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Distinct Diarrhea Profiles During Outpatient Chemotherapy

by
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THESIS
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MASTER OF SCIENCE

in

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Dedications

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Abstract

Distinct Diarrhea Profiles During Outpatient Chemotherapy

by Rafael Diaz

Purpose: Chemotherapy-induced diarrhea (CID) is a common symptom that occurs in 50% to 80% of patients. Given that the majority of the data on the occurrence and severity of CID is based on physician-rated toxicity criteria, this study's purposes were to: identify subgroups of patients with distinct CID profiles and determine how these subgroups differ in terms of demographic and clinical characteristics; severity, frequency, and distress of CID; the co-occurrence of common GI symptoms, and QOL.

Methods: Patients (n=1133) completed the Memorial Symptom Assessment Scale six times over two cycles of chemotherapy (CTX). Latent profile analysis was used to identify subgroups of patients with distinct diarrhea profiles. Differences among these subgroups were evaluated using parametric and nonparametric statistics.

Results: Four distinct diarrhea profiles were identified: none (58.3%), decreasing (22.0%), increasing (5.2%), and high (14.5%). Compared to the none class, patients in the high class had a lower functional status, a worse comorbidity profile, were more likely to have gastrointestinal cancer, and were more likely to receive CTX on a 14 day cycle. No differences were found among the classes in the percentages of patients who received CTX with a targeted therapy.

Conclusion: Given that CID occurred in over 40% of the patients, clinicians should assess for this symptom and other common GI symptoms and initiate appropriate pharmacologic and dietary interventions.

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Introduction

Chemotherapy-induced diarrhea (CID) is a common symptom that occurs in 50% to 80% of patients [33]. While the mechanisms that underlie CID are not well understood, it is defined as an increase in the frequency, above a patient's baseline, of soft, loose, and watery stool [14]. Most of the prevalence rates for CID are derived from studies that used the National Cancer Institute's (NCI) Common Toxicity Criteria for Adverse Events (CTCAE) to grade CID based on its frequency and severity [1,3,27].

While CID is most commonly associated with the administration of fluoropyrimidines, irinotecan, and capecitabine, it can occur with most of the chemotherapy (CTX) drugs that are used to treat the majority of solid tumors (e.g., cisplatin, methotrexate, doxorubicin, paclitaxel, docetaxel) [1,17]. In addition, CID occurs with the administration of targeted therapies (e.g., tyrosine-kinase inhibitors (TKIs), inhibitors of the mammalian target of rapamycin (m-TOR), and epidermal growth factor receptor (EGFR) targeted therapies) [1,17,27,33]. More severe CID (i.e., CTCAE grades 3 and 4) is associated with the administration of combination CTX with or without targeted therapy [1,17,27,33].

While studies are limited, some of the identified risk factors for CID include: older age (>65 years), being female, being White, having a lower performance status, previous episodes of CID, specific cancer diagnoses (e.g., gastrointestinal (GI)), history of bowel problems (e.g., inflammatory bowel disease, malabsorption), and diabetes mellitus [1,4,24,31,34]. In addition, polymorphisms in genes that are associated with the metabolism of fluoropyrimidines contribute to increased toxicity including CID [16].

Given that the mechanisms that underlie the development of CID (e.g., inflammation, apoptosis), involve the entire GI tract [15,17,33], it is not surprising that CID can co-occur with other GI symptoms. While clinical experience suggests that CID is associated with nausea, vomiting, anorexia, and abdominal cramps [37], limited evidence suggests that in oncology outpatients receiving CTX, nausea [30] and changes in the way food tastes [21] are associated with the co-occurrence of CID.

The consequences of severe CID can be significant and include dose reductions, delays in CTX treatments, discontinuation of CTX, or hospitalization [17,27]. In addition, CID can have a negative impact on patients' quality of life (QOL) including higher levels of anxiety, depression, and malnutrition, as well as decreases in performance status and ability to perform routine activities of daily living [1,37]. More recently, in a systematic review of the economic implications of CID and its impact on QOL [36], the authors concluded that CID (i.e., Grades 3 and 4) had a profound impact on patients' QOL. However, they noted that only two of the twenty-two studies reviewed, had CID as the primary study outcome [26,40].

Given that the majority of the data on the occurrence and severity of CID is based on physician-rated CTCAE criteria, as well as the paucity of research on: risk factors for CID; the co-occurrence rates of other GI symptoms with CID; and the impact of CID on patients' QOL, "real world" studies (i.e., data obtained outside the context of randomized clinical trials and generated during routine clinical practice) are needed to better understand this adverse effect of CTX. Therefore, the purposes of this study, in a sample of oncology outpatients undergoing CTX (n=1133), were to: identify subgroups of patients with distinct CID profiles and determine how these subgroups differed in terms of demographic and clinical characteristics; severity, frequency, and distress of CID; the co-occurrence of common GI symptoms, and QOL.

Methods

Patients and settings

This analysis is part of a larger, longitudinal study, funded by the National Cancer Institute, of the symptom experience of oncology outpatients receiving CTX [18,39]. Eligible patients were ≥18 years; had a diagnosis of breast, GI, gynecological, or lung cancer; had received CTX within the preceding four weeks; were scheduled to receive at least two additional cycles of CTX; were able to read, write, and understand English; and provided written informed consent. Patients were recruited from two Comprehensive Cancer Centers, one Veteran's Affairs hospital, and four community-based oncology programs.

Study procedures

The study was approved by the Institutional Review Board at each of the study sites. Of the 2234 patients approached, 1343 consented to participate and 1133 had evaluable data on CID for this analysis. Patients' refusal to participate was primarily due to being overwhelmed with their cancer treatment. Eligible patients were approached in the infusion unit during their first or second cycle of CTX to discuss participation in the study. Patients completed study questionnaires in their homes, a total of six times over two cycles of CTX, namely: prior to CTX administration (i.e., recovery from previous CTX cycle; Assessments 1 and 4), approximately 1 week after CTX administration (i.e., acute symptoms; Assessments 2 and 5), and approximately 2 weeks after CTX administration (i.e., potential nadir; Assessments 3 and 6). Medical records were reviewed for disease and treatment information.

Instruments

Demographic and clinical characteristics – Patients completed a demographic questionnaire, Karnofsky Performance Status (KPS) scale [13], Self-Administered Comorbidity Questionnaire (SCQ) [29], Alchohol Use Disorders Identification Test [2], and a smoking history questionnaire.

Assessment of diarrhea occurrence – The diarrhea item from the Memorial Symptom Assessment Scale (MSAS) was used to assess for the occurrence of CID at each of the six assessments. The MSAS is a valid and reliable symptom assessment instrument that evaluates the occurrence, severity, frequency, and distress of 32 common symptoms [23].

Assessment of additional GI symptoms - The occurrence rates for ten additional GI symptoms (i.e., dry mouth, nausea, feeling bloated, vomiting, lack of appetite, abdominal cramps, difficulty swallowing, mouth sores, weight loss, change in the way food tastes) were evaluated using the MSAS. Data from the enrollment assessment were used to evaluate the co-occurrence of these common GI symptoms with CID.

Quality of life instruments – Generic and disease-specific measures of QOL were used in this study. The Medical Outcomes Study–Short Form (SF-12) was the generic measure of QOL. The SF-12 consists of 12 questions about physical and mental health as well as overall health status. The SF-12 was scored into two components that measure physical (i.e., Physical Component Summary (PCS)) and psychological

(Mental Component Summary (MCS)) function. These scores can range from 0 to 100. Higher PCS and MCS scores indicate better physical and psychological functioning, respectively. The SF-12 has well established validity and reliability [38].

Disease-specific QOL was evaluated using the Quality of Life Scale-Patient Version (QOL-PV)) [22]. This 41-item instrument measures four domains of QOL (i.e., physical, psychological, social, spiritual well-being) in oncology patients, as well as a total QOL score. The QOL-PV has well established validity and reliability [9].

Coding of the CTX regimens

Given the diversity in the cancer diagnoses and absolute number of different CTX regimens, each patient's regimen was coded as follows: received only CTX, received only targeted therapy, or received both CTX and targeted therapy.

Coding of the emetogenicity of the CTX regimens

Using the Multinational Association of Supportive Care in Cancer guidelines [25], each CTX drug was classified as having: minimal, low, moderate, or high emetogenic potential. Emetogenicity of the regimen was categorized into one of three groups (i.e., low/minimal, moderate, high) based on the CTX drug with highest emetogenic potential.

Coding of the antiemetic regimens

Each antiemetic was coded as either a neurokinin-1 (NK-1) receptor antagonist, a serotonin receptor antagonist, a dopamine receptor antagonist, prochlorperazine, lorazepam, or a steroid. The antiemetic regimens were coded into one of four groups: none (i.e., no antiemetics administered); steroid alone or serotonin receptor antagonist alone; serotonin receptor antagonist and steroid; or NK-1 receptor antagonist and two other antiemetics (e.g., serotonin receptor antagonist, dopamine receptor antagonist, prochlorperazine, lorazepam and/or a steroid).

Data analyses

Descriptive statistics and frequency distributions were generated for sample characteristics at enrollment using the Statistical Package for the Social Sciences (SPSS) version 23 [32].

As was done for other symptoms [5,6], unconditional latent class analysis (LCA) was used to identify the profiles of CID occurrence that characterized unobserved subgroups of patients (i.e., latent classes) over the six assessments. Prior to performing the LCA, patients who responded "no" to the diarrhea item on the MSAS for five (n=205) or six (n=456) assessments (i.e., these patients did not experience diarrhea across the two cycles of CTX) were identified and labelled as the "none" class (n=661). Then, the LCA was performed on the remaining 472 patients.

Estimation was carried out with full information maximum likelihood with standard errors and a Chi-square test that are robust to non-normality and non-independence 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 (BIC), Vuong-Lo-Mendell-Rubin likelihood ratio test (VLRM), entropy, and latent class percentages that were large enough to be reliable (i.e., likely to replicate in new samples) [20]. Missing data were accommodated for with the use of the Expectation-Maximization (EM) algorithm [19]. Mixture models, like LCA, are known to produce solutions at local maxima. Therefore, our models were fit with from 800 to 2,400 random starts. This approach ensured that the estimated model was replicated many times and was not due to a local maximum. Estimation was done with Mplus Version 8.2 [20].

Differences among the latent classes in demographic, clinical, and symptom characteristics, as well as QOL outcomes were evaluated using analysis of variance and Kruskal-Wallis or Chi Square tests. A p-value of $<.05$ was considered statistically significant. Post hoc contrasts were done using a Bonferroni corrected p-value of $<.008$ (.05/4 pairwise comparisons).

Results

Latent class analysis

The 661 patients (58.3%) who had ≤1 occurrence of CID over the six assessments were classified as the none class. For the remaining 472 patients whose data were entered into the LCA, a three class solution was selected because its BIC was smaller than the BICs for the 2-class and 4-class solutions (Table 1). In addition, the VLRM was significant for the 3-class solution, but not for the 4-class solution,

which indicates that too many classes were extracted. As shown in Figure 1, the trajectories for the occurrence of CID differed among these latent classes. For the decreasing class (22.0%), the occurrence rate for CID increased slightly from the first to the second assessment, then gradually decreased over the remaining four assessments. For the increasing class (5.2%), the occurrence rates for CID were relatively low over the first three assessments and then increased dramatically over the fourth and fifth assessments. For the high class (14.5%), the occurrence rates for CID remained consistently high over the six assessments.

Demographic and clinical characteristics

As shown in Table 2, for most of the demographic characteristics, no differences were found among latent classes. Compared to the high class, patients in the increasing class were more likely to be married. In terms of clinical characteristics, compared to the none class, patients in the high class had significantly lower KPS scores, higher SCQ scores, were more likely to report depression and diabetes, were more likely to have GI cancer and less likely to have breast or lung cancer, were more likely to receive CTX on a 14-day cycle, and were more likely to receive moderately emetogenic CTX. Compared to the none class, patients in the decreasing class had lower KPS scores, higher MAX2 scores, and were more likely to report ulcer/stomach disease. Compared to the none class, patients in the increasing class were more likely to report diabetes.

Frequency, severity, and distress of CID at enrollment

As shown in Figure 2A, significant differences were found among the classes in the frequency of CID ($p<.001$). Post hoc contrasts found that compared to the increasing and decreasing classes, the patients in the high class reported a higher frequency of CID. In terms of severity (Figure 2B), significant differences were found among the classes ($p<.001$). Post hoc contrasts found that compared to the increasing and decreasing classes, patients in the high class had more severe CID. In addition, compared to the increasing class, patients in the decreasing class had more severe CID. In terms of distress (Figure 2C), significant differences were found among the classes ($p<.001$). Post hoc contrasts found that compared to the increasing and decreasing classes, patients in the high class reported higher distress

ratings for CID. In addition, compared to the increasing class, patients in the decreasing class reported higher distress ratings for CID.

Occurrence of GI symptoms at enrollment

As shown in Table 3, compared to the none class, patients in the high class reported higher occurrence rates for: dry mouth, nausea, feeling bloated, vomiting, lack of appetite, abdominal cramps, difficulty swallowing, mouth sores, weight loss, and change in way food tastes. Compared to the none class, patients in the decreasing class reported higher occurrence rates for: nausea, feeling bloated, lack of appetite, abdominal cramps, and increased appetite. Compared to the high class, patients in the increasing class reported lower occurrence rates for nausea and abdominal cramps.

QOL scores

As shown on Table 4, for the SF-12, compared to the none class, patients in the high class had lower scores for: role physical, general health, vitality, social functioning, mental health, and MCS. Compared to the none class, patients in the decreasing class had lower scores for: physical functioning, role physical, bodily pain, vitality, social functioning, role emotional, mental health, as well as PCS and MCS.

For the MQOLS-PV, compared to the none class, patients in the decreasing and high classes had lower scores for: physical well-being, psychological well-being, and total QOL. In addition, compared to the none class, patients in the high class had lower scores for social well-being.

Discussion

This study is the first to use LCA to identify subgroups of patients with distinct CID profiles; categorize its frequency, severity and distress; describe the co-occurrence of GI symptoms; and describe the impact on CID on patients' QOL. While previous clinical trials reported prevalence rates of between 50% and 80% [33], 42% of our patients reported the occurrence of CID over the six assessments. Of note, 14.5% of our sample had high rates of diarrhea across the two cycles of CTX. In addition, for the majority of the patients in the high class, the frequency, severity and distress associated with CID were in the two highest ranges of each scale (Figure 2).

One of the objectives of this study was to identify risk factors associated with the occurrence of CID. While findings from previous studies suggest that older age, being female, and being White were associated with the occurrence of CID [1,34], the only demographic characteristic that was identified in our study was that compared to the increasing group, the high group was less likely to be married or partnered. Reasons for these inconsistent findings may be related to the heterogeneity in the patients' cancer diagnoses, heterogeneity in CTX regimens, and/or the use of self-report versus clinician-rated measures of CID.

In terms of clinical risk factors, consistent with one review [24], compared to the none class, patients in the increasing and high classes had a poorer functional status. In addition, compared to the none class, patients in the high class had a higher level of comorbidity. Of note, the specific comorbidities that differentiated between the none and the high classes were diabetes and depression. In one review that summarized information on fluorouracil-induced CID in patients with GI cancers [1], diabetes mellitus was a risk factor for CID. Given that severe CID can result in dehydration and electrolyte imbalances, patients with these risk factors as well as with GI and renal disorders warrant ongoing clinical evaluation.

Most of the studies of CID have focused on specific CTX regimens and methods of drug administration [3,24]. Given the heterogeneity in the CTX regimens used in this study, as well as the previously reported high prevalence rates of diarrhea across combination CTX regimens with or without a targeted therapy [1,17,27,33], we categorized the CTX regimens in two ways (i.e., receipt of targeted therapy (yes/no); receipt of only CTX, only targeted therapy, or both CTX and targeted therapy). Quite surprisingly, in our study, no differences were found among the four classes in either of these categorizations. In addition, when this analysis was repeated within each cancer diagnosis, these findings remained consistent. Future studies need to evaluate for molecular mechanisms that may predispose patients to CID independent of the CTX regimen (e.g., GI inflammation, disruption of the gut microbiome).

While the CTX regimens themselves were not associated with latent class membership, a larger percentage of patients with GI cancers were categorized in the high class. This finding is not surprising

given that CTX regimens, like fluorouracil and irinotecan, used to treat GI cancers are associated with an increased risk of CID [1]. However, it should be noted that almost 37.5% of the patients with breast cancer, 40.5% of the patients with gynecological cancer, and 20.5% of the patients with lung cancer were categorized in one of the CID classes. These findings suggest that this symptom warrants ongoing assessment and management during CTX.

While the toxicity of the CTX regimens, that was assessed using the MAX2 score [7,8], only differed between the none and decreasing class, cycle length was a risk factor for CID. As noted in one review [24], findings regarding differences in the occurrence rates of severe CID associated with the administration of irinotecan every two versus every three weeks are inconclusive. In our study, compared to the none and decreasing classes, a larger percentage of patients in the high class received CTX on a 14-day cycle.

Our findings regarding the significantly higher co-occurrence rates for eleven common GI symptoms in the high compared to the none class adds to the growing body of literature on the identification of a GI symptom cluster in patients with breast [35], lung [28], GI [11], and gynecological [12] cancers. In addition, across all four CID classes, greater than 40% of the patients reported the occurrence of dry mouth, nausea, and change in the way food tastes prior to their second or third cycle of CTX. As noted in two reviews [10,17], this constellation of symptoms may be related to the direct effects of CTX on the epithelial cells that line the entire GI tract. CTX acts directly on these rapidly dividing cells which results in apoptosis, the release of pro-inflammatory cytokines, GI inflammation, and disruption of the gut microbiome. While pain and fatigue are routinely assessed in clinical practice, findings from this study, as well as our previous studies [21,30], suggest that clinicians need to perform a systematic assessment of multiple GI symptoms and initiate appropriate interventions.

Consistent with previous reports [1,37], the occurrence of CID had a significant negative impact on both generic and disease-specific domains of QOL. While the scores for the majority of the QOL domains were relatively similar among the decreasing, increasing, and high classes (Table 4), statistically significant and clinically meaningful differences in these QOL scores were found between the none class

and the decreasing and/or high classes. The lack of significant differences associated with membership in the increasing class may be related to its relatively small sample size. Findings from our study suggest that CID has a negative impact on the physical, psychological, and social domains of QOL.

Limitations

Several limitations warrant consideration. Given that patients reported the occurrence of CID prior to their second or third cycle of CTX, future studies need to obtain a detailed history of previous episodes of CID and irritable bowel disease. Given that patients were assessed for only two cycles of CTX, the duration of CID or worsening of CID with subsequent cycles were not evaluated. Given the heterogeneity in this "real world" sample, in terms of cancer diagnoses and CTX regimens, replication of these distinct CID profiles is warranted with more homogenous samples. Future studies need to evaluate for the pharmacologic and nonpharmacologic treatments that patients used to manage their CID. Finally, given the fact that the types of CTX regimens were not associated with the distinct CID profiles, future studies need to account for molecular mechanisms that may place patients at higher risk for CID regardless of their CTX regimen.

Conclusions

Despite these limitations, findings from this large sample of oncology outpatients, who were followed over two cycles of CTX provides useful information for clinicians. While only 14.5% of the patients were in the high class, CID occurred in over 40% of the patients in our sample. Clinicians should be mindful of the risk factors identified in this study including: higher level of comorbidity, occurrence of diabetes and depression, diagnosis of GI cancer, receipt of CTX on a 14-day cycle, and lower functional status during their assessments of patients. Given the high prevalence of other GI symptoms with CID and their potential impact on patients' nutritional and hydration status, referrals to a dietician may be warranted particularly for the patients in the high class.

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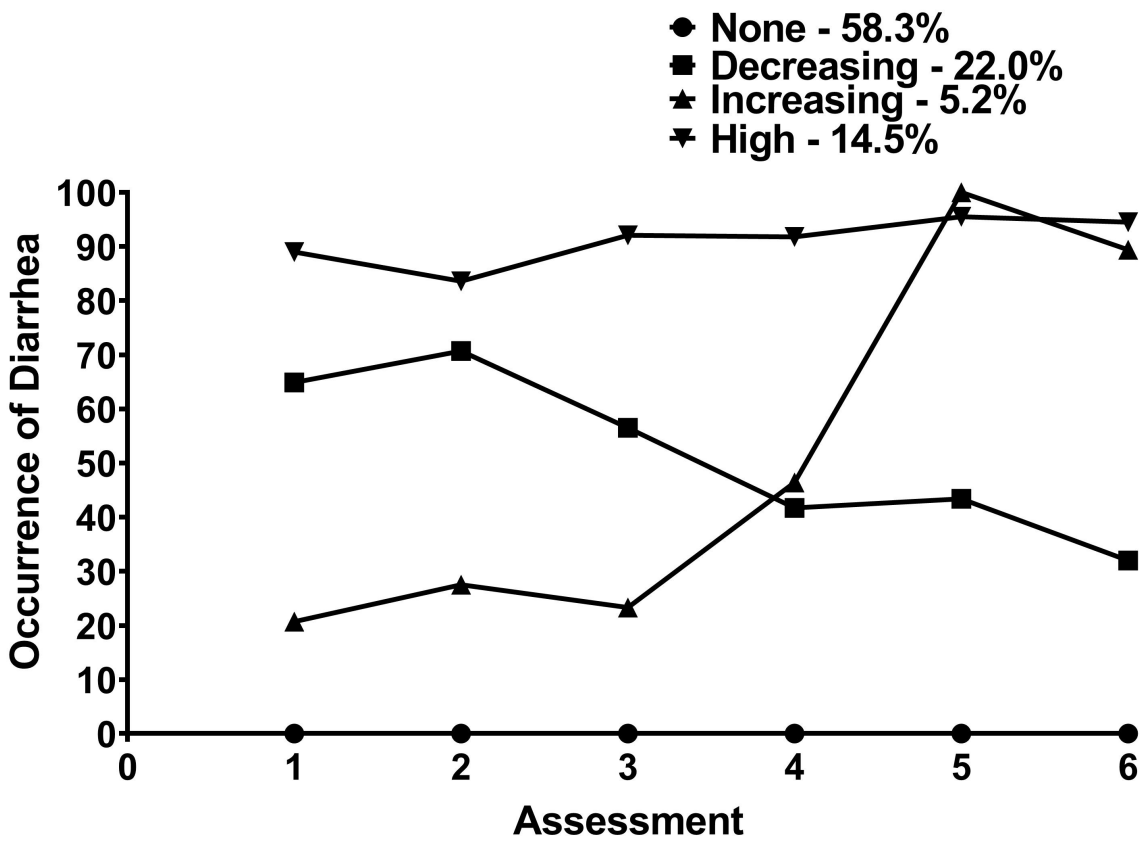

Figure 1 – Chemotherapy-induced diarrhea trajectories for patients in each of the latent classes

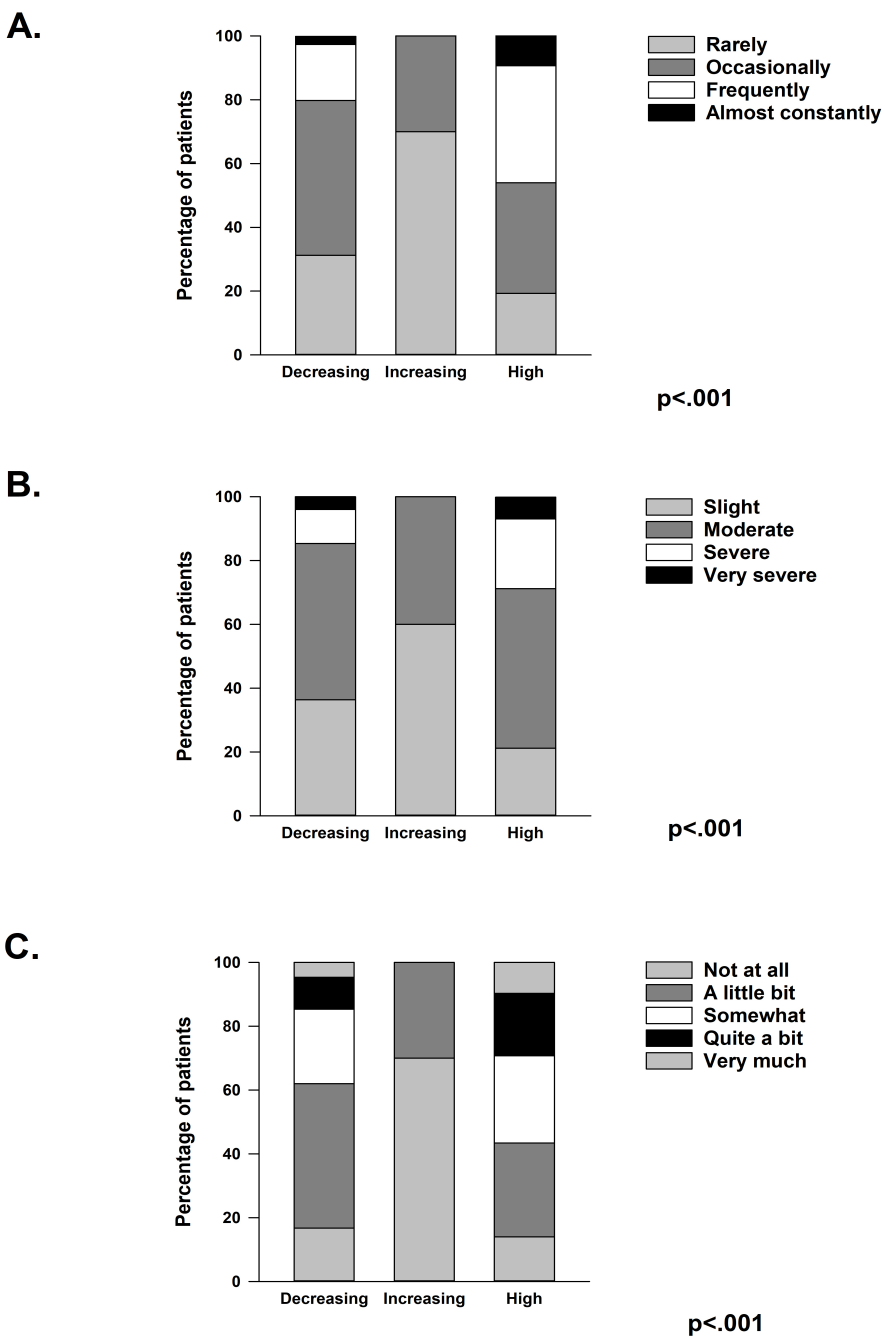

Figure 2 – Percentage of patients in the decreasing, increasing, and high who rated the frequency (A), severity (B), and distress (C) associated with chemotherapy-induced diarrhea.

Table 1 - Solutions and Fit Indices for One- Through Four-Classes for Diarrhea Occurrence Latent Profile Analyses

Model	LL	AIC	BIC	VLMR	Entropy
1 Class	-1665.28	3342.56	3367.50	n/a	n/a
2 Class	-1602.57	3231.14	3285.18	125.42***	.61
3 Class[a]	-1575.92	3191.84	3274.98	53.31***	.64
4 Class	-1564.99	3183.99	3296.22	21.85ns	.69

***p < .001

[a]The 3-class solution was selected because the BIC was smaller than the BICs for both the 2-class and 4-class solutions. In addition, the VLMR was significant for the 3-class solution, indicating that three classes fit the data better than two classes. However, the VLMR was not significant for the 4-class solution, indicating that too many classes had been extracted.

Abbreviations: AIC = Akaike Information Criterion, BIC = Bayesian Information Criterion, LL = log-likelihood, n/a = not applicable, ns = not significant, VLMR = Vuong-Lo-Mendell-Rubin likelihood ratio test for the K vs. K-1 model

Table 2 – Differences in Demographic and Clinical Characteristics Among the Diarrhea Latent Classes

Characteristic	None (0) 58.3% (n=661)	Decreasing (1) 22.0% (n=249)	Increasing (2) 5.2% (n=59)	High (3) 14.5% (n=164)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Age (years)	57.7 (12.5)	55.3 (12.5)	57.6 (11.8)	58.2 (11.7)	F = 2.62, p = 0.050
Education (years)	16.2 (3.1)	15.9 (2.9)	16.5 (2.9)	16.0 (2.9)	F = 1.20, p = 0.310
Body mass index (kg/m^2)	26.0 (5.2)	27.0 (6.4)	25.9 (4.9)	26.9 (6.2)	F = 2.86, p = 0.036 No significant pw contrasts
Alcohol Use Disorders Identification Test score	2.8 (2.2)	2.9 (2.3)	3.8 (3.7)	3.0 (2.7)	F = 1.97, p = 0.117
Karnofsky Performance Status score	81.6 (12.3)	79.1 (12.2)	79.6 (12.8)	77.8 (12.0)	F = 5.34, p = 0.001 0 > 1 and 3
Number of comorbid conditions	2.3 (1.4)	2.5 (1.4)	2.7 (1.6)	2.6 (1.5)	F = 3.47, p = 0.016 No significant pw contrasts
Self-administered Comorbidity Questionnaire score	5.2 (3.0)	5.8 (3.3)	6.0 (3.6)	6.0 (3.3)	F = 4.57, p = 0.003 0 < 3
Time since diagnosis (years)	1.9 (4.1)	2.0 (3.5)	2.8 (6.2)	1.7 (2.9)	KW, p = 0.828
Time since diagnosis (years, median)	0.42	0.43	0.39	0.47	
Number of prior cancer treatments	1.5 (1.5)	1.6 (1.5)	1.5 (1.5)	1.7 (1.4)	F = 0.34, p = 0.795
Number of metastatic sites including lymph node involvement [a]	1.3 (1.2)	1.3 (1.2)	1.2 (1.1)	1.3 (1.2)	F = 0.12, p = 0.947
Number of metastatic sites excluding lymph node involvement	0.8 (1.1)	0.8 (1.0)	0.7 (0.9)	0.8 (1.1)	F = 0.28, p = 0.840
MAX2 score	0.17 (0.08)	0.19 (0.08)	0.16 (0.08)	0.17 (0.08)	F = 4.28, p 0.005 0 < 1
	% (n)	% (n)	% (n)	% (n)	
Gender (% female)	77.1 (508)	77.9 (190)	79.7 (47)	73.6 (120)	X^2 =1.38, p = 0.710
Self-reported ethnicity White Asian or Pacific Islander Black Hispanic, Mixed, or Other	 66.1 (431) 12.7 (83) 9.8 (64) 11.3 (74)	 73.8 (177) 13.8 (33) 4.2 (10) 8.3 (20)	 64.9 (37) 17.5 (10) 8.8 (5) 8.8 (5)	 72.8 (118) 10.5 (17) 6.8 (11) 9.9 (16)	X^2 =12.96, p = 0.164
Married or partnered (% yes)	62.2 (404)	66.0 (159)	78.6 (44)	58.8 (94)	X^2 = 8.10, p = 0.044 2 > 3
Lives alone (% yes)	22.8 (148)	21.5 (52)	12.3 (7)	21.3 (34)	X^2 = 3.49, p = 0.323
Currently employed (% yes)	36.7 (240)	37.4 (91)	23.7 (14)	29.6 (47)	X^2 = 6.81, p = 0.078

Characteristics	None (0) 58.3% (n=661)	Decreasing (1) 22.0% (n=249)	Increasing (2) 5.2% (n=59)	High (3) 14.5% (n=164)	Statistics
	% (n)	% (n)	% (n)	% (n)	
Annual household income					
Less than $30,000	19.0 (111)	15.2 (34)	19.2 (10)	22.1 (32)	KW, p = 0.390
$30,000 to $70,000	21.1 (123)	25.4 (57)	19.2 (10)	22.8 (33)	
$70,000 to $100,000	17.3 (101)	17.9 (40)	9.6 (5)	19.3 (28)	
Greater than $100,000	42.6 (249)	41.5 (93)	51.9 (27)	35.9 (52)	
Child care responsibilities (% yes)	20.2 (130)	21.3 (51)	22.4 (13)	26.9 (43)	$X^2 = 3.40$, p = 0.334
Elder care responsibilities (% yes)	7.8 (46)	7.7 (17)	9.3 (5)	10.1 (15)	$X^2 = 0.99$, p = 0.803
Past or current history of smoking (% yes)	33.0 (213)	34.7 (83)	42.4 (25)	37.9 (61)	$X^2 = 3.06$, p = 0.383
Exercise on a regular basis (% yes)	74.0 (481)	68.4 (162)	73.7 (42)	63.5 (101)	$X^2 = 8.17$, p = 0.043 No significant pw contrasts
Specific comorbid conditions (% yes)					
Heart disease	5.2 (34)	6.1 (15)	13.6 (8)	5.5 (9)	$X^2 = 6.99$, p = 0.072
High blood pressure	30.5 (201)	32.0 (78)	28.8 (17)	34.4 (56)	$X^2 = 1.12$, p = 0.771
Lung disease	12.7 (84)	10.2 (25)	11.9 (7)	6.7 (11)	$X^2 = 5.04$, p = 0.169
Diabetes	6.4 (42)	9.8 (24)	16.9 (10)	20.2 (33)	$X^2 = 32.60$, p < 0.001 0 < 2 and 3; 1 <3
Ulcer or stomach disease	3.2 (21)	7.4 (18)	6.8 (4)	6.7 (11)	$X^2 = 9.16$, p = 0.027 0 < 1
Kidney disease	0.9 (6)	1.6 (4)	1.7 (1)	1.2 (2)	$X^2 = 1.00$, p = 0.800
Liver disease	6.5 (43)	5.7 (14)	6.8 (4)	6.7 (11)	$X^2 = 0.24$, p = 0.970
Anemia or blood disease	10.0 (66)	15.6 (38)	20.3 (12)	15.3 (25)	$X^2 = 10.32$, p = 0.016 No significant pw contrasts
Depression	15.6 (103)	20.9 (51)	20.3 (12)	25.8 (42)	$X^2 = 10.38$, p = 0.016 0 < 3
Osteoarthritis	12.1 (80)	11.9 (29)	15.3 (9)	11.0 (18)	$X^2 = 0.74$, p = 0.865
Back pain	24.9 (164)	25.8 (63)	22.0 (13)	27.6 (45)	$X^2 = 0.89$, p = 0.829
Rheumatoid arthritis	3.2 (21)	3.3 (8)	3.4 (2)	2.5 (4)	$X^2 = 0.284$, p = 0.963
Cancer diagnosis					$X^2 = 65.00$, p < 0.001
Breast cancer	42.0 (277)	39.3 (96)	40.7 (24)	28.2 (46)	0 > 3
Gastrointestinal cancer	25.6 (169)	31.1 (76)	37.3 (22)	55.8 (91)	0 and 1 < 3
Gynecological cancer	17.1 (113)	20.1 (49)	15.3 (9)	11.7 (19)	NS
Lung cancer	15.2 (100)	9.4 (23)	6.8 (4)	4.3 (7)	0 > 3

Characteristics	None (0) 58.3% (n=661)	Decreasing (1) 22.0% (n=249)	Increasing (2) 5.2% (n=59)	High (3) 14.5% (n=164)	Statistics
	% (n)	% (n)	% (n)	% (n)	
Prior cancer treatment					
No prior treatment	27.3 (174)	21.3 (51)	32.1 (18)	22.4 (36)	
Only surgery, CTX, or RT	41.9 (267)	48.1 (115)	41.1 (23)	37.3 (60)	
Surgery and CTX, or surgery and RT, or CTX and RT	19.3 (123)	17.6 (42)	16.1 (9)	24.2 (39)	X^2 = 12.03, p =0.212
Surgery and CTX and RT	11.5 (73)	13.0 (31)	10.7 (6)	16.1 (26)	
Metastatic sites					
No metastasis	30.0 (194)	35.2 (86)	32.2 (19)	29.2 (47)	
Only lymph node metastasis	22.4 (145)	20.1 (49)	20.3 (12)	26.7 (43)	
Only metastatic disease in other sites	21.5 (139)	17.2 (42)	16.9 (10)	23.6 (38)	X^2 = 9.08, p =0.430
Metastatic disease in lymph nodes and other sites	26.1 (169)	27.5 (67)	30.5 (18)	20.5 (33)	
Receipt of targeted therapy					
No	68.4 (442)	73.8 (180)	72.4 (42)	70.6 (115)	X^2 = 2.60, p =0.457
Yes	31.6 (204)	26.2 (64)	27.6 (16)	29.4 (48)	
CTX regimen					
Only CTX	68.4 (442)	73.8 (180)	72.4 (42)	70.6 (115)	
Only targeted therapy	4.2 (27)	0.8 (2)	0.0 (0)	1.8 (3)	X^2 = 10.74, p =0.097
Both CTX and targeted therapy	27.4 (177)	25.4 (62)	27.6 (16)	27.6 (45)	
Cycle length					X^2 = 24.67, p <0.001
14 day cycle	39.7 (261)	39.7 (261)	52.5 (31)	59.5 (97)	0 and 1 < 3
21 day cycle	52.9 (348)	52.9 (348)	37.3 (22)	36.2 (59)	0 and 1 > 3
28 day cycle	7.4 (49)	7.4 (49)	10.2 (6)	4.3 (7)	NS
Emetogenicity of the CTX regimen					X^2 = 14.64, p =0.023
Minimal/low	19.1 (126)	17.2 (42)	20.3 (12)	18.4 (30)	NS
Moderate	58.4 (385)	64.8 (158)	62.7 (37)	71.2 (116)	0 < 3
High	22.5 (148)	18.0 (44)	16.9 (10)	10.4 (17)	0 > 3
Antiemetic regimen					
None	8.2 (53)	5.8 (14)	3.6 (2)	4.5 (7)	
Steroid alone or serotonin receptor anatagonist alone	19.7 (127)	23.7 (57)	25.0 (14)	17.2 (27)	
Serotonin receptor antagonist and Steroid	48.2 (311)	43.2 (104)	51.8 (29)	53.5 (84)	X^2 = 10.85, p =0.286
NK-1 receptor antagonist and two other antiemetics	23.9 (154)	27.4 (66)	19.6 (11)	24.8 (39)	

[a]Total number of metastatic sites evaluated was 9.

Abbreviations: CTX = chemotherapy, kg = kilograms, KW = Kruskal Wallis, m^2 = meters squared, pw = pairwise, NK-1 = neurokinin-1, NS = not significant, RT = radiation therapy, SD = standard deviation

Table 3 – Differences in the Occurrence of Gastrointestinal Symptoms Among the Diarrhea Latent Classes

Occurrence of symptoms	None (0) 58.3% (n=661)	Decreasing (1) 22.0% (n=249)	Increasing (2) 5.2% (n=59)	High (3) 14.5% (n=164)	Statistics
	% (n)	% (n)	% (n)	% (n)	
Dry mouth	41.3 (272)	50.0 (122)	49.2 (29)	57.1 (93)	$X^2 = 15.75$, $p = 0.001$ 0 < 3
Nausea	40.1 (264)	54.1 (132)	40.7 (24)	62.6 (102)	$X^2 = 34.39$, $p < 0.001$ 0 < 1 and 3; 2 < 3
Feeling bloated	24.1 (159)	46.7 (114)	32.2 (19)	41.7 (68)	$X^2 = 50.15$, $p < 0.001$ 0 < 1 and 3
Vomiting	9.7 (64)	16.0 (39)	8.5 (5)	17.8 (29)	$X^2 = 12.61$, $p = 0.006$ 0 < 3
Lack of appetite	33.1 (218)	53.3 (130)	40.7 (24)	51.5 (84)	$X^2 = 39.81$, $p < 0.001$ 0 < 1 and 3
Abdominal cramps	12.4 (82)	37.3 (91)	18.6 (11)	39.3 (64)	$X^2 = 96.90$, $p < 0.001$ 0 < 1 and 3; 1 and 3 > 2
Increased appetite	22.2 (146)	31.6 (77)	25.4 (15)	28.2 (46)	$X^2 = 9.25$, $p = 0.026$ 0 < 1
Difficulty swallowing	9.7 (64)	16.0 (39)	13.6 (8)	24.5 (40)	$X^2 = 26.52$, $p < 0.001$ 0 < 3
Mouth sores	16.7 (110)	24.6 (60)	22.0 (13)	30.1 (49)	$X^2 = 17.51$, $p = 0.001$ 0 < 3
Weight loss	20.6 (136)	27.5 (67)	18.6 (11)	36.8 (60)	$X^2 = 20.99$, $p < 0.001$ 0 < 3
Change in way food tastes	44.8 (295)	53.3 (130)	49.2 (29)	60.7 (99)	$X^2 = 15.49$, $p = 0.001$ 0 < 3

Table 4 – Differences in Quality of Life Scores Among the Diarrhea Latent Classes

Quality of life (QOL) scores	None (0) 58.3% (n=661)	Decreasing (1) 22.0% (n=249)	Increasing (2) 5.2% (n=59)	High (3) 14.5% (n=164)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
SF12 Scores					
Physical functioning	56.0 (34.7)	46.8 (34.1)	54.9 (33.2)	50.3 (33.1)	F = 4.55, p = 0.004 0 > 1
Role physical	56.4 (30.2)	48.0 (28.2)	54.3 (29.1)	46.7 (27.6)	F = 7.65, p < 0.001 0 > 1 and 3
Bodily pain	78.6 (27.3)	71.7 (29.5)	74.6 (29.1)	75.3 (29.5)	F = 3.67, p = 0.012 0 > 1
General health	65.4 (27.5)	60.5 (28.5)	58.7 (27.0)	58.8 (27.1)	F = 3.92, p = 0.008 0 > 3
Vitality	48.4 (27.4)	41.0 (26.6)	46.1 (25.1)	40.9 (26.4)	F = 6.29, p < 0.001 0 > 1 and 3
Social functioning	70.1 (30.0)	63.4 (30.6)	67.2 (29.7)	61.3 (30.6)	F = 5.23, p = 0.001 0 > 1 and 3
Role emotional	78.3 (26.5)	71.7 (27.9)	79.7 (23.0)	72.3 (28.0)	F = 5.01, p = 0.002 0 > 1
Mental health	74.3 (20.2)	69.1 (21.6)	73.3 (18.5)	69.1 (20.6)	F = 5.37, p = 0.001 0 > 1 and 3
Physical component summary score	42.5 (10.6)	39.8 (10.6)	40.6 (10.5)	40.4 (9.6)	F = 4.41, p = 0.004 0 > 1
Mental component summary score	50.1 (10.3)	47.3 (10.2)	49.9 (9.0)	47.4 (10.6)	F = 5.70, p = 0.001 0 > 1 and 3
Multidimensional Quality of Life (QOL) Scale – Cancer					
Physical well-being	6.9 (1.8)	6.3 (1.8)	6.5 (1.6)	6.4 (1.9)	F = 7.40, p < 0.001 0 > 1 and 3
Psychological well-being	5.7 (1.8)	5.2 (1.8)	5.2 (1.8)	5.3 (1.9)	F = 5.92, p = 0.001 0 > 1 and 3
Social well-being	5.9 (2.0)	5.6 (1.9)	5.5 (1.8)	5.4 (2.0)	F = 4.82, p = 0.002 0 > 3
Spiritual well-being	5.6 (2.1)	5.3 (2.1)	5.4 (2.3)	5.3 (1.8)	F = 1.50, p = 0.214
Total QOL score	6.0 (1.4)	5.5 (1.4)	5.6 (1.3)	5.5 (1.5)	F = 8.56, p < 0.001 0 > 1 and 3

Abbreviation: SD = standard deviation

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