotherapy: high vs. low	−0.26	−0.51, −0.01	−2.05	0.04	4.20	0.04
Relationship status: not partnered vs. partnered	−0.26	−0.51, 0.00	−1.98	0.05	3.93	0.05

b = unstandardized regression coefficient estimates; $P > |t|$ = *P*-values for a t-test of significance of an effect or a level of an effect; $P > F$ = *P*-values for an F-test of significance of each effect overall.

revealed acceptable Kaiser-Meyer-Olkin and sphericity values (Table 5), indicating basic assumptions of factor analysis were not violated. Finally, patients included in this study were prescribed one of many potential chemotherapy regimens and so may have had differing treatment-related toxicities that impact symptom experience.

Conclusions

This study builds on the little research available showing the existence of distress-based symptom clusters and their influence on symptom interference with daily life and QoL and also builds on our knowledge of GI symptom clusters through use of a more GI comprehensive symptom assessment. Because of the scarcity of this work, future research should continue to investigate distress-based symptom clusters, including GI symptom clusters, and their outcomes in other patient populations and treatment types. Future work should also investigate predictors of symptom clusters. Currently, researchers are trying to discover if treatment or patient characteristics may be responsible for the presence or severity of co-occurring symptoms.[25–27] However, this research is relatively new and has not yet addressed the predictors of distress-based symptom clusters. Once distress-based symptom clusters and their predictors have been better defined, targeted interventions can be tailored to individuals and their symptom profile to address co-occurring symptoms with a single parsimonious intervention with the intention of making a meaningful impact on symptom interference on daily life and QoL.

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Table 5
KMO Measure of Sampling Adequacy and Bartlett's Test of Sphericity

		Bartlett's Test of Sphericity		
Symptom Cluster	KMO	Approximate X^2	Degrees of Freedom	*P*
Distress-based symptom clusters at Day 7	0.646	1016.49	435	<0.001

KMO = Kaiser-Meyer-Olkin.

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