

Multiple Co-occurring Symptoms in Patients with Gastrointestinal Cancers

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Dissertation submitted in partial fulfillment of  
the requirements for the degree of  
Doctor of Philosophy in Nursing  
in the Graduate School of  
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2021

ABSTRACT

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## **Abstract**

**Background:** Patients with gastrointestinal (GI) cancers experience 10 to 15 co-occurring symptoms during chemotherapy that decrease their functional status, quality of life (QOL), and overall survival. The purposes of this dissertation were to describe symptom experiences and self-management strategies for multiple co-occurring symptoms in patients with gastric cancer; identify the subgroups of patients with GI cancers based on their distinct symptom experience profiles; and determine differences among these subgroups in demographic and clinical characteristics, as well as co-occurring symptoms and QOL outcomes.

**Methods:** An integrative review, a qualitative study, and three quantitative studies (i.e., one was cross-sectional, two were longitudinal) were used in this dissertation. Twenty-five studies were included and systematically evaluated in the review. Ten participants were interviewed for their symptom experiences and self-management strategies. Patients (n=405) completed questionnaires (e.g., the Memorial Symptom Assessment Scale, the Lee fatigue Scale, the General Sleep Disturbance Scale) six times over two cycles of chemotherapy. Content analysis was used to analyze the qualitative data. Latent class/profile analysis was used to identify the subgroups of patients with distinct symptom profiles. Differences in demographic and clinical characteristics as well as co-occurring symptoms and QOL outcomes among the subgroups were evaluated using parametric and non-parametric analyses.

**Results:** The most common symptoms were categorized into physical and affective/cognitive domains. Patients reported a large amount of inter-individual variability and dynamic nature in their experiences of multiple co-occurring symptoms. Four symptom self-management strategies were identified: medications for symptoms, information-seeking from the clinician team, lifestyle modifications, and psychosocial and spiritual support. The risk factors for a higher symptom burden included younger age, not being married/partnered, being unemployed, having childcare responsibilities, lack of regular exercise, having a lower functional status, having a higher comorbidity burden, and self-reported diagnosis of depression. Patients with a more severe symptom profile reported higher levels of morning and evening fatigue, sleep disturbance, anxiety, depressive symptoms, and pain, as well as lower levels of attentional function and QOL scores at enrollment.

**Conclusions and Implications:** This dissertation is the first to identify the subgroups of patients with GI cancers with distinct symptom experience profiles and examine a number of risk factors associated with more severe symptom profiles, as well as describe symptom experiences and self-management strategies for multiple co-occurring symptoms in patients with gastric cancer. Additional research is warranted to explore underlying mechanisms that contribute to the development of multiple co-occurring symptoms during chemotherapy. Clinicians need to assess for common risk

factors and associated co-occurring symptoms, as well as initiate personalized symptom management interventions and referrals.

## **Dedication**

To my grandfather, for bringing me into the field of health care. He was an outstanding and kind surgeon who cared for his patients and saved lives.

To my parents, for raising me and providing me with an excellent education. They believe in me, love me unconditionally, and have allowed me the freedom to be who I am and to pursue my dreams.

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# 1. Introduction

Gastrointestinal (GI) cancers are a set of malignant tumors of the GI tract and digestive organs, including the esophagus, stomach, small intestine, large intestine (colon), biliary system, pancreas, rectum, and anus. GI cancers account for more deaths worldwide than any other cancer (Bray et al., 2018). The American Cancer Society estimates that 338,090 new cases of GI cancers will be diagnosed in 2021 and approximately 169,280 patients will die from their disease (Siegel et al., 2021).

Gastric (stomach) cancer is one of the most common types of GI cancers and is the leading cause of death worldwide (Bray et al., 2018). In the United States, an estimated 116,525 people were living with gastric cancer in 2017, with more than 26,560 estimated new cases in 2021 (Siegel et al., 2021). While it is highly prevalent in Asian countries (e.g., China, Korea, Japan) (Bray et al., 2018), the incidence of gastric cancer has been increasing in Americans under 50 years of age (National Cancer Institute, 2018). More attention needs to be given to this cancer population in the United States.

Patients with GI cancers are treated with a wide range of therapies including chemotherapy, radiation therapy, surgery, targeted therapy, and immunotherapy. Chemotherapy is one primary treatment for GI cancers (Kudo, 2017). Patients experience an array of distressing symptoms associated with their disease and its treatment, including abdominal pain, nausea and vomiting, weight loss, dysphagia, lack of appetite, fatigue, sleep disturbance, and depression (Rausei et al., 2013; Tantoy et al.,

2016). On average, 10 to 15 of these symptoms occur concurrently during chemotherapy (Tantoy et al., 2017). When these symptoms are unrecognized or undertreated, they can negatively impact patients' health-related outcomes, including functional status, quality of life (QOL), and overall survival (Lee et al., 2016; Quinten et al., 2011; Tantoy et al., 2018). These symptoms can also lead to the discontinuation of treatment (Molassiotis & Chan, 2004) and increase the treatment cost (Hess et al., 2016). Defining the characteristics of multiple co-occurring symptoms associated with GI cancers is critical to developing targeted interventions that ameliorate symptoms and thus improve treatment adherence and QOL.

### ***1.1 Multiple Co-occurring Symptoms***

Merriam-Webster (2019) defines "multiple" as something in units of more than one or two, and "co-occurring" as occurring at the same time. The key concept in this dissertation, "multiple co-occurring symptoms", is defined as two or more symptoms that occur at the same time. Patients with GI cancers experience multiple co-occurring symptoms during chemotherapy, with more than 10 symptoms occurring concurrently (Walker et al., 2012). In a cross-sectional study that used the Memorial Symptom Assessment Scale (MSAS) to measure multiple co-occurring symptoms among 104 patients with colorectal cancer during chemotherapy; the most commonly co-occurring symptoms were numbness/tingling in the hands/feet (64%), lack of energy (62%), feeling drowsy (49%), difficulty sleeping (46%), nausea (45%), worrying (44%), shortness of

breath (43%), and dry mouth (42%); the mean number of symptoms was 10.3 (range = 0–32) (Pettersson et al., 2014). Similarly, in another study using the MSAS, patients with colorectal cancer receiving chemotherapy reported an average of 10 co-occurring symptoms; worrying (65%), lack of energy (59%), feeling drowsy (54%), feeling bloated (53%), pain (51%), and difficulty sleeping (50%) were the most prevalent co-occurring symptoms (Rohrl et al., 2016). Lack of energy (fatigue), worrying, feeling drowsy, and difficulty sleeping (sleep disturbance) were the most common and prevalent symptoms in both studies.

## **1.2 Symptom Experiences**

Symptom experience is defined as the perception of the attributes (e.g., severity, frequency) of symptoms as they are produced and expressed (Armstrong, 2003). Five dimensions of the symptom experience have been well documented in the literature: occurrence (i.e., the rate of symptoms occurring), severity (i.e., the strength or intensity of symptoms experienced), frequency (i.e., the number of times that symptoms occur), distress (i.e., the degree to which the person is bothered by symptoms), and meaning (i.e., patients' perception of the symptom and ability to cope and manage it, as well as global representation of their places in the world) (Armstrong, 2003; Zhu et al., 2019).

### **1.2.1 Symptom Occurrence and Severity**

To date, most studies have focused on the occurrence and severity of symptoms. For example, Walker et al. (2012) reported that patients with metastatic colorectal cancer

experienced moderate to severe multiple co-occurring symptoms (the Patient Care Monitor total score  $\geq 4$ ) and 67% of the patients reported fatigue as the most common symptom that occurred at moderate to severe levels. In another study, compared to receiving chemotherapy alone, patients who received chemotherapy and targeted therapy reported lower severity scores for dry mouth and change in the way food tastes, while they reported higher severity scores for “I don’t look like myself” (Tantoy et al., 2017). In a study that used the Chinese version of the M.D. Anderson Symptom Inventory (MDASI) to assess symptom severity in patients with esophageal cancer, the mean scores were 3.62 (SD = 1.66), which indicated mild levels of symptom severity (Wu et al., 2015). These findings suggest a large amount of inter-individual variability in the occurrence and severity of symptoms associated with GI cancers.

### **1.2.2 Symptom Frequency and Distress**

Several studies have reported symptom frequency and distress. In one study that evaluated 32 symptoms using the MSAS, for almost all of the symptoms, patients reported higher scores for frequency than for distress; symptoms with the higher distress scores were lack of energy, difficulty sleeping, and numbness in the hands/feet (Pettersson et al., 2014). A cross-sectional study reported that patients' overall symptom distress level was mild as measured by the MDASI scale (Zhang et al., 2015). The same study also found that anxiety and depression were positively associated with symptom distress (Zhang et al., 2015). These studies suggest that patients with GI cancers

experience a number of symptoms with a relatively high frequency and a mild level of symptom distress related to anxiety, depression, fatigue, sleeping disturbance, and numbness. In addition, no studies were found that explored symptom meaning for patients with GI cancers.

### **1.3 Symptom Predictors**

The relationships between a variety of characteristics and symptom experiences for patients with GI cancers have been examined in a number of studies. For example, in a cross-sectional study of 252 patients with colorectal cancer, age  $\geq 60$  years, female gender, suburban residence, body mass index  $< 18.5$ , and stage III cancer were associated with more severe co-occurring symptoms (Zhang et al., 2015). In addition, age  $\geq 60$  years, female gender, marital status of single or divorced, and suburban residence were associated with greater symptom distress (Zhang et al., 2015). In a study of patients with rectal cancer, cluster analysis identified four subgroups (i.e., minimally symptomatic  $n = 40$ , tired and trouble sleeping  $n = 138$ , moderate symptoms  $n = 42$ , and highly symptomatic  $n = 55$ ) and found that age and being married/partnered were the only two factors that differed among the subgroups (Gosselin et al., 2016). Additionally, occupation after illness, anxiety, type of surgery, whether chemotherapy was on schedule, and confrontation coping strategies were other factors that influenced symptom severity (Wu et al., 2015). In a longitudinal study, being female and having stage IV disease were associated with more severe physical symptoms over time; having

stage II and IV diseases were associated with more severe psychological symptoms over time (Hung et al., 2013). Taken together, these results suggest that older age, being female, being single or divorced, suburban residence, and advanced stage of disease were associated with more severe and higher distress from multiple co-occurring symptoms in patients with GI cancers.

### **1.4 Symptom Outcomes**

Symptom outcomes refer to the “consequences” or “effects” of the multiple co-occurring symptoms. The associations between multiple co-occurring symptoms and QOL outcomes (including functional status) were evaluated in four studies. In one study, higher symptom severity and higher symptom distress were associated with poorer functional status (Zhang et al., 2015). In a second study of patients with esophageal cancer, higher symptom scores were associated with poorer QOL (Wu et al., 2015). Hung et al. (2013) found that QOL scores were extremely poor in patients with stage IV colorectal cancer who had received chemotherapy. In a cross-sectional study of 114 patients with colorectal cancer, higher levels of anxiety and depression were the main predictors of poorer QOL (Graca Pereira et al., 2012). Overall, multiple co-occurring symptoms experienced by individuals with GI cancers were associated with the decreased QOL outcomes.

## **1.5 Symptom Trajectories**

Symptoms change over the course of treatment. In a study of patients with gastric cancer, fatigue increased significantly at year 1 after surgery and then decreased gradually across year 2 through 5 after surgery; dysphagia and eating restrictions worsened at year 1 after surgery and were at higher levels at year 5 than preoperatively (Yu et al., 2016). In a series of reports from one longitudinal study of 120 patients with colorectal cancer, patients experienced greatest severity of lack of energy, numbness/tingling, and nausea in the days following the administration of chemotherapy (Rohrl et al., 2016; Rohrl et al., 2019; Rohrl et al., 2020). In another study of patients with breast cancer undergoing treatment (Kim et al., 2008), psychoneurological symptoms were identified prior to treatment and during treatment. In contrast, in a sample of patients with ovarian cancer being treated with chemotherapy (Huang et al., 2016), the number and type of symptoms varied over time. Given that little information is available on the trajectories of multiple co-occurring symptoms during chemotherapy, additional investigation is warranted.

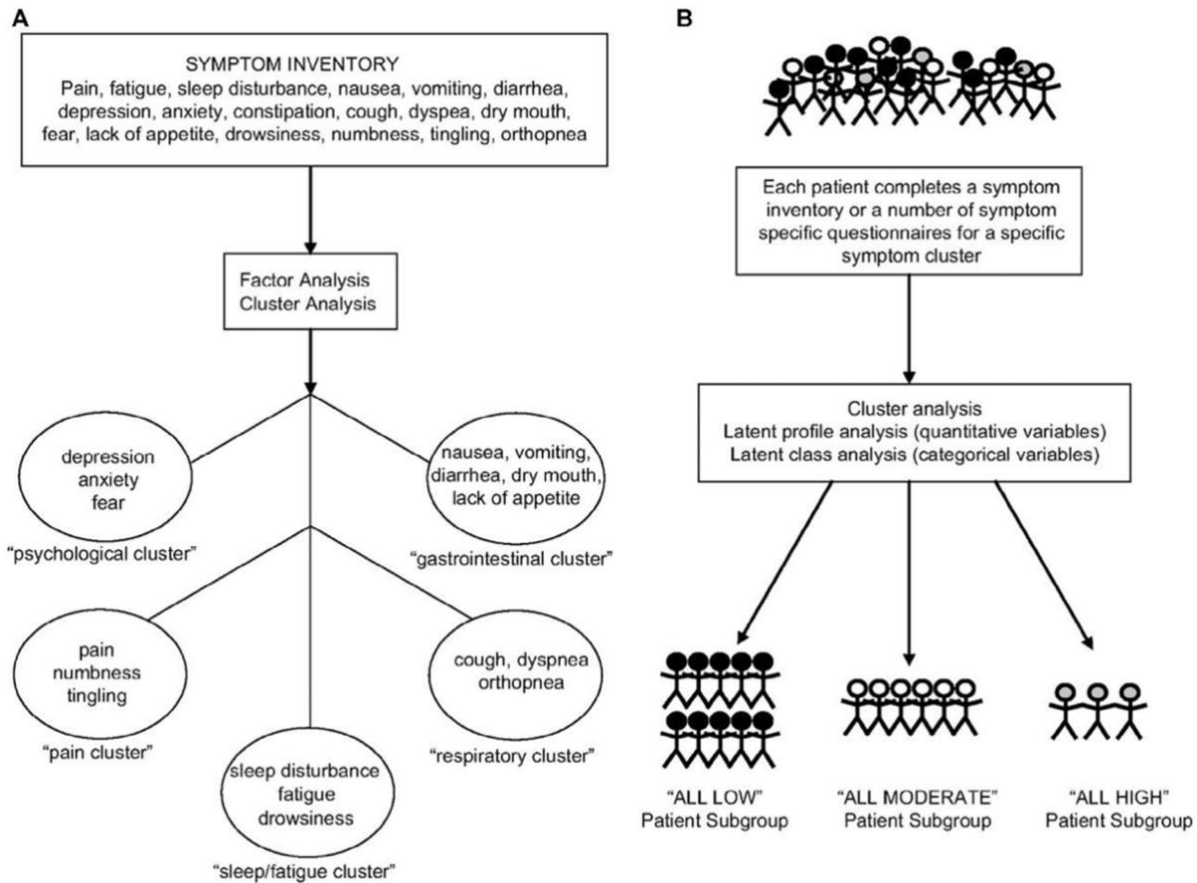
## **1.6 Symptom Self-Management**

Symptom self-management refers to any behavior an individual (patient) engages in specifically to relieve, minimize, or prevent symptoms and improve their QOL (van Dongen et al., 2020). A qualitative study of 27 African Americans with advanced cancer found that making continual adjustments for medications and lifestyles

and finding stability through spirituality were two approaches to symptom self-management (Yeager et al., 2016). A review study described that only five studies tested interventions designed to manage multiple co-occurring symptoms including psychoeducation, cognitive behavioral strategies, and acupuncture to address pain, fatigue, sleep disturbance, breathlessness, and cough (Kwekkeboom, 2016). There are a limited number of studies on symptom management, in particular, symptom self-management strategies for these patients.

### ***1.7 A Person-Centered Approach***

To date, two major strategies (i.e., grouping techniques) are used to study multiple co-occurring symptoms in patients with cancer (Miaskowski, 2016). The first strategy involves the identification of symptom clusters in oncology patients (i.e., grouping the symptoms, Figure 1A). The second strategy involves the identification of different subgroups of oncology patients based on their distinct symptom experiences (i.e., grouping the patients, Figure 1B). Once the subgroups are identified, differences between or among the subgroups in demographic and clinical characteristics (e.g., age, gender, diagnosis, stage of disease, types of cancer treatments), as well as patient outcomes (e.g., response to treatment, mortality, quality of life) can be evaluated. A person-centered approach is widely used for grouping the patients.



pain  
numbness  
tingling

"pain cluster"

sleep disturbance  
fatigue  
drowsiness

"sleep/fatigue cluster"

cough, dyspnea  
orthopnea

"respiratory cluster"



Each patient completes a symptom  
inventory or a number of symptom  
specific questionnaires for a specific  
symptom cluster

Cluster analysis  
Latent profile analysis (quantitative variables)  
Latent class analysis (categorical variables)



"ALL LOW"  
Patient Subgroup



"ALL MODERATE"  
Patient Subgroup



"ALL HIGH"  
Patient Subgroup

**Figure 1: Two Conceptual Strategies for Multiple Co-occurring Symptoms**

(Reprinted from Miaskowski, C., Aouizerat, B. E., Dodd, M., & Cooper, B. (2007). Conceptual issues in symptom clusters research and their implications for quality-of-life assessment in patients with cancer. *J Natl Cancer Inst Monogr*, (37), 39-46. By permission of Oxford University Press.)

In many instances, researchers use a variable-centered approach, such as regression, factor analysis, and structural equation modeling to describe the relationships among variables. The goal is to identify significant predictors of outcomes and describe how dependent and independent variables are related. A person-centered approach, in contrast, includes methods such as latent class/profile analysis, finite mixture modeling, and cluster analysis focusing on the relationships among individuals. The goal is to classify individuals into distinct groups or categories based on individual response patterns so that individuals within a group are more similar than individuals between groups (Jung & Wickrama, 2008). This dissertation used a person-centered approach (i.e., latent class/profile analysis) to identify subgroups of patients with GI cancers based on their distinct symptom experiences.

### ***1.8 Theoretical Framework***

The Multiple Co-occurring Symptoms Model (Figure 2), which is adapted from the Symptom Experience Model (Armstrong, 2003) and the Dynamic Symptom Model (Brant et al., 2010), will be used to guide the study of multiple co-occurring symptoms in patients with GI cancers.

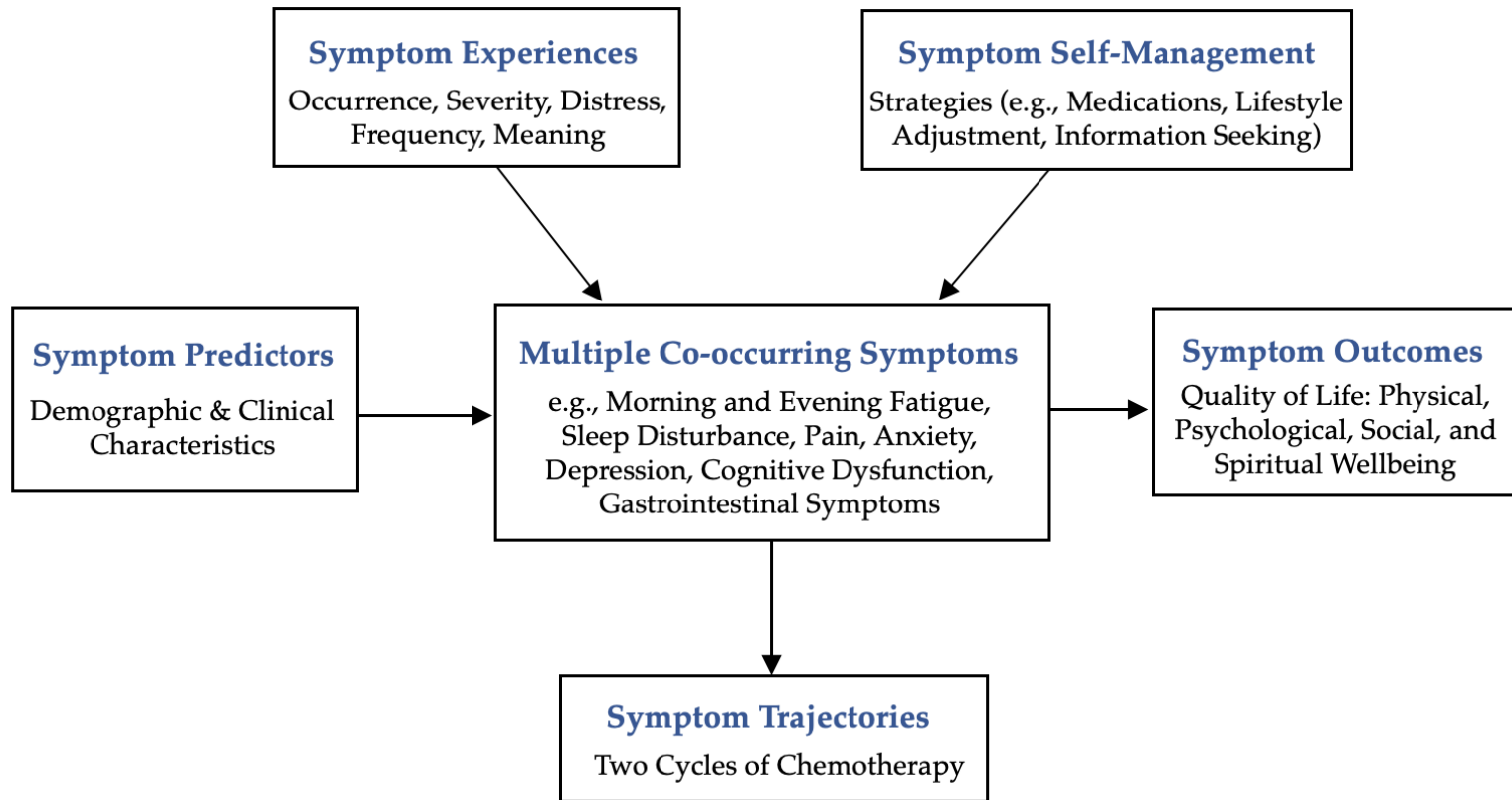


Figure 2: The Multiple Co-occurring Symptoms Model

The model has six major components: multiple co-occurring symptoms, symptom experiences, symptom predictors, symptom outcomes, symptom trajectories, and symptom self-management. The predictors are organized into two categories: demographic characteristics (e.g., age, gender, marital status, education) and clinical characteristics (e.g., cancer stage, type of treatment, comorbidity). These two categories affect the experiences of multiple co-occurring symptoms. Previous studies have documented different aspects of QOL outcomes, including physical, psychological, social, and spiritual status (Tantoy et al., 2018; Rohrl et al., 2020). The experiences of multiple co-occurring symptoms change over time. In this dissertation, we will analyze the trajectories of symptoms (i.e., morning and evening fatigue, sleep disturbance) during two cycles of chemotherapy. Symptom self-management strategies (e.g., medications, lifestyle adjustments) are used to help oncology patients self-manage their multiple co-occurring symptoms.

In the model, predictors (e.g., demographic characteristics) have direct effects on the experiences of multiple co-occurring symptoms, and multiple co-occurring symptoms have direct effects on the outcomes. The predictors may relate to one another and interact to influence other components in the model. Multiple co-occurring symptoms interact and affect each other, impacting a wide array of QOL outcomes. Symptom experiences and symptom self-management for multiple co-occurring symptoms will be explored through qualitative interviews.

This model will frame the research study by identifying multiple co-occurring symptoms in patients with GI cancers and exploring the relationships among the predictors, multiple co-occurring symptoms, and outcomes. The model also suggests symptom self-management of GI cancers through targeting multiple co-occurring symptom experiences, which would ultimately improve the outcomes for patients with GI cancers.

### **1.9 Purposes**

The purpose of this dissertation is to describe the multiple co-occurring symptoms in patients with GI cancers.

This study will address seven aims in the following chapters:

- Aim 1 (Chapter 1): Position the problem in the larger context of symptom science in the GI cancer population.
- Aim 2 (Chapter 2): Conduct an integrative review of the literature on common and co-occurring symptoms experienced by patients with gastric cancer.
- Aim 3 (Chapter 3): Describe symptom experiences and symptom self-management strategies for multiple co-occurring symptoms in patients with gastric cancer using a descriptive qualitative study.
- Aim 4 (Chapter 4): Identify the subgroups of patients with GI cancers based on their distinct symptom experiences with multiple co-occurring symptoms,

determine whether the subgroups differ on a number of demographic and clinical characteristics, and evaluate for differences in QOL outcomes among the subgroups using a cross-sectional study design.

- Aim 5 (Chapter 5): Identify the subgroups of patients with distinct morning and evening fatigue severity profiles and evaluate for differences among these subgroups in demographic and clinical characteristics, as well as co-occurring symptoms and QOL outcomes using a longitudinal study.
- Aim 6 (Chapter 6): Identify the subgroups of patients with their distinct sleep disturbance profiles and evaluate for differences among these subgroups in demographic, clinical, and sleep characteristics, as well as co-occurring symptoms and QOL outcomes using a longitudinal study.
- Aim 7 (Chapter 7): Synthesize findings and propose future directions for nursing research, practice, and policy.

## **2. Common and Co-occurring Symptoms Experienced by Patients with Gastric Cancer: An Integrative Review**

### ***2.1 Introduction***

Gastric (stomach) cancer was the fifth most frequently diagnosed cancer and the third leading cause of cancer deaths worldwide, with an estimated 1 million new cases and 783,000 deaths in 2018 (Bray et al., 2018). In the United States, an estimated 97,915 people were living with gastric cancer in 2015, with more than 26,240 estimated new cases and 10,800 estimated deaths in 2018 (Siegel et al., 2018). Patients diagnosed with gastric cancer have low five-year survival rates (10%–50%) because of advanced staging of disease at the time of diagnosis and the lack of effective treatments (Axon, 2006; Karimi et al., 2014; Venerito et al., 2018). People with gastric cancer experience multiple synergistic disease- and treatment-related symptoms. Investigators found that, on average, 10 to 15 of these symptoms occurred concurrently and included abdominal pain, weight loss, nausea, vomiting, dysphagia, dyspepsia, fatigue, and depression (Kim et al., 2016; Lee et al., 2016; Rausei et al., 2013). The undertreated symptoms can negatively influence patients' health outcomes, such as functional performance, psychological status, quality of life, and survival rate (Kim et al., 2017; Konishi et al., 2016; Maconi et al., 2003; Rausei et al., 2013).

Symptom science is one of the four identified themes in the National Institute of Nursing Research (NINR, 2016) Strategic Plan, and it is an essential component of the

research programs that are supported by the NINR and the National Cancer Institute. Scientists and clinicians emphasized the importance of symptom management in cancer survivorship as a future cancer research priority in the United States (Jaffee et al., 2017). In addition, a new *Symptom Science Center: A Resource for Precision Health* was established by NINR (2019) in June; it emphasized the underlying mechanisms of multiple symptoms and developed personalized approaches for symptom management.

Understanding patients' experience with co-occurring symptoms and their trajectories and predictors is critical to ensure appropriate assessment, education, and symptom management (Hockenberry et al., 2017; Miaskowski et al., 2004; Patrick et al., 2004). For example, pain, fatigue, and sleep disturbance were experienced concurrently by breast cancer survivors and managed effectively through a mind-body intervention (Kwekkeboom et al., 2010). Multiple co-occurring symptoms have been identified in patients with breast (Bower, 2008; Tchen et al., 2003), lung (Cooley, 2000; Wong et al., 2017), prostate (Talcott et al., 2003), colorectal (Pettersson et al., 2014), pancreatic (Burrell et al., 2018a, 2018b) cancers, and leukemia (Albrecht, 2014). However, there is limited evidence of the common symptoms (symptoms frequently occur) and co-occurring symptoms (symptoms occur at the same time) experienced by patients with gastric cancer, which is required to build symptom science in gastric cancer.

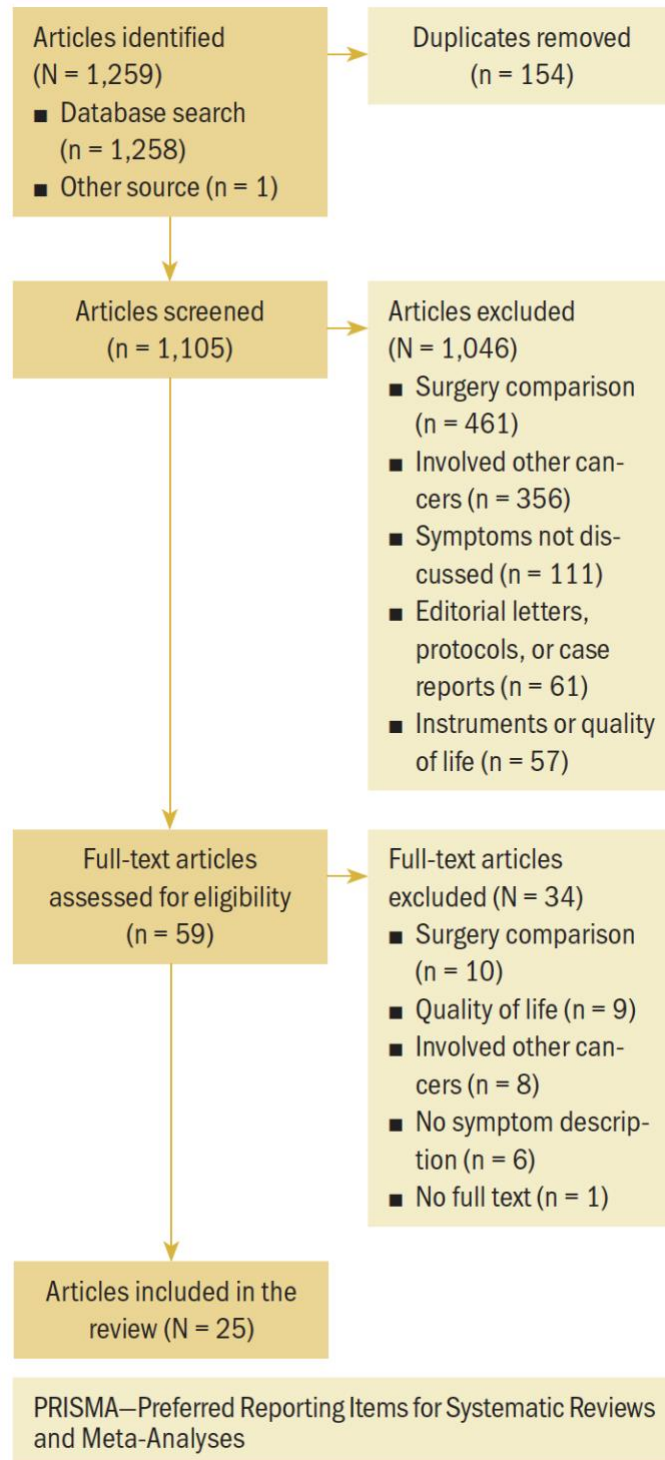
The purposes of this literature review were to describe the common and co-occurring symptoms experienced by patients with gastric cancer, and to synthesize

symptom profiles (i.e., measurement, predictors, trajectories, and management) to create a comprehensive understanding of the state of science on symptoms in people with gastric cancer and inform future nursing research and practice for this population.

## **2.2 Methods**

### **2.2.1 Literature Search**

To understand the complexity of symptom science in patients with gastric cancer, the first author (Y.L.) conducted a comprehensive search of PubMed® (MEDLINE®), CINAHL®, and PsycINFO® for empirical papers published between January 1990 and July 2019. This date range was chosen because symptom-related studies in gastric cancer began to appear in 1990. Search terms *stomach neoplasms*, *stomach*, *gastric*, *cancer*, *neoplasm*, *tumor*, and *tumour* were combined with *symptoms*, *symptoms and signs*, *symptom assessment*, *quality of life*, and *experience* to elicit relevant literature. The article selection process is shown in Figure 3.



**Figure 3: PRISMA Flowchart of Search Strategy and Selection**

## **2.2.2 Inclusion and Exclusion Criteria**

The inclusion criteria were as follows: studies involving symptoms experienced by people with gastric cancer; studies that considered the measurement, predictors, trajectories, and management of symptoms; reviews, systematic reviews, and meta-analyses; and published in English. The following were the exclusion criteria: editorial letters, comments, unpublished manuscripts, research protocols, and case reports; studies that did not report symptoms in their findings; studies that involved other cancer populations; studies that discussed only quality of life; and studies in which symptoms were a secondary outcome to a surgical procedure or medication trial (because these studies did not specifically describe patients' experience with symptoms). The search yielded 1,259 primary research studies; 25 studies were included.

## **2.2.3 Data Evaluation**

Data were evaluated using the hierarchy of evidence described by Melnyk and Fineout-Overholt (2011). The levels of evidence for this review consist of Level II (high quality) to Level VI (low quality); Level II is evidence from well-designed randomized controlled trials, Level III is evidence from well-designed controlled trials without randomization, Level IV is evidence from well-designed case-control and cohort studies, and Level VI is evidence from single descriptive or qualitative studies. For the included studies, the majority of studies (n=20, 80.0%) were Level VI, three were Level II, one was Level III, and one was Level IV (see Table 1). The level of evidence for the body of

literature was low quality. Data were extracted using the matrix method, which involves reading the documents, listing important issues, selecting and adding column topics (Garrard, 2014).

## **2.3 Results**

### **2.3.1 Characteristics of the Studies**

Twenty-five articles were included in this integrative review. All articles used quantitative methodologies; four articles were interventional studies, and the remainder (n = 21) were observational studies. Among the 20 quantitative descriptive studies, 16 reported cross-sectional data and 4 reported longitudinal data. One study used a cohort study design (Hu et al., 2018). The sample sizes ranged from 19 to 28,753 (median = 124). Studies originated from 11 countries or districts, including Korea (n = 10), Japan (n = 4), China (n = 3), Sweden (n = 1), Norway (n = 1), Spain (n = 1), United Kingdom (n = 1), Iran (n = 1), India (n = 1), Israel (n = 1), and Taiwan (n = 1). More than half (52.0%) of these studies were published in the last five years. Ten studies reported individual symptoms, and 15 reported multiple co-occurring symptoms.

### **2.3.2 Common and Co-occurring Symptoms**

The most frequent symptoms were categorized into physical symptoms (i.e., gastrointestinal [GI], fatigue, weight loss, and sleep disturbance), and affective/cognitive symptoms (i.e., anxiety, depression, posttraumatic stress disorder [PTSD] symptoms, and delirium).

**Table 1: Main Findings of the Included Studies for Integrative Review (N = 25)**

Study and Location	Sample	Design and Level of Evidence	Measurement	Findings (Symptom Profiles)
Anderson & MacIntyre, 1995 (United Kingdom)	57 consecutive patients undergoing standard resection	Prospective cross-sectional study; level VI	Checklist of symptoms	<ul style="list-style-type: none"> <li>■ Number: 6</li> <li>■ Occurrence: abdominal pain, nausea, vomiting, dyspepsia, fullness, and dysphagia</li> </ul>
Barad et al., 2014 (India)	158 patients with primary GC (age range = 28-91 years) undergoing surgery	Retrospective cross-sectional study; level VI	Checklist of symptoms	<ul style="list-style-type: none"> <li>■ Number: 7</li> <li>■ Occurrence: vague abdominal discomfort (61%), WL (60%), nausea (40%), early satiety and poor appetite (35%), vomiting (21%), dysphagia (18%), and melena (16%)</li> </ul>
Cho, 2004 (Korea)	103 paired samples of patients with GC ( $\bar{x}$ age = 52.29 years, SD = 10.07) receiving chemotherapy and their family caregivers	Prospective cross-sectional study; level VI	PSQI, CES-D, Lee Fatigue Scale, Brief Pain Inventory, and Quality of Life-Cancer	<ul style="list-style-type: none"> <li>■ Number: 4</li> <li>■ Occurrence: sleep disturbance (50%), depression (53%), pain (28%), and fatigue</li> <li>■ Severity: Average sleep quality = 2.6 (fair); mean global PSQI = 6.92 (SD = 1.45); mean falling asleep time = 22.96 minutes (SD = 19.98); average hours of sleep = 6.74 (SD = 1.45); mean fatigue score = 4.6 (SD = 1.94); mean depression score = 16.57 (SD = 9.12)</li> <li>■ Predictors: Depression was associated with sleep disturbance (<math>p &lt; 0.05</math>); fatigue was not (<math>p &gt; 0.05</math>).</li> </ul>
Climent et al., 2017 (Spain)	76 patients undergoing curative GC resection without recurrence	Prospective longitudinal study; level VI	WL, EORTC QLQ-C30, and EORTC QLQ-STO22	<ul style="list-style-type: none"> <li>■ Occurrence: WL <math>\geq 10\%</math> at 2 years (<math>n = 51, 67\%</math>)</li> <li>■ Predictors: Persistent pain, diarrhea, and N/V were associated with WL at 2 years after surgery (<math>p &lt; 0.05</math>); lower quality of life was also associated with WL at 2 years after surgery (<math>p &lt; 0.05</math>).</li> </ul>
Gunji et al., 2013 (Japan)	19 patients with stage I-II cancer; proximal gastrectomy at least 6 months prior; median age = 73 years (range = 59-79)	Quasiexperimental study of 4-week rikkunshito after surgery; level III	GSRS and VAS	<ul style="list-style-type: none"> <li>■ Number: 7</li> <li>■ Occurrence: GI symptoms (reflux, abdominal pain, ingestion, diarrhea, and constipation), WL, and appetite loss</li> <li>■ Severity: body weight (56.8 kg versus 57.2 kg, <math>p &lt; 0.05</math>), GI symptoms scores (2.2 versus 2.1, <math>p &gt; 0.05</math>) at baseline and after treatment, respectively</li> <li>■ Management: rikkunshito (Japanese medicine)</li> </ul>
Guo & Wang, 2018 (China)	124 patients with advanced GC receiving chemotherapy	Randomized controlled trial of NES for chemotherapy-induced N/V; level II	VAS, MD Anderson Symptom Inventory, and KPS	<ul style="list-style-type: none"> <li>■ Number: 3</li> <li>■ Occurrence: nausea, vomiting, and loss of appetite</li> <li>■ Management: NES reduced nausea (<math>p = 0.02</math>) and vomiting (<math>p = 0.04</math>) severity and improved appetite loss (<math>p = 0.02</math>) compared to the control group.</li> </ul>
Han et al., 2013 (Korea)	391 disease-free stage I-III GC survivors with a mean age of 55 years (SD = 10.6); at least 1 year after surgery	Prospective cross-sectional study; level VI	Beck Depression Inventory (0-63), EORTC QLQ-C30, and EORTC QLQ-STO22	<ul style="list-style-type: none"> <li>■ Number: 4</li> <li>■ Occurrence: depression (<math>n = 172, 44\%</math>), fatigue, dyspnea, and sleep disturbance</li> <li>■ Severity: mean depression score = 13.3 (SD = 8.7)</li> <li>■ Predictors: Lower income (OR = 2.49, 95% CI [1.64, 3.78]); problems with care pretreatment (OR = 1.92, 95% CI [1.23, 2.98]); body image change (OR = 2.23, 95% CI [1.41, 3.53]); and fatigue, dyspnea, and sleep disturbance were associated with depression.</li> </ul>

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Study and Location	Sample	Design and Level of Evidence	Measurement	Findings (Symptom Profiles)
Haugstvedt et al., 1991 (Norway)	855 patients with GC in 51 surgical units; undergoing surgery, chemotherapy, or RT	Prospective cross-sectional multicenter study; level VI	WL	<ul style="list-style-type: none"> <li>■ Occurrence: WL from diagnosis to admission (n = 596, 70%)</li> <li>■ Severity: 11-pound median loss (range = 0–79), 3-pound median loss per month (range = 0–26)</li> <li>■ Predictors: Older age, advanced stage, lower functional status, tumor type (diffused), and tumor location (cardia) were associated with increased WL (p &lt; 0.05).</li> </ul>
Hong et al., 2015 (China)	165 patients with GC without recurrence and metastasis with a mean age of 62 years (SD = 8.82); no treatment within 3 months after diagnosis	Prospective cross-sectional correlational study; level VI	DT, EORTC QLQ-STO22 (revised Chinese version), and Cancer Coping Modes Questionnaire	<ul style="list-style-type: none"> <li>■ Number: 10</li> <li>■ Occurrence: The top five symptoms were pain (62%), worry (61%), indigestion (59%), fatigue (58%), and eating restriction (58%).</li> <li>■ Distress: psychological distress (scored ≥ 4, n = 127, 77%); <math>\bar{X}</math> DT score = 5.13 (SD = 2.39, range = 0–10)</li> <li>■ Predictors: Psychological distress was correlated with abdominal pain, eating restrictions, and anxiety (p &lt; 0.05).</li> </ul>
Hu et al., 2018 (Taiwan)	28,753 patients newly diagnosed with GC (median age = 69 years, range = 55–77) undergoing surgery, chemotherapy, or RT; 28,753 matched patients	Retrospective cohort study; level IV	International Classification of Diseases, 9th Revision, Clinical Modification codes	<ul style="list-style-type: none"> <li>■ Occurrence: depression (n = 670, 9.1 per 1,000 person-years) in the GC cohort higher compared to the matched cohort (aOR = 1.54, 95% CI [1.39, 1.7])</li> <li>■ Predictors: Female gender (HR = 1.46, 95% CI [1.25, 1.7], p &lt; 0.01) and hypertension (HR = 1.27, 95% CI [1.07, 1.52], p &lt; 0.01) were associated with depression.</li> </ul>
Hwang et al., 2014 (Korea)	374 patients with stage I–III GC undergoing surgery, chemotherapy, or RT	Prospective cross-sectional study; level VI	Brief Fatigue Inventory, EORTC QLQ-C30, EORTC QLQ-STO22, and Beck Depression Inventory	<ul style="list-style-type: none"> <li>■ Occurrence: fatigue (n = 192, 51%)</li> <li>■ Predictors: Female gender, low economic status, rural residence, current smoker, lower functional status, depression, early cancer stage, and TG were associated with fatigue (p &lt; 0.05).</li> </ul>
Hwang et al., 2018 (Korea)	163 patients with GC who were scheduled for curative resection; measured preoperatively and at 1, 2, 3, and 7 days after surgery	Prospective longitudinal study; level VI	DRS-R-98, Mini-Mental State Examination, HADS, and PSQI	<ul style="list-style-type: none"> <li>■ Occurrence: delirium (n = 1, 0.6%) and subsyndromal delirium (n = 19, 12%)</li> <li>■ Trajectories: DRS-R-98 scores were generally highest the first day after surgery then gradually decreased.</li> <li>■ Predictors: Older age (OR = 3.85, 95% CI [1.36, 10.92], p &lt; 0.05) and low education level (OR = 3.98, 95% CI [1.39, 11.41], p &lt; 0.05) were risk factors of subsyndromal delirium.</li> </ul>
Jeong & An, 2017 (Korea)	52 pairs of patients with GC and their family caregivers; at least 1 month after surgery	Prospective cross-sectional study; level VI	HADS and Duke-University of North Carolina Functional Social Support Questionnaire	<ul style="list-style-type: none"> <li>■ Occurrence: depression and anxiety</li> <li>■ Predictors: Socioeconomic status and social support were associated with depression and anxiety (p &lt; 0.05).</li> </ul>

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Study and Location	Sample	Design and Level of Evidence	Measurement	Findings (Symptom Profiles)
Kim et al., 2017 (Korea)	229 patients with GC; median age of 56 years (range = 20–86); undergoing surgery, chemotherapy, or RT	Prospective cross-sectional study; level VI	HADS and CES-D	<ul style="list-style-type: none"> <li>■ Number: 3</li> <li>■ Occurrence: sleep disturbance (22%), anxiety (30%), and depression (30%)</li> <li>■ Distress: PD (n = 77, 34%)</li> <li>■ Predictors: Lower education level (p &lt; 0.05) and advanced stage (p &lt; 0.01) were associated with PD.</li> </ul>
Liedman et al., 2001 (Sweden)	32 patients undergoing gastric resection	Prospective cross-sectional study; level VI	GSRS, Sick Impact Profile, Body Symptom Scale, Comprehensive Psychopathological Rating Scale, Mood Adjective Check List, and KPS	<ul style="list-style-type: none"> <li>■ Number: 7</li> <li>■ Occurrence: GI symptoms (abdominal pain, reflux, indigestion, diarrhea, and constipation), WL, and loss of appetite</li> <li>■ Predictors: Patients with good appetite had fewer GI symptoms (p &lt; 0.05) and less fatigue and anxiety (p &lt; 0.05). Those who had reconstruction had fewer GI symptoms (p &lt; 0.05) in the long term.</li> </ul>
Maeda et al., 2006 (Japan)	82 patients receiving gastrectomy with a mean age of 64 years (SD = 10.2) with no indication of recurrence; had surgery within the past 3 years	Prospective cross-sectional correlational study; level VI	Checklist of symptoms, SDS, self-repression scale, interpersonal dependency scale, self-esteem scale, and emotional support scale	<ul style="list-style-type: none"> <li>■ Number: more than 8</li> <li>■ Occurrence: depression, GI symptoms (heartburn, abdominal pain, nausea, diarrhea, bloating, belching), and others</li> <li>■ Frequency: postoperative symptoms frequency, mainly sometimes (48%)</li> <li>■ Predictors: Interpersonal dependency, emotional support, and marital status had indirect effect on depression; self-esteem had direct effect (p &lt; 0.001).</li> </ul>
Maeda & Munakata, 2008 (Japan)	82 patients receiving gastrectomy with a mean age of 64 years (SD = 10.2) with no indication of recurrence; had surgery within the past 3 years	Prospective cross-sectional correlational study; level VI	Checklist of symptoms, checklist of eating habits, emotional support scale, and SDS	<ul style="list-style-type: none"> <li>■ Number: more than 8</li> <li>■ Occurrence: postoperative symptoms (e.g., diarrhea [30%], belching [28%], heartburn [15%]), depression, and others</li> <li>■ Frequency: postoperative symptoms frequency: rare (29%), sometimes (48%), often (10%), and very often (13%)</li> <li>■ Predictors: Marital status (<math>\beta = -0.32</math>) and depression (<math>\beta = 0.21</math>) were associated with frequency (p &lt; 0.05). Health status and eating habits were not associated with occurrence (p &gt; 0.05).</li> </ul>
Mine et al., 2010 (Japan)	1,153 patients who had undergone gastrectomy without a sign of recurrence or metastasis after surgery; 6–66 months after surgery	Prospective cross-sectional study; level VI	VAS and dumping syndrome questionnaire (13 symptoms)	<ul style="list-style-type: none"> <li>■ Number: 13</li> <li>■ Occurrence: EDS symptoms: abdominal pain or fullness (47%), diarrhea (38%), faintness (22%), N/V (20%), palpitations (16%), cold sweats (13%), and flushing (8%); LDS symptoms: hunger (21%), faintness (21%), dizziness (14%), cold sweats (10%), tremors (10%), and loss of consciousness (2%); occurrences of EDS and LDS: 68% and 38%, respectively.</li> <li>■ Predictors: EDS was associated with WL, younger age, and TG (p &lt; 0.05). LDS was associated with WL, female gender, and TG (p &lt; 0.05).</li> </ul>

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Study and Location	Sample	Design and Level of Evidence	Measurement	Findings (Symptom Profiles)
Nikbaksh et al., 2016 (Iran)	30 (15 experimental, 15 control) patients with GC receiving chemotherapy (measured at the 4th and 8th week after treatment)	Randomized clinical trial of olanzapine in GC survivors receiving chemotherapy; level II	HADS, World Health Organization Quality of Life–Brief, Rhodes index	<ul style="list-style-type: none"> <li>■ Number: 5</li> <li>■ Occurrence: nausea, vomiting, loss of appetite, anxiety, and depression</li> <li>■ Severity: anxiety (<math>\bar{X}</math> = 6.73, SD = 2.76 versus <math>\bar{X}</math> = 12.2, SD = 5.43) and depression (<math>\bar{X}</math> = 6.53, SD = 3.92 versus 10, SD = 5.38) in the experimental and control groups, respectively (<math>p &lt; 0.05</math>).</li> <li>■ Trajectories: Anxiety and depression had a rising trend from beginning to 8th week in the control group and a decreasing trend in the experimental group.</li> <li>■ Management: olanzapine</li> </ul>
Oh et al., 2018 (Korea)	100 patients who underwent gastrectomy for GC with an average age of 58.5 years (range = 52.3–67)	Prospective cross-sectional study; level VI	Laboratory examinations: endoscopic examination, messenger RNA expression, and polymerase chain reaction	<ul style="list-style-type: none"> <li>■ Occurrence: GI symptoms (esophageal reflux symptom [47%], early satiety, bloating, abdominal discomfort)</li> <li>■ Predictors: postoperative duration, H+/K+-ATPase mRNA expression level and gastroesophageal flap valve disruption were associated with esophageal reflux symptom (<math>p &lt; 0.05</math>).</li> </ul>
Palgi et al., 2011 (Israel)	123 outpatients with stage I–IV GC; mean age of 57 years (SD = 12.7); undergoing surgery, chemotherapy, or RT	Prospective cross-sectional study; level VI	The short CES-D and the Post-Traumatic Stress Disorder Checklist–Civilian Version	<ul style="list-style-type: none"> <li>■ Occurrence: PTSD symptoms</li> <li>■ Predictors: female gender, married status, and less social support were related to higher PTSD symptoms (<math>p &lt; 0.05</math>). Risk of clinical level of PTSD increased the risk of clinical level of depression by 15 times (OR = 15.73, 95% CI [3.16, 78.32], <math>p &lt; 0.01</math>).</li> </ul>
Park et al., 2015 (Korea)	199 GC survivors without recurrence; mean age of 58 years (SD = 10.9); undergoing surgery, chemotherapy, or RT	Retrospective cross-sectional study; level VI	FSS and self-administered symptoms questionnaire (13 symptoms)	<ul style="list-style-type: none"> <li>■ Occurrence: fatigue (FSS <math>\geq 4</math>, <math>n = 42</math>, 21%)</li> <li>■ Severity: <math>\bar{X}</math> = 2.728, SD = 1.441</li> <li>■ Predictors: Arthralgia (aOR = 12.95, 95% CI [3.21, 52.34]), dyspnea (aOR = 10.54, 95% CI [2.94, 37.8]), dyspepsia (aOR = 8.25, 95% CI [2.63, 25.96]), changed bowel habits (aOR = 4.56, 95% CI [1.09, 19.11]), and anemia (aOR = 3.18, 95% CI [1.26, 8.05]) were associated with fatigue. Regular exercise (aOR = 0.31, 95% CI [0.12, 0.77]) and advanced GC (aOR = 0.34, 95% CI [0.13, 0.89]) were associated with lower fatigue.</li> </ul>
Shim et al., 2019 (Korea)	242 patients with GC admitted for resection surgery with a mean age of 62.05 years (SD = 10.6)	Prospective longitudinal study; level VI	DRS-R-98, FACT-Cog, Korean version of the Mini-Mental State Examination, and HADS; measured before and 1, 2, 3, and 7 days after surgery	<ul style="list-style-type: none"> <li>■ Occurrence: subsyndromal delirium, 22 patients (9%) at POD 1, 9 (4%) at POD 2, 7 (3%) at POD 3, and 5 (2%) at POD 7</li> <li>■ Trajectories: Delirium symptom severity declined over 3 days after surgery (<math>p &lt; 0.001</math>).</li> <li>■ Predictors: Older age and longer anesthesia time were associated with the higher initial level of delirium symptom severity (<math>p &lt; 0.05</math>); a medication history for memory complaints and using propofol as an anesthetic agent were risk factors.</li> </ul>

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Study and Location	Sample	Design and Level of Evidence	Measurement	Findings (Symptom Profiles)
Yu et al., 2016 (Korea)	254 patients who underwent a curative gastrectomy for primary GC with a mean age of 55 years (SD = 10.7)	Prospective longitudinal study; level VI	EORTC QLQ-C30 and EORTC QLQ-STO22; measured preoperatively and 1, 2, 3, 4, and 5 years after surgery	<ul style="list-style-type: none"> <li>■ Number: 17</li> <li>■ Occurrence: fatigue, nausea, vomiting, pain, dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, dysphagia, reflux, eating restriction, anxiety, dry mouth, taste, body image, and hair loss</li> <li>■ Severity: The severity score of these symptoms ranged from 6.2–38.2 at 5 years after surgery.</li> <li>■ Trajectories: Fatigue and anxiety increased significantly 1 year after surgery and then decreased gradually (<math>p &lt; 0.001</math>). Dysphagia and eating restrictions increased 1 year after surgery (<math>p &lt; 0.001</math>).</li> </ul>
Zhou et al., 2017 (China)	56 (28 control, 28 experimental) patients with advanced GC with an average age of 57 years (range = 41–68); receiving standard chemotherapeutic regimen	Randomized controlled trial of 2-week acupuncture therapy during chemotherapy; level II	Self-reported symptoms questionnaire and World Health Organization Quality of Life questionnaire-100	<ul style="list-style-type: none"> <li>■ Number: 4</li> <li>■ Occurrence: nausea, vomiting, abdominal pain, and diarrhea</li> <li>■ Frequency: nausea (<math>\bar{X} = 11</math> minutes, SD = 3 versus <math>\bar{X} = 32</math> minutes, SD = 5), vomiting (<math>\bar{X} = 2</math> times, SD = 1 versus <math>\bar{X} = 4</math> times, SD = 1), abdominal pain (<math>\bar{X} = 7</math> minutes, SD = 2 versus <math>\bar{X} = 16</math> minutes, SD = 5), and diarrhea (<math>\bar{X} = 1</math> time, SD = 1, versus <math>\bar{X} = 3</math>, SD = 1) were in the experimental and control groups, respectively (<math>p &lt; 0.05</math>).</li> <li>■ Management: acupuncture therapy</li> </ul>

aOR—adjusted odds ratio; CES-D—Center for Epidemiologic Studies–Depression; CI—confidence interval; DRS-R-98—Delirium Rating Scale–Revised–98; DT—distress thermometer; EDS—early dumping syndrome; EORTC QLQ-C30—European Organisation for the Research and Treatment of Cancer Quality-of-Life Questionnaire–Core 30; EORTC QLQ-STO22—European Organisation for the Research and Treatment of Cancer Quality-of-Life Questionnaire gastric module; FACT-Cog—Functional Assessment of Cancer Therapy–Cognitive; FSS—Fatigue Severity Scale; GC—gastric cancer; GI—gastrointestinal; GSRS—Gastrointestinal Symptom Rating Scale; HADS—Hospital Anxiety and Depression Scale; HR—hazard ratio; KPS—Karnofsky Performance Status; LDS—late dumping syndrome; NES—Nerve Electrical Stimulation; N/V—nausea and vomiting; OR—odds ratio; PD—psychological distress; POD—postoperative day; PSQI—Pittsburgh Sleep Quality Index; PTSD—post-traumatic stress disorder; RT—radiation therapy; SDS—Self-Rating Depression Scale; TG—total gastrectomy; VAS—visual analog scale; WL—weight loss

**Note.** The number of symptoms is provided only for studies that described multiple co-occurring symptoms.

Patients with gastric cancer experienced multiple co-occurring symptoms at varying points before, during, and after treatment. Three to 17 symptoms (median = 7) were reported to occur concurrently in 15 studies.

Based on the Symptom Experience Model (Armstrong, 2003), the studies were conceptually organized into four dimensions: occurrence, severity, frequency, and distress. All articles reported the occurrence of symptoms; seven studies reported symptom severity using different measures (Cho, 2004; Gunji et al., 2013; Han et al., 2013; Haugstvedt et al., 1991; Nikbakhsh et al., 2016; Park et al., 2015; Yu et al., 2016); three studies reported symptom frequency (Maeda & Munakata, 2008; Maeda et al., 2006; Zhou et al., 2017); and two articles assessed symptom distress (Hong et al., 2015; Kim et al., 2017). Not all study reports of common symptoms described all four dimensions of symptom experience; most reported one to two dimensions.

*GI symptoms.* GI symptoms were the most frequently occurring symptoms among gastric cancer survivors. Eight studies reported that patients experienced a wide range of GI symptoms. A retrospective study in a sample of 158 gastric cancer survivors showed that abdominal pain (61%) was the most common GI symptom reported by patients, followed by nausea (40%), early satiety and poor appetite (35%), vomiting (21%), dysphagia (18%), and melaena (16%) (Barad et al., 2014). Mine et al. (2010) conducted a cross-sectional study among 1,153 patients with gastric cancer and found the occurrence of GI symptoms included abdominal pain or fullness (47%), diarrhea

(38%), and nausea/vomiting (20%). Together, these results indicate that abdominal pain is the most prevalent of GI symptoms. Other common GI symptoms include nausea, vomiting, diarrhea, constipation, dysphagia, and reflux (Anderson & MacIntyre, 1995; Maeda & Munakata, 2008; Maeda et al., 2006; Oh et al., 2018; Zhou et al., 2017).

**Fatigue.** Three studies described fatigue among patients with gastric cancer. The prevalence ranged from 21% (Park et al., 2015) to 51% (Hwang et al., 2014). Park et al. (2015) reported that the mean fatigue severity score was 2.728 (SD = 1.441), as measured by the Fatigue Severity Scale (score range = 1–7), which indicated a moderate level of fatigue. In a study of 254 patients who underwent gastrectomy, Yu et al. (2016) reported mild levels of fatigue severity at baseline and five years after surgery. Therefore, the occurrence of fatigue was moderate, and the severity was mild among patients with gastric cancer.

**Weight loss.** Weight loss was prevalent in patients with gastric cancer. The occurrence of weight loss was described in three studies as ranging from 60% (Barad et al., 2014; Climent et al., 2017) to 70% (Haugstvedt et al., 1991). In addition, Haugstvedt et al. (1991) reported a median weight loss of 11 pounds (range = 0–79) from the time of diagnosis through admission, and the median loss of weight was 3 pounds per month following treatment (range = 0–26). These studies indicate a high level of weight loss occurrence and severity in patients with gastric cancer.

*Sleep disturbance.* Disturbance in sleep was found to be problematic in two studies of patients with gastric cancer. The rate of sleep disturbance was reported as 22% in a sample of 229 patients with gastric cancer (Kim et al., 2017). In a study by Nikbakhsh et al. (2016), using the Pittsburgh Sleep Quality Index (PSQI), the average sleep quality was rated as 2.6 (fair sleep), the average hours slept were 6.74 hours (SD = 1.45), and the average time to fall asleep was 22.96 minutes (SD = 19.98). This suggests that patients with gastric cancer experienced sleep disturbance, with lower than the nationally recommended seven to nine hours of sleep and a longer time to fall asleep (Hirshkowitz et al., 2015).

*Anxiety and depression.* Anxiety and depression were the most prevalent affective symptoms experienced by patients with gastric cancer. Four studies described anxiety and depression. Hu et al. (2018) conducted a large-scale cohort study of 28,753 patients who were newly diagnosed with gastric cancer and found that depression among the gastric cancer cohort was 1.5 times higher than the matched control cohort (adjusted odds ratio [OR] = 1.54, 95% confidence interval [CI] = [1.39, 1.70],  $p < 0.05$ ). In a cross-sectional study of 229 gastric cancer survivors, Kim et al. (2017) reported anxiety (30%) and depression (30%) using a modified distress thermometer. The mean severity score of depression, assessed using the Beck Depression Inventory, was 13.3 (SD = 8.7), which indicated a mild level of severity (Han et al., 2013). Distress levels of anxiety and depression were reported to be as high as 77% in a study by Hong et al. (2015). In

summary, these studies suggest that patients with gastric cancer experience anxiety and depression that is mild in severity but high in occurrence and distress.

*PTSD symptoms.* Cancer-related PTSD symptoms include feeling emotionally numb and feeling distant from other people (Palgi et al., 2011). In a cross-sectional study of 123 outpatients with stage I to III gastric cancer, investigators found an association between PTSD symptoms and depressive symptoms ( $r = 0.474$ ,  $p = 0.001$ ) (Palgi et al., 2011).

*Delirium.* Delirium was a neurocognitive symptom reported in two articles published by the same Korean research team. Hwang et al. (2018) reported that 19 patients (12%) with a mean age of 70.11 year ( $SD = 7.49$ ) experienced postoperative subsyndromal delirium, measured by the Delirium Rating Scale-Revised-98 (DRS-R-98 = 8-14) and one patient (1%) experienced delirium ( $DRS-R-98 \geq 15$ ) in a sample of 163 participants; the severity of subsyndromal delirium was the highest on the first day after surgery and then gradually decreased. Shim et al. (2019) found that the occurrence of subsyndromal delirium was 9%, 4%, 3%, and 2% at 1, 2, 3, and 7 days after surgery, respectively, among 242 patients with gastric cancer ( $\bar{x}$  age = 62.05 years,  $SD = 10.6$ ). The severity of subsyndromal delirium decreased at three days after surgery. Taken together, these results suggest that delirium is prevalent in those undergoing gastrectomy; its severity gradually decreased after surgery.

### 2.3.3 Synthesis of Symptom Profiles

The authors organized descriptions of the symptom profiles into four themes: symptom measurement, symptom predictors, symptom trajectories, and symptom management.

*Symptom measurement.* A range of instruments, with established validity and reliability, were used to measure symptoms in patients with gastric cancer.

The most commonly used instruments for multiple co-occurring symptoms included the European Organization for the Research and Treatment of Cancer Quality-of-Life Questionnaire-Core 30 (EORTC QLQ-C30) and its gastric module (EORTC QLQ-STO22), and the Gastrointestinal Symptom Rating Scale. The use of self-designed questionnaires, which lacked established validity and reliability, was reported in a small number of studies (Anderson & MacIntyre, 1995; Park et al., 2015; Zhou et al., 2017). The remaining studies used non-disease-specific symptom instruments (i.e., PSQI, DRS-R-98) with established validity and reliability to evaluate a single symptom experienced by patients with gastric cancer (Hwang et al., 2018; Kim et al., 2017).

*Symptom predictors.* Predictors of symptoms varied by studies and types of symptoms. Table 2 summarizes associations between different symptoms among patients with gastric cancer. Older age, female gender, low socioeconomic status (SES), low social support, advanced cancer stage, and total gastrectomy were associated with a higher number and severity of symptoms. Older age was associated with weight loss

(Haugstvedt et al., 1991) and subsyndromal delirium (Hwang et al., 2018), whereas female gender was related to fatigue (Hwang et al., 2014), anxiety and depression (Hu et al., 2018), and PTSD symptoms (Palgi et al., 2011). Four studies reported that lower SES was associated with depression and anxiety (Han et al., 2013; Jeong & An, 2017; Kim et al., 2017) and fatigue (Hwang et al., 2014). In addition, Liedman et al. (2001) and Hwang et al. (2014) both found that patients who had undergone total gastrectomy had more symptoms (i.e., GI symptoms and fatigue) than patients who had other types of surgery ( $p < 0.05$ ). Advanced cancer stage was a risk factor that was associated with increased weight loss (Haugstvedt et al., 1991) and psychological distress (Kim et al., 2017). However, Hwang et al. (2014) and Park et al. (2015) found that advanced cancer stage was related to lower levels of fatigue. Therefore, it is difficult to draw a conclusion on predictors of a variety of symptoms.

*Symptom trajectories.* Symptoms experienced by patients with gastric cancer were found to change over time. Four prospective longitudinal studies reported findings related to the trajectories of symptoms (Hwang et al., 2018; Nikbakhsh et al., 2016; Shim et al., 2019; Yu et al., 2016). For example, Yu et al. (2016) measured symptoms yearly for five years after surgery and found that fatigue increased significantly at year 1 and then decreased gradually ( $p < 0.001$ ). This study also reported that dysphagia and eating restrictions worsened at year 1 ( $p < 0.001$ ) and were at higher levels at year 5 than preoperatively ( $p < 0.001$ ).

**Table 2: Common and Co-occurring Symptoms by Domain in Patients with Gastric Cancer**

Symptom	Measurement	Predictor
<b>Affective/cognitive symptoms</b>		
Delirium/subsyndromal delirium	Delirium Rating Scale	Older age, low SES, longer anesthesia time, memory loss history, and using propofol
Depression/anxiety	Hospital Anxiety and Depression Scale and Distress Thermometer	Female gender, low SES, advanced cancer stage, hypertension, low social support, married status, and negative self-esteem; other symptoms (fatigue, dyspnea, sleep disturbance, body image change, abdominal pain, and eating restriction)
PTSD symptoms	PTSD Checklist	Female gender, married status, and low social support; depression
<b>Physical symptoms</b>		
GI symptoms: abdominal pain, nausea, vomiting, diarrhea, constipation, reflux, dysphagia, and loss of appetite	EORTC QLQ-C30, EORTC QLQ-STO22, and Gastrointestinal Symptom Rating Scale	Total gastrectomy and weight loss
Fatigue	Brief Fatigue Inventory and Fatigue Severity Scale	Female gender, low SES, rural residence, current smoker, early cancer stage, depression, total gastrectomy, and lack of regular exercise; other symptoms (arthralgia, dyspnea, dyspepsia, changed bowel habits, and anemia)
Sleep disturbance	Pittsburgh Sleep Quality Index	Depression
Weight loss	Body weight loss	Older age, advanced cancer stage, tumor type (diffuse), tumors location (cardia), and lower physical function; other symptoms (persistent pain, diarrhea, and nausea/vomiting)
EORTC QLQ-C30—European Organisation for the Research and Treatment of Cancer Quality-of-Life Questionnaire—Core 30; EORTC QLQ-STO22—European Organisation for the Research and Treatment of Cancer Quality-of-Life Questionnaire gastric module; PTSD—post-traumatic stress disorder; SES—socioeconomic status		

In addition, Hwang et al. (2018) reported that subsyndromal delirium severity was highest on the first day after surgery and then gradually decreased in the following week ( $p < 0.05$ ), whereas another study (Shim et al., 2019) found that the severity of subsyndromal delirium decreased over three days after surgery. Nikbakhsh et al. (2016) found that the severity of anxiety and depression increased from the beginning to eighth week in the control group and decreased in the experimental group ( $p < 0.05$ ). Together, these findings provide important insights into trajectories of common symptoms with both short-term (days) and long-term (years) observation.

*Symptom management.* Interventions have been developed and tested to help patients with gastric cancer self-manage their symptoms. Four studies examined the effects of complementary and alternative approaches and pharmaceutical therapy for the management of multiple symptoms in gastric cancer, and evaluated the feasibility and efficacy of the interventions (Gunji et al., 2013; Guo & Wang, 2018; Nikbakhsh et al., 2016; Zhou et al., 2017). In a randomized controlled trial of nerve electrical stimulation treatment for chemotherapy-induced nausea and vomiting, Guo and Wang (2018) reported that the severity of nausea and vomiting decreased and loss of appetite improved significantly in 124 patients with advanced gastric cancer ( $p < 0.05$ ). Similarly, another randomized controlled trial of acupuncture conducted by Zhou et al. (2017) found that the duration of nausea and abdominal pain and the frequency of vomiting and diarrhea were lower in the experimental group than in the control group ( $p < 0.05$ ).

In a quasi-experimental study of four-week rikkunshito (Japanese herbal therapy) administered after surgery, Gunji et al. (2013) found that the severity of abdominal pain, reflux, diarrhea, and constipation experienced by participants significantly decreased ( $p < 0.01$ ). These results suggested that alternative therapies can decrease the severity and frequency of symptoms. In addition, in a randomized clinical trial of olanzapine among 30 patients with gastric cancer receiving chemotherapy (Nikbakhsh et al., 2016), the severity of anxiety and depression was lower in the experimental group compared to the control group ( $p < 0.05$ ). In summary, three of four studies used different alternative therapies for GI symptom management, and one study effectively treated anxiety and depression using a pharmaceutical therapy.

## **2.4 Discussion**

The purpose of this integrative review was to describe common and co-occurring symptoms and their symptom profiles, including measurement, predictors, trajectories, and management in patients with gastric cancer, and to address the state of symptom science in gastric cancer. The studies in this review were mainly conducted with Asian patients (21 of 25, 84.0%), perhaps because of higher rates of gastric cancer within this population. The latest global cancer statistics show that incidence rates of gastric cancer are highest in Eastern Asia (particularly in Korea, Japan, and China) (Bray et al., 2018). However, the incidence of cancers of the lower stomach has been increasing among Americans aged younger than 50 years, according to a National Cancer Institute (NCI,

2018)-led study. To date, no studies have been conducted in the United States regarding symptoms in patients with gastric cancer. Therefore, more attention must be given to issues related to symptoms experienced by this population.

A number of instruments was used to assess common and co-occurring symptoms. However, no standard instrument was identified to measure multiple co-occurring symptoms in patients with gastric cancer, which set difficulties for comparison studies. The EORTC QLQ-C30 and EORTC QLQ-STO22 scales were the instruments used most frequently to measure symptoms in gastric cancer survivors. Although these two scales provide a simple and rapid assessment, they have some disadvantages. They may only allow for the evaluation of the occurrence and severity of symptoms and may not reflect other dimensions (e.g., distress, meaning), and they do not measure affective/cognitive symptoms. Several investigator-designed instruments were used, but these lacked validity and reliability indices (Park et al., 2015; Zhou et al., 2017), which may lead to inaccurate assessment of symptoms among patients with gastric cancer. In a literature review summarizing measurement tools for patient-reported outcomes in advanced gastric cancer, three additional instruments were widely used: the Functional Assessment of Cancer Therapy (FACT)-General, FACT-Gastric, and MD Anderson Symptom Inventory for GI Cancer (Xu et al., 2013). In addition, two leading patient-reported outcomes (PROs) measures, the PROs version of the Common Terminology Criteria for Adverse Events and PROs Measurement Information System,

developed by the National Institute of Health, are quickly becoming the standard in patient-reported health measurement (Basch et al., 2014; Lee et al., 2020; Reeve et al., 2007). These systematically and rigorously tested instruments may provide a more comprehensive measure of multiple aspects of co-occurring symptoms in patients with gastric cancer.

The current review reported that 3 to 17 symptoms (median = 7) were experienced concurrently by patients with gastric cancer. Similarly, researchers have acknowledged the multiple co-occurring symptoms in patients with gastric cancer (Kawamura et al., 2014; Tey et al., 2014). In 2001, Dodd et al. first introduced the concept of symptom clusters. A symptom cluster has been defined as two or more symptoms occurring concurrently with or without sharing a common etiology (Aktas, 2013; Barsevick, 2016). It has been proposed that symptom clusters may have common underlying mechanisms that could benefit cancer symptom management (Miaskowski et al., 2017). In the past two decades, research on symptom clusters has continued to grow. To date, the authors found only one paper identifying symptom clusters in GI cancers (Han et al., 2019b). However, the authors did not find any study focused on symptom clusters in patients with gastric cancer, suggesting that symptom clusters research in this population is at an early stage of development. Future research is needed that focuses on symptom clusters to identify the phenotypes of groups of symptoms. This will enhance more efficient symptom assessment and management.

In this integrative review of 25 studies, GI symptoms (e.g., abdominal pain, dysphagia, constipation, nausea, vomiting) were among the most frequent, bothersome, and co-occurring symptoms experienced by patients with gastric cancer. This is consistent with previous findings (Cherwin et al., 2019; Cherwin, 2012) of GI symptoms being prevalent among patients with cancer. Other previous studies partially explained the etiology of this set of symptoms. For example, abdominal pain, nausea, and diarrhea are prominent issues that could be explained by bloating and abnormal movement of remnant stomach or intestinal (Hejazi et al., 2010), and vomiting was because of a lower ability to store food (Kawamura et al., 2014). Increasing the need for effectively assessing and managing GI symptoms is crucial for gastric cancer survivors.

Symptom experience is a multidimensional concept with four components (Armstrong, 2003); however, very few studies have examined symptom frequency and symptom distress, and no studies have explored symptom meaning for patients with gastric cancer. These oversights are critical in the understanding of symptoms that are of particular importance, such as those based on patients' concomitant meanings (Maguire et al., 2014). Also, the most severe or frequently occurring symptoms are not always the most distressing or meaningful to patients with cancer (Boehmke & Dickerson, 2005). These issues should be considered when systematically and comprehensively describing symptom experience in patients with gastric cancer.

Research on symptom trajectories is limited. Understanding how symptoms and symptom clusters change over time is critical to ensure appropriate symptom self-management (Dodd et al., 2001). Therefore, it is crucial to conduct longitudinal studies of symptoms in gastric cancer population. In addition, the science behind predictors of symptoms (e.g., advanced cancer stage) reports conflicting or inconsistent results. Symptom trajectories and predictors of symptom clusters are also absent in the literature. Further investigation is needed in those areas.

Developing and testing effective symptom interventions is critical for managing co-occurring symptoms and improving quality of life for patients with cancer (Kwekkeboom, 2016). Complementary and alternative therapies have been tested for their efficacy at relieving symptoms for patients with gastric cancer. For example, herbal therapy was found to relieve the symptoms of fatigue, nausea and vomiting, pain, loss of appetite, and constipation (Xu et al., 2017). Acupuncture was also found to minimize GI symptoms after gastrectomy (Lu & Rosenthal, 2013). However, key design issues in this set of studies prevent understanding of their efficacy; these issues include small samples (19–56) and lack of well-designed randomized controlled trial designs. Therefore, further research is needed to understand the impact of alternative therapies among patients with gastric cancer who experience multiple co-occurring symptoms.

### **2.4.1 Limitations**

The generalizability of the results of this literature review may be limited by several characteristics of the studies. More than half (21 of 25) of the studies are from Asian countries where gastric cancer rates are the highest globally, and the review was limited to articles written in English. Therefore, it may omit relevant articles published in other languages, particularly in Asian. There also was a very wide variability in stage of gastric cancer and stage of treatment. Studies included participants who were newly diagnosed, patients with advanced cancer, patients diagnosed with a range of earlier stage disease (e.g., I, II), patients undergoing chemotherapy, and those who underwent gastrectomy. This variability may result in different symptoms experienced by people with gastric cancer and, consequently, inaccurate findings on symptom profiles.

### **2.4.2 Implications for Nursing Practice and Research**

The study of symptoms in patients with gastric cancer and their application to practice is vital to nursing research and practice. Three implications were identified to guide researchers and nurse clinicians in the future. First, nurses and researchers should identify common data elements (defined as variables that are operationalized and measured in identical ways across studies) for symptoms in patients with gastric cancer (Redeker et al., 2015). This would be helpful for advancing symptom science in gastric cancer, and comparison across studies and populations (e.g., cancer, heart disease). Second, evidence indicates that people living with gastric cancer experience a wide

range of symptoms. Healthcare providers should be directed to strengthen awareness of assessing co-occurring symptoms and symptoms clusters in this population and discover potential symptoms with common etiology. Third, clinicians and researchers should partner to develop innovative interventions to support self-management of symptoms, including targeting the symptom clusters instead of individual symptoms. Further exploration of symptom clusters will provide a foundation for developing future interventions for efficient, effective symptom management in patients with gastric cancer.

## **2.5 Conclusion**

The authors reviewed relevant studies on symptom experience, measurement, predictors, trajectories, and management in patients with gastric cancer. This area of science remains in its infancy because robust evidence related to these symptoms is not available. Symptom predictors and trajectories have yet to be fully studied and described in patients with gastric cancer. Identification of symptom clusters may help to determine how symptoms are related to one another and how they influence patients' outcomes. This emphasizes the need for further research to establish the science. Interventions targeted to symptom clusters may help to improve the efficacy of symptom management in patients with gastric cancer.

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### **3. Symptom Experience and Self-management for Multiple Co-occurring Symptoms in Patients with Gastric Cancer: A Qualitative Study**

#### ***3.1 Introduction***

Gastric cancer (stomach cancer) was the fifth most diagnosed cancer and the third leading cause of cancer deaths worldwide with over 1,000,000 estimated new cases and 783,000 deaths in 2018 (Bray et al., 2018). In the United States, an estimated 113,054 people were living with gastric cancer in 2016, and more than 27,600 estimated new cases and 11,010 estimated deaths will occur in 2020 (Siegel et al., 2020). More than 75% of gastric cancer deaths are due to advanced stage diagnosis and the lack of effective treatments (Axon, 2006; Syngal et al., 2015).

Patients living with gastric cancer experience an increased symptom burden with multiple co-occurring symptoms, defined as two or more symptoms occurring at the same time. On average, 10 to 15 symptoms co-occur and include pain, fatigue, sleep disturbance, nausea, vomiting, dysphagia (difficulty swallowing), lack of appetite, weight loss, and depression (Barad et al., 2014; Maeda & Munakata, 2008). When multiple co-occurring symptoms remain unrecognized or undertreated by providers, they can have a deleterious impact on patient-reported outcomes (PROs) including functional performance, emotional status, quality of life (QOL), as well as survival rate. (Dodd et al., 2001; Hong et al., 2015; Yu et al., 2016). To date, most of studies on multiple co-occurring symptoms have focused on other cancer populations, such as breast (Nho

et al., 2018), lung (Wang & Fu, 2014), prostate (Lemanska et al., 2017), and colorectal (Pettersson et al., 2014) cancers. However, little is known about multiple co-occurring symptoms in patients with gastric cancer.

The symptom experience for patients with gastric cancer is multidimensional. Our recent integrative review summarized the findings of 25 quantitative studies on symptom experiences by evaluating occurrence, severity, frequency, and distress in patients with gastric cancer (Lin et al., 2020a). The common symptoms in gastric cancer included physical symptoms (e.g., fatigue, sleep disturbance, weight loss) and affective/cognitive symptoms (e.g., depression, anxiety, delirium) (Han et al., 2013; Hwang et al., 2018; Mine et al., 2010). Older age, female gender, advanced cancer stage, lower socioeconomic status, and total gastrectomy were associated with a greater number and severity of symptoms among patients with gastric cancer (Hwang et al., 2014; Park et al., 2015). However, there is a dearth of information on the qualitative symptom experience of patients with gastric cancer. A deeper understanding of patients' experiences and perceptions of their symptoms will help ensure appropriate assessment, education, and management (Patrick et al., 2004).

Symptom self-management refers to any behavior an individual (patient) engages in specifically to relieve, minimize, or prevent symptoms and improve their QOL (van Dongen et al., 2020). A qualitative study of 27 African Americans with advanced cancer found that making continual adjustments for medications and lifestyles

and finding stability through spirituality were two approaches for symptom self-management (Yeager et al., 2016). Three quantitative studies (Gunji et al., 2013; Guo & Wang, 2018; Zhou et al., 2017) have tested symptom interventions (e.g., alternative therapies, medications) in patients with gastric cancer; however, there is a paucity of symptom self-management strategies for these patients.

Understanding multiple co-occurring symptoms as well as patients' experiences and how they use self-management strategies will help develop personalized interventions that support patient symptom self-management. Therefore, the purpose of this study was to describe multiple co-occurring symptoms, symptom experiences, and symptom self-management strategies in patients with gastric cancer. The research questions are:

Question 1: How do patients with gastric cancer describe their multiple co-occurring symptoms?

Question 2: What are the symptom experiences (e.g., severity, distress) of multiple co-occurring symptoms for patients with gastric cancer?

Question 3: What symptom self-management strategies are used by patients with gastric cancer?

### **3.2 Methods**

In this qualitative descriptive study, we used a semi-structured interview guide to explore the experiences of patients with gastric cancer. Qualitative descriptive studies

provide a fundamental and direct description of the phenomenon of interest (Sandelowski, 2000). This approach is widely used to collect descriptions of patient experiences to address important clinical questions (Sandelowski, 2010). The Standards for Reporting Qualitative Research (SRQR checklist) was used to enhance the transparency of the study (O'Brien et al., 2014).

### **3.2.1 Participants and Setting**

Purposive sampling was used to recruit participants with gastric cancer at the Duke Cancer Institute. Participants who met the following criteria were invited to participate in the study: a) diagnosed with a malignant neoplasm of the stomach (International Classification of Diseases for Oncology (ICD-O), C16); b) 18 years of age or older; c) received at least one of the following therapies: gastrectomy, chemotherapy, radiation therapy, immunotherapy, and targeted therapy; d) were able to read, write and understand English. Exclusion criteria were patients: a) diagnosed with a major psychiatric illness; b) cognitive impairment. A total of 16 patients were approached, and ten patients consented to participate. The most common reason for refusal was being overwhelmed with their cancer treatment. Guided by the concept of information power (i.e., the more information provided by the sample participants, the smaller the number of participants needed) for qualitative interview studies (Malterud et al., 2016), and given the purpose of this qualitative study to collect in-depth descriptions of symptoms,

experiences, and self-management strategies, a purposive sample of ten participants with diverse experiences provided sufficient information power.

### **3.2.2 Ethical Considerations**

The study protocol (Pro00057512) was approved by the Institutional Review Board at Duke University Health System (DUHS). Written informed consent was obtained from the participants before each interview. Participants were reminded that they did not have to answer any questions that made them feel uncomfortable and that they could stop the interview at any time. All protected health information (PHI) of the participants, such as names and addresses, were removed from the data and pseudonyms were used. All electronic files and audio recordings were securely stored on an encrypted laptop at DUHS, and all hard copies of documents were stored in a locked cabinet that only the researchers could access.

### **3.2.3 Data Collection**

Participants were recruited from July 2018 to January 2019. The researcher (YL) screened eligible patients in the electronic health record system, then reached out to health care providers at the clinic who confirmed eligibility and assessed the patient's interest. If the potential participant was interested, the researcher explained the study and obtained consent. The participant completed a 5-minute demographic questionnaire and then participated in an interview. The interviews (lasting from 30 to 65 minutes) were conducted by the researcher in a private infusion room at the clinic. A semi-

structured interview guide was developed from the existing literature and included open-ended questions and probes. Sample questions included the following: a) What symptoms do you experience because of your illness or treatment? b) Please tell me about your experiences with each symptom. c) What types of symptoms do you think occur together or happen at the same time? d) Please tell me how you manage/take care of multiple co-occurring symptoms. All interviews were audio recorded and transcribed, and field notes were taken to capture non-verbal expressions. At the end of the interviews, the participants were thanked and compensated (\$20.00) for their participation in the study.

### **3.2.4 Data Analysis**

A content analysis procedure was used to analyze the data (Hsieh & Shannon, 2005; Vaismoradi et al., 2013). Coding was conducted by two authors (YL & DB) with backgrounds in oncology nursing and qualitative methodology. NVivo software was used to support data analysis which was completed in four steps. a) Data preparation (Sandelowski, 1995): two authors read the transcripts together to get a sense of the whole picture; the first author identified symptoms and self-management strategies, key topics and storylines (e.g., diagnostic story, daily life), and categorized informational content (e.g., patients' experiences, perspectives). b) Writing memos: using the transcripts and field notes, the first author wrote analytic memos and a brief case description of each participant. c) Coding (Saldaña, 2015): two cycles of coding were

used. The first author used a priori codes from the literature and clinical practice to create a codebook. The first cycle included codes developed a priori coding, descriptively, and in vivo (Saldaña, 2015). The last (senior) author reviewed the coding scheme and provided feedback; the first author revised the codebook by adding or combining codes. Once the first cycle of coding was completed, the two authors reviewed the findings and developed larger categories of data using pattern coding and theoretical coding (Saldaña, 2015). The second cycle was used to organize and group codes that were similar or shared common characteristics. d) Categorizing and connecting: the first author constructed tables and matrices to organize, condense, and display the codes and data samples into categories, all authors helped search for patterns, trends, and paradoxes across all participants, then summarized the descriptions and developed the themes (Maxwell & Miller, 2008).

### **3.2.5 Assuring Rigor**

Confirmability, dependability, credibility, and transferability are criteria used to build rigor and trustworthiness in qualitative findings (Miles et al., 2014). Confirmability was achieved during the interviews by encouraging the participants to speak freely and the interviewer clarifying the meaning of what was being expressed, as a form of member checking. The participants were provided opportunities to describe their experiences in their own words and tell their stories. Dependability was achieved by the two coders checking the interview transcriptions for accuracy and using a codebook for

consistency. Credibility and transferability were ensured by critically appraising each decision and actively reflecting on the researchers' biases and how those biases could influence the research process. For example, the authors compared findings with current symptom science literature and discussed assumptions about the interrelationship among multiple co-occurring symptoms in patients with gastric cancer before the data collection and during the data analysis and manuscript preparation.

### **3.3 Results**

Demographic and clinical characteristics of the participants are detailed in Table 3. The median age of the participants was 52.5 years, and half of the participants were female and used the Medicare health insurance. A majority of the participants were African American (n = 7), married (n = 7), and not employed (n = 7), with more than 12 years of education (n = 8), and medium to high family income (n = 7). All participants had advanced gastric cancer and had received chemotherapy.

We organized the findings into four themes pertaining to the participants' accounts of their symptom experiences and self-management strategies for multiple co-occurring symptoms (see Figure 4).

**Table 3: Demographic and Clinical Characteristics of Study Participants (N = 10)**

Pseudonym	Age (year)	Gender	Race /Ethnicity <sup>a</sup>	Marital Status	Education (year)	Employment	Family Income <sup>b</sup>	Insurance	Treatment	Cancer Stage
James	45	Male	White	Married	12	Retired	High	Medicare	CTX, surgery	III
Tom	59	Male	Black	Married	14	Project manager	Medium	Other	CTX, RT	IV
John	46	Male	White	Married	16	Mortgage banker	High	Other	CTX, IMT	IV
Susan	46	Female	Black	Married	17	Unemployed	Low	Medicaid	CTX	IV
Randall	75	Male	Black	Married	14	Unemployed	Low	Medicare	CTX, surgery	IV
Matt	68	Male	Black	Married	16	Retired	Medium	Medicare	CTX, RT	III
Claire	70	Female	White	Married	15	Retired	High	Medicare	CTX	IV
Diana	<30	Female	Black	Single	8	Unemployed	Low	Other	CTX, surgery	IV
Nicole	71	Female	Black	Widowed	14	Information technology	Medium	Medicare	CTX, RT	IV
Kate	40	Female	Black	Single	4	Unemployed	Medium	Medicaid	CTX, IMT	IV

Note: CTX = chemotherapy, IMT = immunotherapy, RT = radiation therapy

<sup>a</sup> Ethnicity: all participants were Non-Hispanic

<sup>b</sup> Family income (after tax): low < \$30,000, medium \$30,000 ~ \$60,000, high >\$60,000

### 3.3.1 Perceptions of Multiple Co-occurring Symptoms

Participants with gastric cancer experienced a complex array of symptoms. They reported between 6 and 13 symptoms that included both physical and psychological symptoms. The most common physical symptoms were gastrointestinal (GI) symptoms (i.e., abdominal pain, bloating, acid reflux, lack of appetite, nausea, vomiting, diarrhea, constipation, and dysphagia), fatigue, sleep disturbance, pain, weight loss, changes in eating, numbness, and changes in skin. The most common psychological symptoms were depression, anxiety, worrying, and irritation. Participants' accounts described the relationships and concurrence of multiple symptoms. Four groups of multiple co-occurring symptoms were reported by the participants.

*Dysphagia – abdominal pain – vomiting.* The co-occurrence of these three symptoms was associated with significant suffering. For example, a 45 years-old man (James) stated, *“It’s hard to keep food down when I swallowed [it] feel like my food [is] easily stuck. I have much pain ... and I end up throwing up. So I throw up about 15 times a day.”* He reported episodes of severe dysphagia, which caused pain in his throat and abdomen when eating and drinking. He felt like food got stuck in his throat and stomach, because there was little space for his food to pass through or that his food sat in the stomach. He kept vomiting to get the food out of his stomach. Vomiting caused pain and pain exacerbated his dysphagia. These three symptoms were commonly co-occurred and

seemed to be associated with and escalated by each other. The pain in this symptom group was esophageal and/or stomach pain.

*Pain – constipation – diarrhea.* The co-occurring symptoms of pain, constipation, and diarrhea featured prominently in participants' descriptions. For example, more than half of the participants reported they used pain medication, and that the pain medication led to constipation. Participants would take laxatives that caused diarrhea. One participant shared, *"I did have a lot of constipation, which is brought by the pain medicine. Then I used the medication for constipation, I had diarrhea every once in a while, but it then goes back to be constipated."* (Tom, 59)

Participants described their experiences with pain, constipation, and diarrhea as a "vicious circle", where one symptom triggered another symptom. It was an unrelenting and ever-present process for them; namely, treating one symptom which led to another symptom.

*Stomach discomfort – sleep disturbance – fatigue.* Stomach discomfort (i.e., abdominal pain, bloating, flatulence, acid reflux) was reported by most participants. Two participants described how stomach discomfort had a negative impact on their sleep. They woke up many times during the night and did not sleep well. A lack of sleep left participants feeling fatigued and lacking in energy during the day. Stomach discomfort, sleep disturbance, and fatigue were viewed as occurring together. *"There was no burning, no pain, just feeling uncomfortable, cause sick in the stomach. They can come*

*anytime, day and night, mostly come at night or early in the morning. My stomach is not right, I can't go to sleep ... then I felt a lack of energy the next day."* (Randall, 75)

*Nausea/vomiting/constipation/diarrhea – lack of appetite – weight loss.* All participants reported GI symptoms including nausea, vomiting, constipation, and diarrhea. These four symptoms contributed to a lack of appetite, which resulted in weight loss. The effects of GI symptoms were additive. Participants described these four symptoms occurring both separately and, in many instances, simultaneously. They could individually or concurrently lead to a loss of appetite and weight loss.

Of note, some participants described that one symptom (e.g., pain) started and other symptoms (e.g., constipation, diarrhea) followed, with these symptoms continuing on together. Two participants did not describe symptoms as co-occurring and instead focused on the single symptom that bothered them most.

### **3.3.2 Complex and Dynamic Nature of Symptom Experiences**

*Inter-individual variability.* The narratives of participants indicated that the severity, frequency, and distress of multiple co-occurring symptoms varied markedly among individuals. For example, some participants reported severe fatigue, while for others, the severity of fatigue was relatively low. One participant said, *"I feel really tired, so the fatigue is bad... It keeps me in bed at home a lot, so I'm restricted to go anywhere."* (John, 46) Another participant stated, *"I keep busy, so I don't think about it [fatigue]. But if I am in a*

*settled place, I may probably think about it.” (Susan, 46)* This description suggested marked variability in symptom severity across participants.

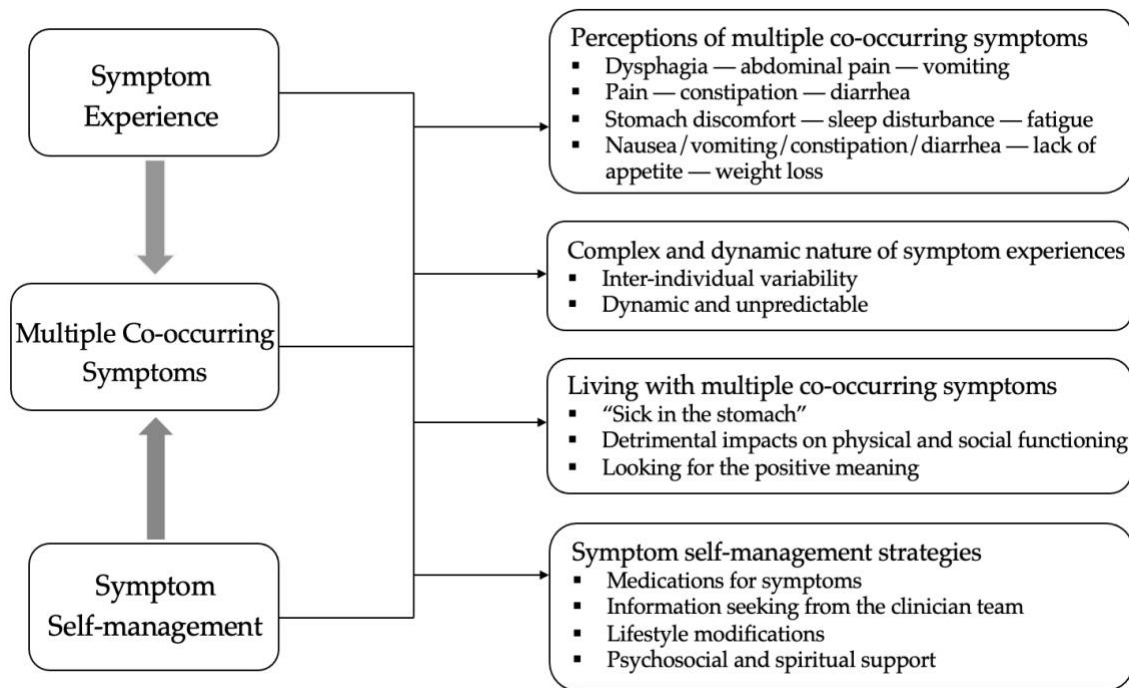
The frequency of vomiting across participants ranged from a single time to 10–15 times a day following chemotherapy. Additionally, differences were reported in eating-related symptom distress ranging from it not being an issue to being debilitating. One participant described eating as a chore and burden and reported that they experienced a lot of psychological pressure when eating. Some participants described they could eat normally and had little distress or changes with eating.

***Dynamic and unpredictable.*** Participants reported that their symptoms changed dramatically over time from diagnosis through surgery and over treatment. One young woman stated, *“In the beginning, the pain was horrible, so like nine [on a 0–10 scale] burning pain in my lower stomach, I was always hunched over, or like trying to stick my hands into [my stomach] kind of relieve it, all [the pain] went away after surgery.” (Diana, < 30)*

Participants also described symptoms that seemed to occur randomly and lacked predictability. *“I had pretty severe acid reflux, and reflux also wakes me out of my sleep, but it was just kind of come on randomly, and be so bad I had to stop what I was doing, kind of regain myself in a way, and then when I started vomiting the stomach acid, um, that’s maybe like eight or nine [score].” (Diana, < 30)*

The unpredictability of symptoms contributed to psychological symptoms, including worrying, anxiety, and depression, which negatively impacted their QOL. A

male participant reported his depressive feelings, *“It’s just worrying because not really a fix for what I have, there is no cure, so kind of sit here, doing chemo to stay alive and there is no way to tell what tomorrow brings, so kind of depressing.”* (James, 45)



**Figure 4: Study Themes and Subthemes**

### 3.3.3 Living with Multiple Co-occurring Symptoms

*“Sick in the stomach”*. We developed the theme “sick in the stomach” to capture the rich descriptions of symptom experiences that were prevalent in the data. GI symptoms were reported by all participants and were described as the worst and most distressing symptoms. A middle-aged man described his experiences with abdominal pain during his treatment. *“For me, the biggest treatable is [abdominal] pain, if I deal with the pain, that takes away a lot of things, but it brings a lot of side effects ... Because I have much*

*pain, the pain kind of distracts you from a lot of things, so that becomes your focus.” (Tom, 59)*

Another participant stated, *“The one that irritates me the most is those in the stomach. The belching, the stomach being irritable. Do you know what I mean? I get gas in the stomach, that one, if I can get rid of it, I get it to the minimal, I will do fine.” (Matt, 68).*

Additionally, half of the participants had difficulty for eating, either because of difficulty swallowing or loss of appetite, and these symptoms were associated with worry and anxiety. *“[I had] a lot [of] pressure on eating, I mean I need to eat, if I want to continue my lifestyle, I have to have enough fuel to keep my body going ... It’s just very difficult to get my body to digest what I put into it, just sometimes swallowing, just it’s difficult, very difficult.” (Claire, 70)*

***Detrimental impact on physical and social functioning.*** For many participants, multiple co-occurring symptoms had a detrimental impact on physical and social functioning. Participants were unable to engage in a number of activities that they enjoyed before cancer diagnosis. For example, one participant enjoyed playing sports with his sons, but because of fatigue, vomiting, and stomach discomfort, he lost interest in everything. Another participant was a musician, and he described a lack of desire to do the things he wanted to do. *“The most impacted I would say, it’s the spontaneity of your life. You no longer spontaneously do things because you are kind of a slave to the disease and those symptoms.” (Tom, 59)*

GI symptoms played a central role in patients' symptom experiences and these were often the symptoms that patients believed carried the most serious consequences for their daily lives and work. A participant described vomiting, *"I remember going out to the movies, going out to the restaurant, and I always have to throw up, so it was kind of hard to be in public places, with like the pain, or nausea, you can hide it, but vomiting it was more stressful being around other people... maybe like hide it from people, I don't want to disrupt like my regular life or routine."* (Diana, <30) Seventy percent of participants in this study were not employed and said they had no choice but to stay at home and decrease activities because of symptoms, mostly GI symptoms. They reduced social activities due to abdominal pain and vomiting and avoided public situations.

***Looking for the positive meaning.*** Despite the intense and disruptive experience of multiple co-occurring symptoms, the participants described a desire to look for the positive meaning in their lives. One participant took part in a non-profit organization that was aimed at helping survivors living with gastric cancer. *"We [my wife and I] are part of the organization, ... I want to help other people. Because when we found out about the stomach cancer, there is nobody to help us that knew anything about cancer. So I want to make people aware to help them with the same thing."* (James, 45). This focus on helping other people with gastric cancer appeared to come from his own challenges associated with living with gastric cancer and multiple symptoms. For this participant, finding meaning was an important source of support.

Another female participant stated, *“You do really understand is [that] cancer is not the disease that acute, it’s chronic, it’s gonna take time. You gonna have your highs, you gonna have your lows, the thing is just to stay positive, there is a light at the end of tunnel, you keep moving one foot in front of the other. And you have to expect that you will have these down times.”* (Claire, 70)

### **3.3.4 Symptom Self-management Strategies**

*Medications for symptoms.* Participants often took medications to provide symptom relief. While health care professionals prescribed the medications, the participants were responsible for taking them and often adjusted them to suit their needs. Adjustments included personalizing the type, dose, and timing of the medication. However, the participants described challenges with medication management. They took medications for pain, sleep disturbance, constipation, nausea, blood clots, depression, and anxiety, and for their cancer treatment. *“I take chemotherapy drug for two weeks, I take XARELTO for my blood clots. They’ve got me on iron and a vitamin D supplement, um I still take the Prilosec for heart burn. I take Propecia to keep the hair on my head ... I take Zofran to help with nausea, take that before I take chemotherapy drug then I haven’t gotten nauseas.”* (John, 46)

*Information-seeking from the clinician team.* Nearly all of the participants (n = 9) described the importance of asking clinicians for assistance when they encountered something new or needed to make a medical decision. They used a range of methods to

reach out to clinicians including phone calls, emails, and MyChart and adjusted their methods and frequencies of obtaining information from the clinicians. Participants found that, depending upon the advice given, they often had to follow up with the provider or search for information using other sources. *“Usually, it will be something that I look up online for answers, or deal with the MyChart, I usually won’t make medical decision on my own, and I try to find all the answers beforehand. So if I’m at home, and I’m experiencing something new, will look it up and if we can’t find the easy answer, then we will reach out [doctors] and make a phone call.” (Tom, 59)*

***Lifestyle modifications.*** Participants made changes to their lifestyles to self-manage multiple co-occurring symptoms. Most participants described adjusting their diet in order to reduce their symptoms. They altered their eating patterns, food choices, or quantity to relieve symptoms, such as dysphagia and constipation. *“I try to eat mainly vegetables, organic, or natural food, versus what I ate in prior, and I drink a lot of water, because I don’t drink a lot of water before.” (Susan, 46)*

To reduce abdominal pain, participants decreased the intake of hot and spicy foods. To manage dysphagia, individuals ate soft, bland food, such as mashed potatoes and chicken noodle soup. They cautiously evaluated their diets and made changes to obtain organic and fresh foods. Participants increased their intake of fiber-rich vegetables, fruits, and water for constipation, and they gardened or watched the television as a distraction to self-manage their fatigue.

***Psychosocial and spiritual support.*** It was another strategy used by most of participants. A 71-year-old woman who was newly diagnosed with gastric cancer said, *“I talk to them [other patients], I have a co-worker that’s in the same building with me, she was done her treatment, and there [are] other people in the organization that I work for is someone you know that having treatment, I have lots, lots of support. I have support from my family.”* (Nicole, 71) Social support as a self-management strategy includes support from a patient’s family, friends, and community.

Another woman stated, *“I’m going to tell you the type of work that I did was mental health. So I took classes, courses, and training about how to deal with patients with mental health all the time, issue and stuff like that, so I take a lot of stuff, training and stuff just put it in use, stuff that I know.”* (Kate, 40) Participants also attended church and read the Bible to obtain spiritual support.

### **3.4 Discussion**

This qualitative descriptive study of a diverse sample of patients with gastric cancer explored their experiences with multiple co-occurring symptoms and symptom self-management strategies. The findings from this study add depth and breadth to our understanding of the symptom experiences in those living with gastric cancer. In addition, the findings capture a range of self-management strategies for managing multiple co-occurring symptoms. While these findings are preliminary, they are novel

and can serve as a step toward developing personalized interventions for self-managing multiple co-occurring symptoms.

The concept of multiple co-occurring symptoms provides an important frame for intervening with patients with cancer as they rarely experience symptoms in isolation (Kim et al., 2009). In this study, we used patients' descriptions of symptoms that "occurred together" as multiple co-occurring symptoms. Four groups of multiple co-occurring symptoms were identified that appeared to influence each other, suggesting that these symptoms might occur in clusters. Our findings are consistent with several quantitative studies of patients with GI cancers that identified a GI symptom cluster that included diarrhea, nausea, constipation, and abdominal cramps (Burrell et al., 2018a; Han et al., 2019a; Han et al., 2019b). Our findings add to this literature by suggesting interconnections between symptom clusters, with GI symptoms influencing other clusters (e.g., stomach discomfort – sleep disturbance – fatigue, pain – constipation – diarrhea). Quantitative analytic approaches (e.g., exploratory factor analysis, cluster analysis, and network analysis) are needed to confirm symptom clusters based on the four groups of multiple co-occurring symptoms we identified. Future investigations would benefit from mixed methods approach to advance the science of symptom clusters research.

Compared to previous descriptive quantitative studies that described symptom experiences (e.g., occurrence, severity) in patients with gastric cancer (Hu et al., 2018;

Kim et al., 2017), our findings highlighted the inter-individual variability in patients' symptom experiences. In the era of precision health (Collins & Varmus, 2015), it is critical to understand inter-individual variability to enhance personalized symptom interventions targeted to the patients at the highest risk for multiple co-occurring symptoms. One preferable analytic approach to capturing inter-individual variability is to identify subgroups of patients based on their distinct symptom profiles (Miaskowski et al., 2014). This person-centered approach may allow identification of patients who are at risk of a higher symptom burden (Papachristou et al., 2018). Future research on the identification of inter-individual variability of symptom experiences in patients with gastric cancer warrant additional investigation. In addition, our finding lends support to the Dynamic Symptoms Model (Brant et al., 2016) that suggests that the symptom experiences of patients with gastric cancer are dynamic and changing over time. Longitudinal trajectories in both quantitative and qualitative studies should be incorporated in symptom science research to capture the dynamic nature of symptom experiences.

Individuals living with multiple co-occurring symptoms did not describe all symptoms as being of equal importance. Instead, they gave certain multiple co-occurring symptoms (e.g., GI symptoms) priority over others, based on the symptoms that patients believed carried the most serious consequences for their clinical outcomes. In our study, patients perceived multiple co-occurring symptoms as having a negative

impact on their physical and social functioning as well as QOL. This finding is consistent with published qualitative studies of multiple co-occurring symptoms in other cancer populations, such as breast cancer and lung cancer (Kim et al., 2020; Molassiotis et al., 2011). Compared to patients with lung cancer focusing on individual symptoms that are of particular importance or associated meanings (e.g., breathlessness associated with fear of death and cough associated with embarrassment in public) among multiple concurrent symptoms (Maguire et al., 2014), patients with gastric cancer sought positive meaning while living with multiple co-occurring symptoms. Taken together, these findings suggest that researchers and clinicians need to focus not only on the number and severity of symptoms, but also on the symptoms that are identified as the most bothersome and meaningful for patients with gastric cancer.

Previous studies described symptom interventions for patients with gastric cancer (e.g., alternative therapies) (Gunji et al., 2013; Guo & Wang, 2018) as well as symptom self-management strategies identified similar themes in regard to medications, lifestyle modifications, and spirituality in patients with advanced cancer (Hammer et al., 2015; Yeager et al., 2016). Our findings on self-management strategies, including information-seeking from the medical team and psychosocial support, contribute to the literature on symptom self-management. The results of our study also provide insights into the basis for the development of person-centered/oriented symptom self-management interventions, targeting those symptoms that are most bothersome to

patients and exploring their impact on physical and social functioning and providing targeted symptom interventions for patients who are at risk for a higher symptom burden. A person-centered, symptom self-management intervention is particularly imperative, because it allows for individual differences in patients' needs, treatment preferences, and distinct symptoms (Kwekkeboom et al., 2010). Additional research is required to substantiate this approach.

### **3.4.1 Limitations**

To our knowledge, this study is the first to use qualitative methods to explore the symptom experience and self-management for multiple co-occurring symptoms in patients with gastric cancer. However, the findings from this study should be interpreted with some caution. First, while ten participants with diverse experiences provided sufficient information power, the sample size in our study was small. Larger samples are needed to replicate the findings in the future. Second, we conducted one-time interviews with participants, thus there was no information on the changes in symptom experiences and self-management strategies over time. Third, there was little variability in stage of gastric cancer and treatment plans. Patients with earlier stage disease and those who have not received chemotherapy may report different symptom experiences and self-management strategies. Finally, the participants were all Caucasian and African American and thus results may not be generalizable to patients of other races or ethnicities.

### **3.4.2 Implications**

Findings from our study have three implications for researchers and clinicians. First, a qualitative method allows for in-depth descriptions of the experience and self-management of multiple co-occurring symptoms in these patients. Second, findings suggested that patients' symptom experiences were complex and dynamic. Clinicians need to assess symptoms on an ongoing basis, educate patients about multiple co-occurring symptoms, and evaluate for common underlying mechanisms. Third, clinicians and researchers need to develop and test person-centered self-management interventions on multiple co-occurring symptoms for patients with gastric cancer.

### **3.5 Conclusion**

The results of this study provide new insights into the way that patients with gastric cancer perceive and interpret their multiple co-occurring symptoms, contributing to our understanding of symptom experiences and self-management strategies in this cancer population. Such findings highlight the role that inter-individual variability and dynamics might play in patients' experiences and self-management of multiple co-occurring symptoms and thus inform the development and testing of person-centered symptom self-management interventions.

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## **4. Distinct Profiles of Multiple Co-occurring Symptoms in Patients with Gastrointestinal Cancers Receiving Chemotherapy**

### **4.1 Introduction**

In 2020, an estimated 333,680 new cases of gastrointestinal (GI) cancers will be diagnosed in the USA and 167,790 patients will die from their disease (Siegel et al., 2020). While patients with GI cancers are treated with surgery, radiation therapy (RT), targeted therapy (TT), and/or immunotherapy, chemotherapy (CTX) is one of its primary treatments. Patients with GI cancers experience 10 to 15 concurrent symptoms during CTX (Lin et al., 2020a; Tantoy et al., 2016). These multiple co-occurring symptoms can decrease patients' functional status, quality of life (QOL), and overall survival (Bailey et al., 2015; Walker et al., 2012; Wu et al., 2015).

Previous studies of multiple co-occurring symptoms in patients with GI cancers have focused on an evaluation of multiple dimensions of the symptom experience and the identification of symptom clusters. In a study that compared differences in symptom experiences between patients with GI cancers who received CTX with and without TT (Tantoy et al., 2017), those who received CTX alone reported higher symptom occurrence rates for lack of energy, cough, feeling drowsy, and difficulty sleeping, and higher severity scores for dry mouth and change in the way food tastes. In another study that evaluated for changes in patients' symptom experiences (Tantoy et al., 2018), while

the occurrence rates for pain, lack of energy, feeling drowsy, difficulty sleeping, and change in the way food tastes declined over two cycles of CTX, severity and distress scores showed more complex patterns. In a series of reports from one longitudinal study of 120 patients with colorectal cancer (Rohrl et al., 2016; Rohrl et al., 2019; Rohrl et al., 2020), patients reported an average of 10 symptoms; no differences were found in the symptom experiences of patients who received curative compared to palliative CTX; and a higher symptom burden was associated with poorer QOL.

In terms of symptom clusters, in two studies of patients with GI cancers undergoing CTX (Han et al., 2019a; Han et al., 2019b), a total of five symptom clusters (i.e. psychological distress, CTX-related, GI, weight change, and epithelial) were identified over one cycle of CTX. While these studies provide some evidence about multiple co-occurring symptoms and symptom clusters, none of them used a person-centered approach (e.g., latent variable modeling (Jung & Wickrama, 2008)) to describe inter-individual variability in the symptom experience of patients with GI cancers.

Latent class analysis (LCA) allows for the identification of homogeneous subgroups of patients (i.e., latent classes) with distinct symptom profiles (Kongsted & Nielsen, 2017).

To date, only four studies have used LCA to identify subgroups of oncology patients based on their reports of symptom occurrence using the Memorial Symptom Assessment Scale (MSAS) (Astrup et al., 2017; Miaskowski et al., 2014; Miaskowski et al., 2015; Papachristou et al., 2018). Across these four studies, sample sizes ranged from 534

(Astrup et al., 2017) to 1329 (Papachristou et al., 2018b); cancer diagnoses were heterogeneous; cancer treatments included: only CTX (Miaskowski et al., 2014; Papachristou et al., 2018), only RT (Astrup et al., 2017), and CTX and/or RT (Miaskowski et al., 2015). While the number of latent classes ranged from 3 (Miaskowski et al., 2014) to 4 (Astrup et al., 2017; Miaskowski et al., 2015; Papachristou et al., 2018), across all four studies, All Low and All High classes were identified. The number of symptoms in the All Low class ranged from 3.9 (Miaskowski et al., 2015) to 6.7 (Papachristou et al., 2018) and in the All High class from 20.3 (Miaskowski et al., 2015) to 20.6 (Papachristou et al., 2018). Consistent risk factors associated with membership in the All High class were: younger age, a higher level of comorbidity, and a lower functional status. In addition, membership in the All High class was associated with poorer QOL outcomes. While an All Low and an All High class and some common risk factors were identified across all four studies, the number of classes and risk factors associated with a higher symptom burden were inconsistent. These inconsistent findings may be attributed to differences in sample sizes, as well as heterogeneity in cancer diagnoses and treatments. Therefore, additional studies are warranted with more homogenous samples, particularly in terms of cancer diagnoses to identify subgroups of patients with distinct symptom profiles and associated risk factors.

Given that no studies were identified that used a person-centered approach to evaluate for symptom profiles in patients with GI cancers, the purposes of this study

were to identify subgroups of these patients based on their distinct experiences with multiple co-occurring symptoms and evaluate for differences among these subgroups in demographic and clinical characteristics and QOL outcomes.

## **4.2 Methods**

### **4.2.1 Patients and Settings**

This cross-sectional study was part of a prospective longitudinal study of symptom clusters in oncology outpatients who received CTX (Wright et al., 2019). Eligible patients for the parent study: were  $\geq 18$  years of age; 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. A total of 2,234 patients were approached and 1,343 consented to participate (60.1% response rate) in the parent study. The major reason for refusal was being overwhelmed with their cancer treatment. For this study, only patients with GI cancers ( $n = 399$ ) were included. The main types of GI cancers included colon (45.6%), rectal (19.8%), pancreatic (18.3%), esophageal (5.3%), and gastric (4.9%).

### 4.2.2 Instruments

A demographic questionnaire was used to obtain information on age, gender, ethnicity, marital status, living arrangements, education, employment status, and income. Medical records were reviewed for disease and treatment information. Patients rated their functional status using the Karnofsky Performance Status (KPS) scale that ranged from 30 (I feel severely disabled and need to be hospitalized) to 100 (I feel normal; I have no complaints or symptoms) (Karnofsky et al., 1977). The Self-administered Comorbidity Questionnaire (SCQ) evaluated the occurrence, treatment, and functional impact of 13 common comorbid conditions (e.g., diabetes, arthritis). Patients indicated if they had the condition; if they received treatment for it (proxy for disease severity) and if it limited their activities (indication of functional limitations). For each condition, the patient can receive a maximum of 3 points. The total SCQ score ranges from 0 to 39. The SCQ has well-established validity and reliability (Sangha et al., 2003).

The 10-item Alcohol Use Disorders Identification Test (AUDIT) assesses alcohol consumption, alcohol dependence, and the consequences of alcohol abuse in the last 12 months. The AUDIT gives a total score that ranges between 0 and 40. Scores of  $\geq 8$  are defined as hazardous use and scores of  $\geq 16$  are defined as use of alcohol that is likely to be harmful to health. The AUDIT has well established validity and reliability (Babor et al., 2001).

A modified version of the MSAS was used to evaluate the occurrence, severity, frequency, and distress of 38 symptoms commonly associated with cancer and its treatment. In addition to the original 32 MSAS symptoms, the following six symptoms were assessed: hot flashes, chest tightness, difficulty breathing, abdominal cramps, increased appetite, and weight gain (Portenoy et al., 1994). Using the MSAS, patients were asked to indicate whether or not they had experienced each symptom in the past week (i.e., symptom occurrence). The validity and reliability of the MSAS are well established in studies of oncology inpatients and outpatients (Portenoy et al., 1994).

Quality of life (QOL) was evaluated using disease specific (i.e., Quality of Life Scale-Patient Version [QOL-PV]) and generic (i.e., Medical Outcomes Study-Short Form-12 [SF-12]) measures. The QOL-PV is a 41-item instrument that assesses four dimensions of QOL (i.e., physical, psychological, social and spiritual well-being) in cancer patients, as well as a total QOL score. Each item was rated on a 0 to 10 numeric rating scale (NRS) with higher scores indicating a better QOL. The QOL-PV has established validity and reliability (Padilla et al., 1990). The SF-12 consists of 12 questions about physical and mental health as well as overall health status. The individual items on the SF-12 are evaluated and the instrument is scored into two components, namely a physical component summary (PCS) score and a mental component summary (MCS) score. These scores can range from 0 to 100. Higher PCS and MCS scores indicate a better QOL. The SF-12 has well established validity and reliability (Ware et al., 1996).

### **4.2.3 Study Procedures**

The parent study was approved by the Committee on Human Research at the University of California, San Francisco, by the Institutional Review Board (IRB) at each of the study sites, and by the IRB of Duke University. Eligible patients were approached by a research staff member in the infusion unit, during their first or second cycle of CTX, to discuss participation in the study. Written informed consent was obtained from all patients. Patients completed the questionnaires in their home and returned them in a postage paid envelope prior to their second or third cycle of CTX (i.e., enrollment assessment).

### **4.2.4 Data Analysis**

LCA was used to identify subgroups of patients (i.e., latent classes) with distinct experiences of multiple co-occurring symptoms based on patients' ratings of symptom occurrence (Nylund et al., 2007). LCA was performed using Mplus™, version 8 (Muthen & Muthen, 2020). In order to have a sufficient number of patients with each symptom to perform the LCA, the MSAS symptoms that occurred in  $\geq 15\%$  and  $\leq 85\%$  of the patients was used to identify the distinct latent classes. For these binary outcomes, all of the data were complete and estimation was carried out using robust maximum-likelihood with a logit link and the expectation maximization algorithms (Muthen & Shedden, 1999). The optimal number of latent classes was selected based on the Bayesian Information Criterion (BIC), and the Vuong, Lo, Mendel, and Rubin (VLMR) likelihood ratio test

(Muthen & Shedden, 1999). The optimal fitting model should “make sense” conceptually and its classes should differ as might be expected on variables not used in the generation of the model (Kim, 2014).

Descriptive statistics and frequency distributions were calculated for demographic and clinical characteristics and QOL outcomes using SPSS, version 23 (IBM Corporation, Armonk, NY). For each analytic approach, differences in demographic, clinical, and symptom characteristics and QOL outcomes, among the subgroups, were evaluated using analyses of variance (ANOVA), Kruskal-Wallis, and chi-square analyses. Post hoc contrasts were calculated using the Bonferroni corrected alpha based on the number of latent classes identified (i.e.,  $0.05/3 = 0.017$ ).

## **4.3 Results**

### **4.3.1 Results of LCA**

The fit indices for the candidate models are shown in Table 4. The 3-class solution was selected because its BIC was lower than 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. The VLMR was not significant for the 4-class solution, indicating that too many classes were extracted.

**Table 4: Latent Profile Solutions and Fit Indices for One Through Four Class Solutions**

Model	LL	AIC	BIC	Entropy	VLMR
1 Class	-8186.84	16441.67	16577.30	n/a	n/a
2 Class	-7523.11	15184.21	15459.45	.88	1327.46 <sup>+</sup>
3 Class <sup>a</sup>	-7378.19	14964.39	15379.24	.86	289.83 <sup>*</sup>
4 Class	-7288.16	14854.32	15408.79	.86	180.07 <sup>ns</sup>

Baseline LL is not applicable for the one class solution

\*p < .05; +p < .00005

<sup>a</sup>The three class solution was selected because the BIC for that solution was lower than the BIC for 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 were extracted.

Abbreviations: AIC = Akaike's 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

As shown in Figure 5, the three classes were named based on the probability of occurrence of the 34 MSAS symptoms that occurred in  $\geq 15\%$  and  $\leq 85\%$  of the patients. The All Low class consisted of 36.6% (n = 146) of the sample who reported relatively low occurrence rates for most of the symptoms. The Moderate class was the largest and consisted of 49.4% (n = 197) of the sample who reported moderate occurrence rates for the majority of the MSAS symptoms. The All High class was the smallest with 14.0% (n = 56) of the sample who reported high occurrence rates for the majority of the symptoms.

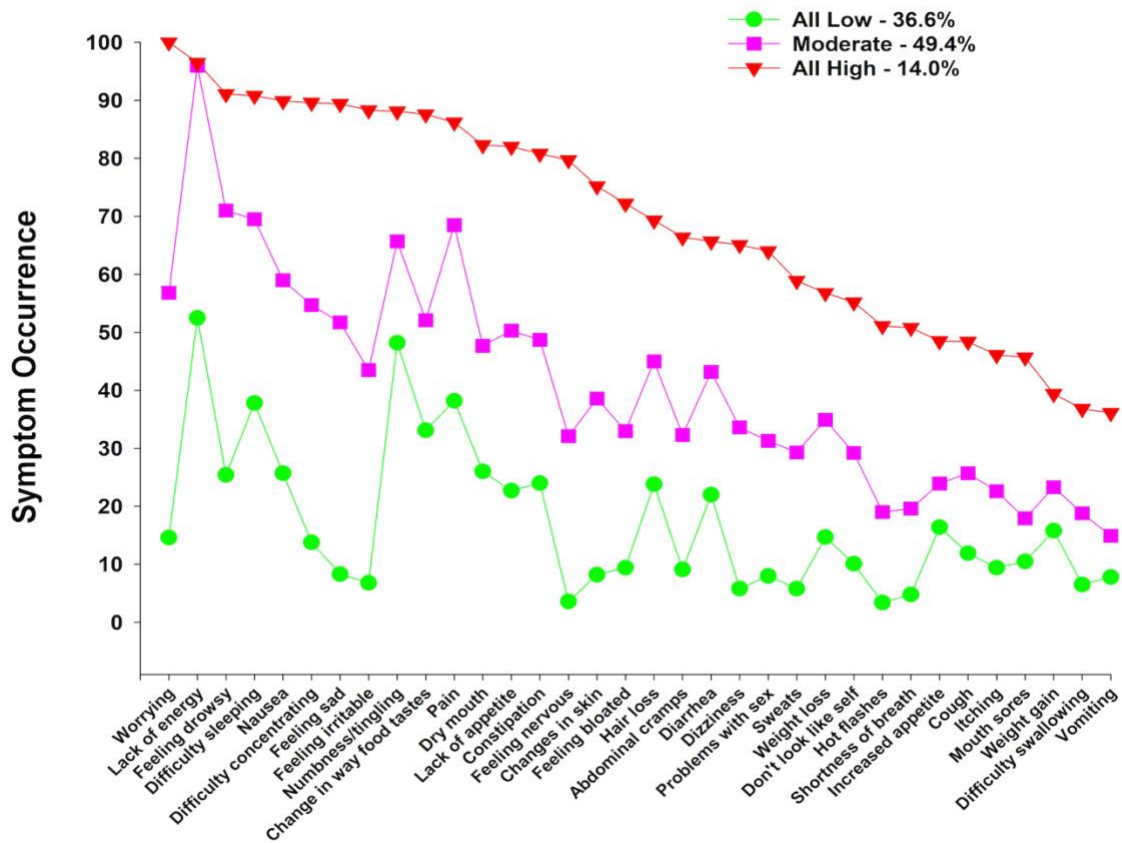


Figure 5: Symptom Occurrence for Each Latent Class Analysis for Multiple Co-occurring Symptoms

### 4.3.2 Differences in Demographic and Clinical Characteristics

Table 5 summarizes the differences in demographic and clinical characteristics among the three classes. Compared to the All Low class, patients in the other two classes were significantly younger and were more likely to report depression and back pain. Compared to the other two classes, patients in the All High class had fewer years of education and a higher number of comorbidities. Significant differences were found among the three classes for KPS scores (i.e., All Low > Moderate > All High), as well as

for SCQ scores, female representation, and total number of MSAS symptoms (i.e., All Low < Moderate < All High).

### **4.3.3 Rank Order of Symptom Occurrence**

For each class, the ten symptoms with the highest occurrence rates are listed in Table 6. Six of these symptoms were reported by all three classes, namely: lack of energy, difficulty sleeping, feeling drowsy, nausea, numbness or tingling in hands or feet, and change in the way food tastes. Worrying was reported by 100% of the patients in the All High class. Lack of energy had the highest occurrence rate in both the All Low and Moderate classes.

### **4.3.4 Differences in QOL Outcomes**

As shown in Table 7, for the QOL-PV, except for the spiritual well-being subscale, all of the subscale and total scores followed the expected pattern (i.e., All Low > Moderate > All High). For the PCS score of the SF-12, compared to the All Low class, patients in the other two classes had significantly lower scores. For the MCS scores, the differences among the three classes followed the expected pattern (i.e., All Low > Moderate > All High).

**Table 5: Differences in Demographic and Clinical Characteristics Among the Patient Subgroups with Distinct Symptom Profiles**

Characteristic	All Low (0) 36.6% (n=146)	Moderate (1) 49.4% (n=197)	All High (2) 14.0% (n=56)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	
Age (years)	61.2 (10.9)	57.0 (11.9)	53.8 (11.4)	F=9.92, p<0.001 0 > 1 and 2
Education (years)	16.1 (3.2)	16.4 (2.9)	14.8 (3.0)	F=5.94, p=0.003 0 and 1 > 2
Body mass index (kg/m <sup>2</sup> )	25.6 (4.9)	26.0 (5.5)	25.1 (5.0)	F=0.78, p=0.458
Karnofsky Performance Status score	87.1 (9.9)	79.2 (11.9)	70.2 (11.5)	F=46.31, p<0.001 0 > 1 > 2
Number of comorbidities	2.1 (1.3)	2.3 (1.3)	2.9 (1.6)	F=6.04, p=0.003 0 and 1 < 2
SCQ score	4.6 (2.6)	5.5 (2.8)	6.7 (3.8)	F=10.82, p<0.001 0 < 1 < 2
Time since cancer diagnosis (years)	1.4 (2.4)	1.5 (3.2)	1.4 (2.4)	KW=0.50, p=0.780
Time since diagnosis (median)	0.40	0.45	0.43	
Number of prior cancer treatments	1.2 (1.2)	1.4 (1.4)	1.6 (1.3)	F=1.95, p=0.144
Number of metastatic sites including lymph node involvement	1.5 (1.1)	1.5 (1.1)	1.4 (1.1)	F=0.24, p=0.791
Number of metastatic sites excluding lymph node involvement	1.0 (1.0)	1.0 (1.0)	0.8 (0.9)	F=0.72, p=0.485
AUDIT score	3.6 (2.3)	3.3 (3.2)	2.9 (3.0)	F=0.68, p=0.506
MAX2	0.14 (0.16)	0.14 (0.06)	0.14 (0.05)	F=0.11, p=0.899
Total number of MSAS symptoms (out of 32)	5.5 (2.6)	13.3 (3.1)	22.2 (3.1)	F=735.33, p<0.001 0 < 1 < 2
Total number of MSAS symptoms (out of 38)	6.0 (2.8)	14.6 (3.3)	25.1 (4.0)	F=753.64, p<0.001 0 < 1 < 2

Characteristic	All Low (0)	Moderate (1)	All High (2)	Statistics
	36.6% (n=146)	49.4% (n=197)	14.0% (n=56)	
	% (n)	% (n)	% (n)	
Female	30.8 (44)	48.5 (95)	69.6 (39)	$X^2=26.39$ , $p<0.001$ $0 < 1 < 2$
Ethnicity				$X^2=14.73$ , $p=0.022$
White	67.9 (93)	72.4 (139)	51.9 (28)	$1 > 2$
Asian or Pacific Islander	10.9 (15)	10.4 (20)	16.7 (9)	NS
Black	13.1 (18)	6.8 (13)	9.3 (5)	NS
Hispanic Mixed or Other	8.0 (11)	10.4 (20)	22.2 (12)	$0 < 2$
Married or partnered (% yes)	70.9 (100)	64.4 (125)	69.6 (39)	$X^2=1.70$ , $p=0.427$
Lives alone (% yes)	19.3 (27)	19.5 (38)	16.1 (9)	$X^2=0.35$ , $p=0.840$
Childcare responsibilities (% yes)	17.5 (24)	19.4 (37)	33.9 (19)	$X^2=6.98$ , $p=0.030$
				No significant pairwise contrasts
Adult care responsibilities (% yes)	4.6 (6)	8.9 (16)	7.8 (4)	$X^2=2.14$ , $p=0.344$
Currently employed (% yes)	36.4 (51)	34.7 (67)	27.3 (15)	$X^2=1.50$ , $p=0.472$
Income				
< \$30,000+	18.5 (23)	19.3 (35)	29.4 (15)	
\$30,000 to <\$70,000	19.4 (24)	21.0 (38)	13.7 (7)	$KW=1.42$ , $p=0.491$
\$70,000 to < \$100,000	15.3 (19)	17.7 (32)	17.6 (9)	
> \$100,000	46.8 (58)	42.0 (76)	39.2 (20)	
Specific comorbidities (% yes)				
Heart disease	4.9 (7)	5.1 (10)	5.4 (3)	$X^2=0.02$ , $p=0.991$
High blood pressure	38.5 (55)	30.6 (60)	32.1 (18)	$X^2=2.35$ , $p=0.309$
Lung disease	5.6 (8)	4.1 (8)	12.5 (7)	$X^2=5.65$ , $p=0.059$
Diabetes	16.1 (23)	10.7 (21)	14.3 (8)	$X^2=2.16$ , $p=0.340$
Ulcer or stomach disease	3.5 (5)	6.6 (13)	7.1 (4)	$X^2=1.85$ , $p=0.396$
Kidney disease	1.4 (2)	0.5 (1)	5.4 (3)	$X^2=6.86$ , $p=0.032$
				No significant pairwise contrasts
Liver disease	11.2 (16)	9.7 (19)	19.6 (11)	$X^2=4.24$ , $p=0.120$

Characteristic	All Low (0) 36.6% (n=146)	Moderate (1) 49.4% (n=197)	All High (2) 14.0% (n=56)	Statistics
	% (n)	% (n)	% (n)	
Anemia or blood disease	5.6 (8)	9.2 (18)	17.9 (10)	$\chi^2=7.36$ , $p=0.012$ $0 < 2$
Depression	5.6 (8)	18.4 (36)	23.2 (13)	$\chi^2=15.00$ , $p=0.001$ $0 < 1$ and $2$
Osteoarthritis	7.7 (11)	10.7 (21)	10.7 (6)	$\chi^2=0.96$ , $p=0.619$
Back pain	11.2 (16)	25.0 (49)	37.5 (21)	$\chi^2=18.74$ , $p<0.001$ $0 < 1$ and $2$
Rheumatoid arthritis	2.8 (4)	2.6 (5)	1.8 (1)	$\chi^2=0.17$ , $p=0.920$
Exercise on a regular basis (% yes)	66.4 (95)	70.6 (137)	55.6 (30)	$\chi^2=4.37$ , $p=0.113$
Current or history of smoking (% yes)	31.4 (44)	32.1 (61)	29.6 (16)	$\chi^2=0.12$ , $p=0.942$
Type of prior cancer treatment				
No prior treatment	31.9 (45)	30.2 (57)	18.2 (10)	
Only surgery, CTX, or RT	36.2 (51)	38.1 (72)	43.6(24)	$\chi^2=4.04$ , $p=0.671$
Surgery & CTX, or Surgery & RT, or CTX & RT	22.0 (31)	20.6 (39)	25.5 (14)	
Surgery & CTX & RT	9.9 (14)	11.1 (21)	12.7 (7)	
Colon and rectal cancer (% yes)	62.7 (89)	63.1 (123)	67.3 (37)	$\chi^2=0.39$ , $p=0.821$
CTX regimen				
FOLFIRI	13.7 (20)	13.2 (26)	16.1 (9)	$\chi^2=2.19$ , $p=0.902$
FOLFOX	41.8 (61)	43.1 (85)	48.2 (27)	
FOLFIRINOX	10.3 (15)	12.2 (24)	7.1 (4)	
Other	34.2 (50)	31.5 (62)	28.6 (16)	
CTX cycle length				
14 day	80.1 (117)	83.7 (164)	87.5 (49)	$\chi^2=2.53$ , $p=0.639$
21 day	15.8 (23)	14.3 (28)	10.7 (6)	
28 day	4.1 (6)	2.0 (4)	1.8 (1)	

Characteristic	All Low (0) 36.6% (n=146)	Moderate (1) 49.4% (n=197)	All High (2) 14.0% (n=56)	Statistics
	% (n)	% (n)	% (n)	
<b>Emetogenicity of CTX</b>				
Minimal/low	13.7 (20)	16.2 (32)	12.5 (7)	X <sup>2</sup> =3.35, p=0.502
Moderate	80.8 (118)	81.2 (160)	85.7 (48)	
High	5.5 (8)	2.5 (5)	1.8 (1)	
<b>Antiemetic regimens</b>				
None	5.6 (8)	4.7 (9)	7.1 (4)	X <sup>2</sup> =7.22, p=0.301
Steroid alone or serotonin receptor antagonist alone	9.2 (13)	11.9 (23)	10.7 (6)	
Serotonin receptor antagonist and steroid	69.7 (99)	57.5 (111)	60.7 (34)	
NK-1 receptor antagonist and two other antiemetics	15.5 (22)	25.9 (50)	21.4 (12)	

Abbreviations: AUDIT = Alcohol Use Disorders Identification Test, CTX = chemotherapy, dl = deciliter; FOLFIRI = leucovorin/5-fluorouracil/irinotecan, FOLFIRINOX = leucovorin/5-fluorouracil/irinotecan/oxaliplatin, FOLFOX = leucovorin/5-fluorouracil/oxaliplatin, gm = grams; kg = kilograms, m<sup>2</sup> = meter squared, min = minutes, NK-1 = neurokinin 1NS = not significant, RT = radiation therapy, SCQ = Self-Administered Comorbidity Questionnaire, SD = standard deviation, MSAS = Memorial Symptom Assessment Scale

**Table 6: Ten Symptoms with the Highest Occurrence Rates Among the Patient Subgroups**

Rank	All Low (0) 36.6% (n=146)		Moderate (1) 49.4% (n=197)		All High (2) 14.0% (n=56)	
	Symptom	%	Symptom	%	Symptom	%
1	Lack of energy	52.5	Lack of energy	96.0	Worrying	100.0
2	Numbness/tingling in hands/feet	48.2	Feeling drowsy	71.0	Lack of energy	96.5
3	Pain	38.2	Difficulty sleeping	69.5	Feeling drowsy	91.1
4	Difficulty sleeping	37.8	Pain	68.5	Difficulty sleeping	90.8
5	Change in the way food tastes	33.1	Numbness/tingling in hands/feet	65.7	Nausea	89.9
6	Dry mouth	26.0	Nausea	59.0	Difficulty concentrating	89.6
7	Nausea	25.7	Worrying	56.8	Feeling sad	89.4
8	Feeling drowsy	25.4	Difficulty concentrating	54.7	Feeling irritable	88.3
9	Constipation	24.0	Change in the way food tastes	52.1	Numbness/tingling in hands/feet	88.1
10	Hair loss	23.8	Feeling sad	51.7	Change in the way food tastes	87.6

**Table 7: Differences in QOL Scores Among the Patient Subgroups with Distinct Symptom Profiles**

QOL Scores	All Low (0) 36.6% (n=146)	Moderate (1) 49.4% (n=197)	All High (2) 14.0% (n=56)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	
<b>Multidimensional Quality of Life Scale- Patient Version</b>				
Physical well-being	8.0 (1.4)	6.4 (1.6)	5.1 (1.8)	F=79.60, p<0.001 0 > 1 > 2
Psychological well-being	7.0 (1.5)	5.4 (1.6)	4.5 (1.4)	F=71.43, p<0.001 0 > 1 > 2
Social well-being	7.0 (1.7)	5.3 (1.8)	4.4 (1.7)	F=55.90, p<0.001 0 > 1 > 2
Spiritual well-being	5.4 (2.2)	5.0 (2.0)	5.7 (2.0)	F=2.80, p=0.062
Total QOL score	6.9 (1.1)	5.5 (1.2)	4.8 (1.3)	F=80.95, p<0.001 0 > 1 > 2
<b>Medical Outcomes Study- Short Form 12</b>				
Physical Component Summary score	46.0 (9.5)	40.0 (10.1)	37.0 (10.0)	F=21.91, p<0.001 0 > 1 and 2
Mental Component Summary score	54.7 (7.3)	47.6 (9.0)	42.6 (11.2)	F=42.85, p<0.001 0 > 1 > 2

Abbreviations: QOL = quality of life, SD = standard deviation

## 4.4 Discussion

This study is the first to identify subgroups of patients with GI cancers with distinct symptom profiles and evaluate for differences in demographic and clinical characteristics as well as QOL outcomes among these subgroups. In our study, 63.4% of the patients had a moderate to high symptom burden prior to their second or third cycle of CTX, namely a time of recovery from the previous cycle. The percentages of patients in our All Low (36.6%) and All High (14.7%) classes are consistent with previous studies of patients with heterogeneous types of cancers (i.e., 28.0% (Miaskowski et al., 2015) to 36.1% (Miaskowski et al., 2014) for the All Low and 13.4% (Papachristou et al., 2018) to 27.8% (Astrup et al., 2017) for the All High classes). These findings suggest that regardless of the cancer diagnosis, a subgroup of oncology patients is at higher risk for an extremely high symptom burden.

In terms of the mean number of symptoms, our findings are consistent with previous LCA studies that found that the All Low classes reported between 3.9 (Miaskowski et al., 2015) to 6.3 (Papachristou et al., 2018) symptoms and that the All High classes reported between 20.3 (Miaskowski et al., 2015) to 26.1 (Papachristou et al., 2018) symptoms. It should be noted that in two reviews of symptoms in patients with gastric (median 7, range 3 to 17) (Lin et al., 2020a) and colorectal (mean 10.3, range 0 to 32) (Tantoy et al., 2016) cancers, the mean number and range of symptoms suggest a high degree of inter-individual variability exists in symptom occurrence rates that is

primarily dependent on the number of symptoms included in the instrument. Taken together, these findings suggest that the calculation of an arithmetic mean will underestimate the symptom burden of patients with GI cancers.

While these findings suggest that clinicians need to perform a comprehensive assessment of the patient's symptom experience using an instrument like the MSAS, the findings in Table 6 provide information to guide an initial and focused assessment. Our findings regarding the ten most frequently occurring symptoms across the three latent classes is consistent with the findings from a systematic review (Tantoy et al., 2016) and two studies of patients with colorectal cancer that used the MSAS (Pettersson et al., 2014; Rohrl et al., 2019). It is not surprising that numbness and tingling was reported by 48.2% to 88.1% of our patients given that the majority of them received a CTX regimen that contained oxaliplatin (Kang et al., 2020). Fatigue was the first or second most common symptom among our three latent classes which is consistent with previous reports of occurrence rates of between 60% and 90% (Thong et al., 2020). While not assessed as frequently as fatigue (Savard & Morin, 2001), sleep disturbance was reported by 37.8% to 90.8% of our patients. Equally important because of their potential negative impact on adherence with the treatment regimen (Theofilou & Panagiotaki, 2012), functional status (Gonzalez-Saenz de Tejada et al., 2017), and QOL (Zhou et al., 2005), the high rates of worrying and feeling sad in our Moderate and All High classes warrant evaluation by clinicians and the initiation of appropriate referrals. In terms of GI symptoms, across the

two reviews (Lin et al., 2020a; Tantoy et al., 2016) and consistent with our findings, nausea occurred in 25.7% to 89.9% of our patients. However, while reported as frequently occurring symptoms (Lin et al., 2020a; Tantoy et al., 2016), diarrhea and abdominal pain were not in our top ten list of symptoms. Reasons for these differences may be related to when the assessments were done during the course of a patient's disease trajectory (e.g., during CTX versus postoperatively)

One of the major advantages of using a person-centered approach like LCA, to evaluate the symptom burden of patients with GI cancers, is that one can identify salient demographic and clinical characteristics that place patients at increased risk for a higher symptom burden. Clinicians can use these findings to risk profile patients; conduct more detailed symptom assessments, and target more intense symptom management interventions and/or referrals for specific patients. Consistent with previous reports (Astrup et al., 2017; Miaskowski et al., 2014), patients in our Moderate and All High classes were significantly younger. Possible explanations for this finding include: younger patients may receive higher doses of CTX (Kumar et al., 2007); age-related decreases in an individual's response to stress may predispose older adults to experience fewer or less severe symptoms (Bower et al., 2008; Gaffey et al., 2016); and/or older patients may experience a "response shift" in their perception of symptoms (Sprangers & Schwartz, 1999). While results are inconsistent regarding gender differences in symptom burden in oncology patients (Astrup et al., 2017; Pud et al.,

2008), in our study, women were more likely to be in the All High class. Previous inconsistencies were attributed to differences in the relative proportion of male and female patients in previous studies and/or the heterogeneity in the treatment regimens. However, it should be noted that GI cancers occur relatively equally in men and women (Siegel et al., 2019). Therefore, our findings may reflect meaningful gender-related differences in symptom burden.

While previous studies found that patients in the All High class were less likely to be married/partnered (Miaskowski et al., 2014) and more likely to be unemployed (Hockenberry et al., 2017) and have a lower annual household income (Akin et al., 2010; Miaskowski et al., 2014), in our study, only being non-White and having a lower level of education were associated with a higher symptom burden. While social determinants of health are known to influence risk of, treatment for, and survival from GI cancer (Ashktorab et al., 2017; Carethers & Doubeni, 2020; Coughlin, 2020), additional research is warranted on how these characteristics individually and collectively influence the symptom burden of these patients.

Consistent with previous studies (Papachristou et al., 2018; Wright et al., 2017), as symptom burden increased, patients reported higher levels of comorbidity and poorer functional status. In terms of specific comorbidities, almost 20% of the patients in the Moderate and All High classes reported a clinical diagnosis of depression and at least 25% reported a diagnosis of back pain. In addition, 18% of the patients in the All

High class reported anemia. All three of these co-occurring comorbidities can contribute to decrements in functional status. It should be noted that compared to the All Low class, the decreases in KPS scores reported by patients in the other two classes represent not only statistically significant but clinically meaningful decrements in physical function (i.e.,  $d = 0.6$  to  $1.4$ ) (Osoba, 1999). These findings suggest that these patients with relatively high levels of comorbidity and substantial decrements in physical function would benefit from referrals to physical therapy. While across two reviews (Lin et al., 2020a; Tantoy et al., 2016), more advanced disease was associated with a higher symptom burden, in our study and consistent with previous reports (Papachristou et al., 2018; Pud et al., 2008), none of the other disease or treatment characteristics (i.e., time since cancer diagnosis, MAX 2 score, CTX regimen) were associated with a high symptom burden. Additional research is warranted to determine the phenotypic and molecular characteristics that contribute to a higher symptom burden in these patients.

In terms of QOL outcomes, except for the spiritual well-being scale of the QOL-PV and the PCS score of the SF-12, as symptom burden increased, decrements in QOL decreased and these decreases represent clinically meaningful decrements ( $d = 0.2$  to  $1.3$ ). Consistent with the KPS scores, for the generic measure of QOL (i.e., SF-12) patients in all three classes reported PCS scores of  $<50$  which is lower than the normative score for the general population. In addition, for the Moderate and All High classes the same trend was observed for the MCS scores. Consistent with previous LCA studies (Astrup

et al., 2017; Miaskowski et al., 2014; Miaskowski et al., 2015; Papachristou et al., 2018) and descriptive studies of patients with GI cancers (Tantoy et al., 2018; Yu et al., 2016), a higher symptom burden was associated with clinically meaningful decrements in QOL.

#### **4.4.1 Limitations**

Our study has some limitations. First, because this study was cross-sectional, future studies need to use latent transition analysis to determine the stability of these patients' latent class symptom profiles (Miaskowski et al., 2017). Second, given that the majority of the patients were White and well-educated, our findings may not generalize to more diverse patient samples. Third, 64% of our patients were diagnosed with colorectal cancer. While no differences were found among the latent classes in the occurrence rates of colorectal versus other cancers, future studies need to perform similar evaluations of patients with specific GI cancers (e.g., gastric, pancreatic, liver).

#### **4.5 Conclusion**

Despite these limitations, this study is the first to identify subgroups of patients with GI cancers based on distinct multiple co-occurring symptom profiles and identify risk factors associated with a higher symptom burden. Based on the high symptom burden identified in most of these patients, clinicians can begin their assessment with the top ten most frequently co-occurring symptoms, evaluate additional symptoms as warranted using an instrument like the MSAS, and initiate appropriate and personalized symptom management interventions and referrals.

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Lin, Y., Bailey, D. E., Jr., Docherty, S. L., Porter, L. S., Cooper, B. A., Paul, S. M., Kober, K. M., Hammer, M. J., Wright, F., Dunn, L. B., Conley, Y. P., Levine, J. D., & Miaskowski, C. (2021). Distinct profiles of multiple co-occurring symptoms in patients with gastrointestinal cancers receiving chemotherapy. *Supportive Care in Cancer*. Advance online publication. doi: 10.1007/s00520-020-05946-4

## **5. Distinct Morning and Evening Fatigue Profiles in Patients with Gastrointestinal Cancers Receiving Chemotherapy**

### **5.1 Introduction**

While fatigue is the most common symptom reported by oncology patients during chemotherapy (Bower, 2014), less is known about its occurrence, severity, and impact in patients with gastrointestinal (GI) cancers. Findings suggest that in these patients, fatigue occurrence rates range from 62.0% (Pettersson et al., 2014) to 83.3% (Tantoy et al., 2017) and that severity scores range from 2.03 (Rohrl et al., 2016) to 2.16 (Tantoy et al., 2017) using the 1 to 4 scale on the Memorial Symptom Assessment Scale (MSAS). In a longitudinal study of 21 patients with colorectal cancer (Berger et al., 2010), mean fatigue severity scores were in the mild range prior to and increased to moderate levels over the course of three cycles of chemotherapy. These findings suggest that a significant number of patients with GI cancers report mild to moderate levels of fatigue during chemotherapy.

In two studies of patients with GI cancers (Tantoy et al., 2017; Tantoy et al., 2018), younger age, a longer time from cancer diagnosis, receipt of a higher number of cancer treatments, and receipt of FOLFIRINOX (i.e., leucovorin/5-fluorouracil/irinotecan /oxaliplatin) were associated with higher fatigue occurrence rates. For patients with colorectal cancer, younger age, female gender, and receipt of surgery contributed to a higher occurrence of fatigue (Han et al., 2020). In terms of associations between fatigue

and co-occurring symptoms, cognitive dysfunction (Vardy et al., 2016), depressive symptoms (Mota et al., 2012; Vardy et al., 2016; Wright et al., 2015), sleep disturbance (Mota et al., 2012; Wright et al., 2015), and pain (Tantoy et al., 2016) were associated with higher occurrence rates. Fatigue has a negative impact on patients' quality of life (QOL) (Tantoy et al., 2018; Vardy et al., 2016) and decreases their ability to tolerate chemotherapy (Dimsdale et al., 2007; Molassiotis & Chan, 2004). While these studies provided important information on fatigue in patients with GI cancers, several limitations warrant consideration. First, only two studies evaluated for changes over time in fatigue severity in patients with GI cancers receiving chemotherapy (Rohrl et al., 2019; Tantoy et al., 2018). Second, only three studies identified risk factors for higher levels of fatigue (Han et al., 2020; Tantoy et al., 2017; Tantoy et al., 2018). In addition, none of these studies used a person-centered analytic approach to evaluate for distinct fatigue severity profiles in patients with GI cancers.

Because fatigue severity varies markedly over the course of a day (Abid et al., 2017), an emerging area of research is an evaluation of diurnal variability in fatigue (Kober et al., 2016; Lerdal et al., 2011). Work by our team demonstrated that morning and evening fatigue are distinct symptoms both in terms of risk factors and trajectories (Dhruva et al., 2013; Wright et al., 2017). For example, in one study of patients undergoing chemotherapy (Wright et al., 2015), risk factors associated with higher levels of morning fatigue included: younger age, higher body mass index (BMI), and lack of

regular exercise. To date, no studies have evaluated for diurnal variations in fatigue severity in patients with GI cancers. Therefore, the purposes of this study were to identify subgroups of patients with GI cancers with distinct morning and evening fatigue severity profiles and evaluate for differences among these subgroups in demographic and clinical characteristics, co-occurring symptoms, and QOL outcomes.

## **5.2 Methods**

### **5.2.1 Patients and Settings**

Details regarding this prospective longitudinal study of symptom clusters in oncology outpatients receiving chemotherapy were published previously (Wright et al., 2017; Wright et al., 2019). In brief, eligible patients for the parent study: were  $\geq 18$  years of age; had a diagnosis of breast, GI, gynecological, or lung cancer; had received chemotherapy within the preceding four weeks; were scheduled to receive at least two additional cycles of chemotherapy; and were able to read, write, and understand English. Patients were recruited from two Comprehensive Cancer Centers, one Veteran's Affairs hospital, and four community-based oncology programs. A total of 2,234 patients were approached and 1,343 consented to participate (60.1% response rate) in the parent study. The major reason for refusal was being overwhelmed with their cancer treatment. For this study, only patients with GI cancers who had complete data for morning ( $n = 404$ ) and evening ( $n = 405$ ) fatigue were included.

## 5.2.2 Instruments

Patients completed a demographic questionnaire, the Karnofsky Performance Status (KPS) scale (Karnofsky et al., 1977), and the Self-administered Comorbidity Questionnaire (SCQ) (Sangha et al., 2003). Patients' medical records were reviewed for disease and treatment information.

*Assessment of morning and evening fatigue.* The 18-item Lee Fatigue Scale (LFS) (Lee et al., 1991) was designed to assess physical fatigue and energy. Each item was rated on a 0 to 10 numeric rating scale (NRS). Fatigue and energy scores were calculated as the mean of the 13 fatigue and 5 energy items. Higher scores indicate greater fatigue severity and higher levels of energy. Patients were asked to rate each item based on how they felt within 30 minutes of awakening (i.e., morning fatigue, morning energy) and prior to going to bed (i.e., evening fatigue, evening energy). The LFS has cut-off scores for clinically meaningful levels of fatigue (i.e.,  $\geq 3.2$  for morning fatigue,  $\geq 5.6$  for evening fatigue) and energy (i.e.,  $\leq 6.2$  for morning energy,  $\leq 3.5$  for evening energy) (Fletcher et al., 2008). In our study, the Cronbach's alphas were 0.96 for morning and 0.93 for evening fatigue and 0.95 for morning and 0.93 for evening energy.

*Assessment of common co-occurring symptoms.* All of the instruments that were used to assess six common co-occurring symptoms are valid and reliable. The symptoms that were assessed included: state and trait anxiety (Spielberger State-Trait Anxiety Inventories [STAI-T] and [STAI-S] (Spielberger et al., 1983)); depressive symptoms

(Center for Epidemiological Studies-Depression scale [CES-D] (Radloff, 1977)); sleep disturbance (General Sleep Disturbance Scale [GSDS] (Lee, 1992)); cognitive dysfunction (Attentional Function Index [AFI] (Cimprich et al., 2011)); and pain (Brief Pain Inventory [BPI] (Daut et al., 1983)).

*Assessment of QOL.* Quality of life was evaluated using generic (i.e., Medical Outcomes Study-Short Form-12 [SF-12]) and disease-specific (i.e., Quality of Life Scale-Patient Version [QOL-PV]) measures. The 41-item QOL-PV evaluated four dimensions of QOL (i.e., physical, psychological, social, and spiritual well-being) in oncology patients, as well as a total QOL score (Padilla et al., 1990). The SF-12 is scored into two components (i.e., physical component summary (PCS) and mental component summary (MCS) scores). Higher PCS and MCS scores indicate a better QOL (Ware et al., 1996).

### **5.2.3 Ethics Statement**

The parent study was approved by the Committee on Human Research at the University of California, San Francisco, by the Institutional Review Board (IRB) at each of the study sites, and by the IRB of Duke University. Written informed consent was obtained from all patients.

### **5.2.4 Study Procedures**

Patients were approached by a research staff member in the infusion unit, during their first or second cycle of chemotherapy, to discuss participation in the study. Depending on the length of their chemotherapy cycles, patients completed

questionnaires in their home, a total of six times over two cycles of chemotherapy (i.e., recovery from previous chemotherapy cycle (i.e., assessments 1 and 4), approximately 1 week after chemotherapy administration (i.e., acute symptoms, assessments 2 and 5), and approximately 2 weeks after chemotherapy administration (i.e., potential nadir, assessments 3 and 6)).

### **5.2.5 Data Analysis**

Latent profile analysis (LPA) was used to identify subgroups of patients with distinct morning and evening fatigue severity profiles over the six assessments. Separate LPAs were done for morning and evening fatigue. 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. To determine the best fitting model, multiple information criteria were used. Lower values for the Akaike Information Criteria (AIC) and Bayesian Information Criterion (BIC) represent better fitting models. Entropy values classify the quality of the model, in which values close to 1 indicate good classification. When using the Vuong-Lo-Mendell-Rubin likelihood ratio test (VLMR) to compare the models, a significant p-value suggests that one estimated model fits the data better than another model with one fewer group (Kim, 2014; Nylund et al., 2007). Estimation of model fit was conducted with Mplus Version 8 with 1,000 to 2,400 random starts.

Using SPSS, version 27 (IBM Corporation, Armonk, NY), differences in demographic and clinical characteristics, co-occurring symptoms, and QOL outcomes, among the subgroups, were evaluated using parametric and non-parametric tests. Post hoc contrasts were calculated using the Bonferroni procedure. A p-value of <0.05 was considered statistically significant.

## **5.3 Results**

### **5.3.1 Latent Classes for Morning Fatigue**

The fit indices and details regarding selection of the two class model for morning fatigue are shown in Table 8. The trajectories for morning fatigue differed between the latent classes (Figure 6). For the Very High class (35.6%), severity scores remained relatively constant across the six assessments. In contrast, for the Low class (64.4%), severity scores changed over the two cycles of chemotherapy, with slightly higher scores reported at assessments 2 and 5 (i.e., one week following the administration of chemotherapy).

**Table 8: Morning and Evening Fatigue Latent Profile Solutions and Fit Indices Over Six Assessments**

Model	LL	AIC	BIC	Entropy	VLMR
Morning fatigue					
1 Class	-4031.95	8105.90	8189.93	n/a	n/a
2 Class <sup>a</sup>	-3855.19	7766.37	7878.41	0.86	353.53 <sup>+</sup>
3 Class	-3787.73	7645.45	7785.50	0.86	134.92 <sup>ns</sup>
Evening fatigue					
1 Class	-3951.43	7944.86	8028.95	n/a	n/a
2 Class	-3829.55	7715.11	7827.21	0.77	243.76 <sup>+</sup>
3 Class <sup>b</sup>	-3769.68	7609.35	7749.49	0.77	119.76 <sup>*</sup>
4 Class	-3739.63	7563.25	7731.42	0.82	60.10 <sup>ns</sup>

Abbreviations: AIC = Akaike's 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

\*p <.05; +p <.01

Entropy and VLMR are not applicable for the one-class solution

<sup>a</sup>For morning fatigue, the two-class solution was selected because the BIC for that solution was lower than the BIC for the 1-class solution. In addition, the VLMR was significant for the 2-class solution, indicating that two classes fit the data better than one class. While the BIC was smaller for the 3-class than for the 2-class solution, the VLMR was not significant for the 3-class solution, indicating that too many classes were extracted. In addition, the 3-class solution included a small predicted class (only 42 predicted cases; approximately 10% of the sample), raising the concern that the solution may not generalize to other samples.

<sup>b</sup>For evening fatigue, the three-class solution was selected because the BIC for that solution was lower than the BIC for the 2-class solution. 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 were extracted. While the BIC for the 4-class solution was smaller than the BIC for the 3-class solution, one predicted class in the 4-class solution was very small (only eight predicted cases; less than 2% of the sample), raising the concern that the solution would not generalize to other samples.

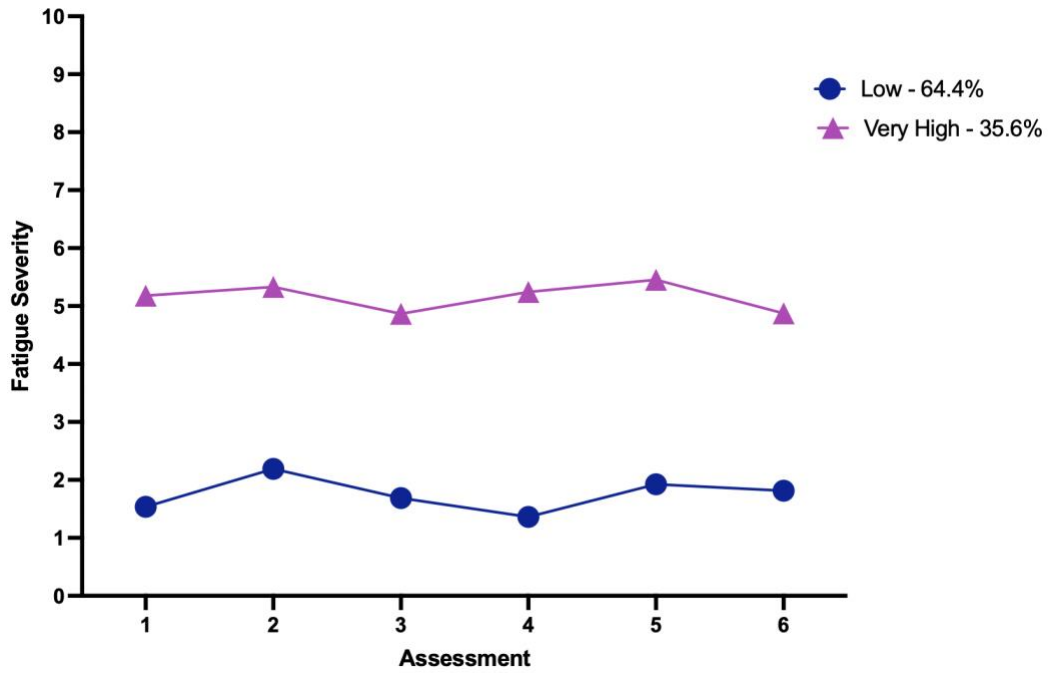


Figure 6: Trajectories of Morning Fatigue for the Latent Classes

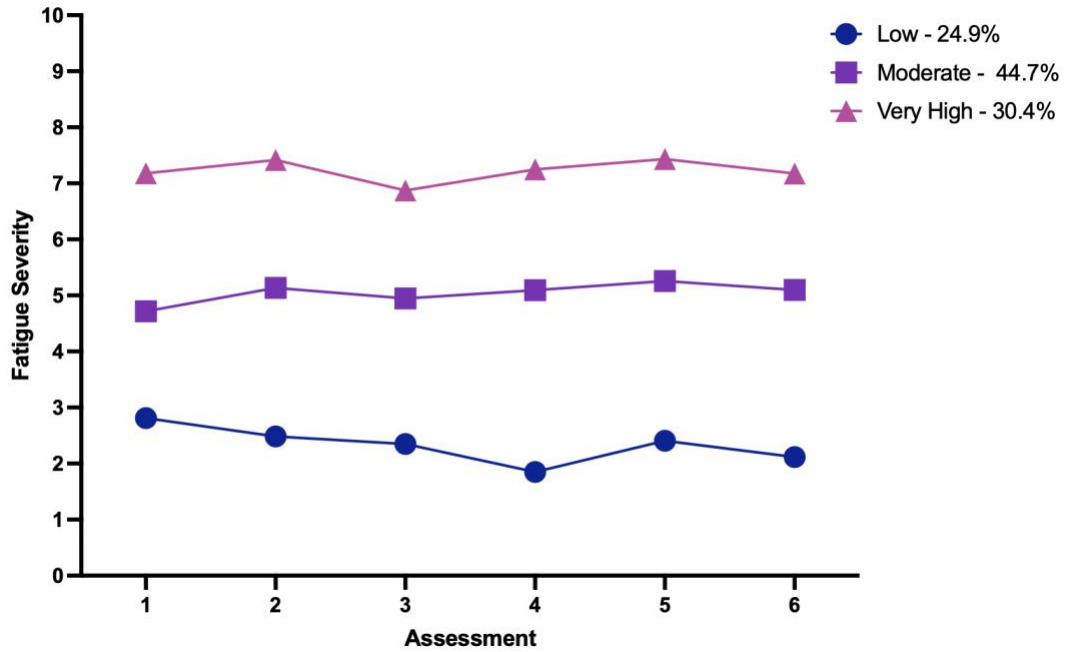


Figure 7: Trajectories of Evening Fatigue for the Latent Classes

### **5.3.2 Differences in Demographic and Clinical Characteristics Between Morning Fatigue Classes**

Compared to the Low class, patients in the Very High class were significantly younger, more likely to be female, less likely to be married or partnered, more likely to live alone, more likely to have childcare responsibilities, less likely to be employed, reported a lower annual household income, and were less likely to exercise on a regular basis (Table 9). In addition, compared to the Low class, patients in the Very High class had a lower KPS score, a higher SCQ score, a higher number of comorbidities, and a higher number of prior cancer treatments, and were more likely to self-report anemia and depression.

### **5.3.3 Differences in Symptom Scores and QOL Between Morning Fatigue Classes**

Compared to the Low class, patients in the Very High class had higher trait anxiety, state anxiety, depression, sleep disturbance, morning fatigue, and evening fatigue scores, and had lower morning energy, evening energy, and attentional function scores at enrollment (Table 10). Compared to the Low class, a higher percentage of patients in the Very High class reported pain. For the patients who had pain, compared to the Low class, patients in the Very High class had higher worst pain intensity and pain interference scores.

**Table 9: Differences in Demographic and Clinical Characteristics Between the Morning Fatigue Classes**

Characteristic	Low AM Fatigue 64.4% (n=260)	Very High AM Fatigue 35.6% (n=144)	Statistics
	Mean (SD)	Mean (SD)	
Age (years)	59.7 (10.9)	54.9 (12.6)	t=3.81, p<.001
Education (years)	16.1 (3.1)	15.8 (3.0)	t=0.90, p=.368
Body mass index (kg/m <sup>2</sup> )	25.5 (4.9)	26.0 (5.7)	t=-0.88 p=.379
Karnofsky Performance Status score	84.4 (10.8)	73.9 (12.2)	t=8.53, p<.001
Number of comorbidities	2.2 (1.3)	2.5 (1.4)	t=-2.16 p=.031
Self-administered Comorbidity Questionnaire score	4.9 (2.6)	6.1 (3.3)	t=-3.76, p<.001
Time since cancer diagnosis (years)	1.4 (3.0)	1.6 (2.7)	U, p=.080
Time since diagnosis (median; years)	0.40	0.45	
Number of prior cancer treatments	1.3 (1.2)	1.7 (1.4)	t=-2.65, p=.009
Number of metastatic sites including lymph node involvement	1.4 (1.1)	1.5 (1.2)	t=-0.73, p=.469
Number of metastatic sites excluding lymph node involvement	0.9 (0.9)	1.0 (1.0)	t=-0.28, p=.783
AUDIT score	3.3 (2.7)	3.4 (3.4)	t=-0.04, p=.967
Hemoglobin (gm/dl)	11.9 (1.5)	11.9 (1.6)	t=-0.17, p=.865
Hematocrit (%)	35.8 (4.0)	35.8 (4.6)	t=0.13, p=.900
MAX-2 score	0.14 (0.06)	0.14 (0.06)	t=1.14, p=.255
Gender (% female)	40.0 (104)	55.6 (80)	FE, p=.003
Ethnicity			X <sup>2</sup> =4.58, p=.205
White	69.7 (177)	63.2 (91)	
Asian or Pacific Islander	11.8 (30)	13.2 (19)	
Black	9.8 (25)	8.3 (12)	
Hispanic Mixed or Other	8.7 (22)	15.3 (22)	
Married or partnered (% yes)	73.2 (188)	56.9 (82)	FE, p=.001
Lives alone (% yes)	15.6 (40)	24.5 (35)	FE, p=.033
Childcare responsibilities (% yes)	16.9 (43)	27.1 (38)	FE, p=.019
Adult care responsibilities (% yes)	5.4 (13)	9.9 (13)	FE, p=.136
Currently employed (% yes)	38.6 (98)	25.9 (37)	FE, p=.011
Income			U, p=.002
< \$30,000	13.6 (31)	30.8 (41)	
\$30,000 to < \$70,000	20.2 (46)	18.8 (25)	
\$70,000 to < \$100,000	19.3 (44)	13.5 (18)	
> \$100,000	46.9 (107)	36.9 (49)	
Specific comorbidities (% yes)			
Heart disease	5.8 (15)	3.5 (5)	FE, p=.350
High blood pressure	35.8 (93)	29.2 (42)	FE, p=.188
Lung disease	5.8 (15)	6.3 (9)	FE, p=.829
Diabetes	11.5 (30)	16.0 (23)	FE, p=.220

Characteristic	Low	Very High	Statistics
	AM Fatigue 64.4% (n=260)	AM Fatigue 35.6% (n=144)	
	% (n)	% (n)	
Ulcer or stomach disease	6.2 (16)	4.9 (7)	FE, p=.660
Kidney disease	1.2 (3)	2.1 (3)	FE, p=.671
Liver disease	11.2 (29)	13.9 (20)	FE, p=.430
Anemia or blood disease	6.5 (17)	13.9 (20)	FE, p=.019
Depression	8.1 (21)	25.7 (37)	FE, p<.001
Osteoarthritis	8.5 (22)	9.7 (14)	FE, p=.717
Back pain	20.4 (53)	24.3 (35)	FE, p=.380
Rheumatoid arthritis	1.5 (4)	2.8 (4)	FE, p=.463
Exercise on a regular basis (% yes)	73.7 (191)	54.6 (77)	FE, p<.001
Current or history of smoking (% yes)	31.3 (80)	32.1 (44)	FE, p=.909
Type of prior cancer treatment			X <sup>2</sup> =4.90, p=.179
No prior treatment	31.2 (78)	24.8 (35)	
Only surgery, CTX, or RT	39.2 (98)	34.7 (49)	
Surgery & CTX, or Surgery & RT, or CTX & RT	19.6 (49)	27.0 (38)	
Surgery & CTX & RT	10.0 (25)	13.5 (19)	
Colon and rectal cancer (% yes)	59.5 (153)	68.5 (98)	FE, p=.084
CTX regimen			X <sup>2</sup> =7.50, p=.058
FOLFIRI	11.1 (28)	19.6 (28)	
FOLFOX	42.5 (107)	44.1 (63)	
FOLFIRINOX	12.7 (32)	7.7 (11)	
Other	33.7 (85)	28.6 (41)	
CTX cycle length			X <sup>2</sup> =0.27, p=.876
14 day	82.2 (213)	84.0 (121)	
21 day	15.1 (39)	13.9 (20)	
28 day	2.7 (7)	2.1 (3)	
Emetogenicity of CTX			X <sup>2</sup> =0.06, p=.970
Minimal/low	15.0 (39)	14.1 (20)	
Moderate	81.5 (212)	82.4 (117)	
High	3.5 (9)	3.5 (5)	
Antiemetic regimen			X <sup>2</sup> =5.18, p=.159
None	3.9 (10)	7.9 (11)	
Steroid alone or serotonin antagonist alone	11.4 (29)	10.8 (15)	
Serotonin receptor antagonist and steroid	65.1 (166)	56.1 (78)	
NK-1 receptor antagonist and two other antiemetics	19.6 (50)	25.2 (35)	

Abbreviations: AUDIT = Alcohol Use Disorders Identification Test, CTX = chemotherapy, dl = deciliter; FOLFIRI = leucovorin/5-fluorouracil/irinotecan, FOLFIRINOX = leucovorin/5-fluorouracil/irinotecan/oxaliplatin, FOLFOX = leucovorin/5-fluorouracil/oxaliplatin, gm = grams, kg = kilograms, m<sup>2</sup> = meter squared, NK-1 = neurokinin-1, NS = not significant, RT = radiation therapy, SD = standard deviation, U = Mann Whitney U test

**Table 10: Differences in Symptom Scores and QOL Outcomes Between the Morning Fatigue Classes**

	Low AM Fatigue 64.4% (n=260)	Very High AM Fatigue 35.6% (n=144)	Statistics
	Mean (SD)	Mean (SD)	
<b>Symptom scores</b>			
Trait anxiety ( $\geq 31.8$ )	30.4 (7.7)	40.2 (10.4)	t=-9.77, p<.001
State anxiety ( $\geq 32.2$ )	29.5 (9.5)	40.3 (12.3)	t=-9.02, p<.001
Depressive symptoms ( $\geq 16.0$ )	8.5 (6.3)	18.0 (9.4)	t=-10.84, p<.001
Sleep disturbance ( $\geq 43.0$ )	41.9 (16.8)	65.1 (17.4)	t=-12.82, p<.001
Attentional function ( $\leq 7.5$ )	7.3 (1.5)	5.3 (1.6)	t=11.99 p<.001
Morning fatigue ( $\geq 3.2$ )	1.5 (1.2)	5.2 (1.8)	t=-21.62, p<.001
Evening fatigue ( $\geq 5.6$ )	4.2 (2.2)	6.4 (1.7)	t=-11.00, p<.001
Morning energy ( $\leq 6.2$ )	4.8 (2.5)	3.9 (2.1)	t=3.51, p=.001
Evening energy ( $\leq 3.5$ )	3.8 (2.1)	3.0 (1.8)	t=3.58, p<.001
	% (n)	% (n)	
<b>Pain type</b>			X <sup>2</sup> =15.67, p=.001
No pain	37.9 (97)	20.4 (29)	0 > 1
Only non-cancer pain	23.0 (59)	31.0 (44)	NS
Only cancer pain	16.0 (41)	14.1 (20)	NS
Both cancer and non-cancer pain	23.0 (59)	34.5 (49)	NS
<b>For patients with pain</b>	Mean (SD)	Mean (SD)	
Worst pain intensity score	5.3 (2.4)	6.5 (2.8)	t=-3.48, p=.001
Pain interference score	2.2 (2.0)	4.1 (2.6)	t=-6.21, p<.001
<b>Multidimensional Quality of Life Scale- Patient Version</b>			
Physical well-being	7.5 (1.5)	5.4 (1.6)	t=12.95, p<.001
Psychological well-being	6.4 (1.6)	4.7 (1.6)	t=10.29, p<.001
Social well-being	6.4 (1.8)	4.6 (1.8)	t=9.57, p<.001
Spiritual well-being	5.3 (2.1)	5.2 (2.1)	t=0.65, p=.516
Total QOL score	6.5 (1.2)	4.9 (1.2)	t=11.75, p<.001
<b>Medical Outcomes Study- Short Form 12</b>			
Physical Component Summary score	43.7 (9.9)	37.4 (10.3)	t=5.78, p<.001
Mental Component Summary score	52.9 (7.5)	43.4 (10.6)	t=9.10, p<.001

Abbreviations: NS = not significant, QOL = quality of life, SD = standard deviation

For the QOL-PV, compared to the Low class, patients in the Very High class had lower subscale (except for the spiritual well-being subscale) and total QOL scores. For

the PCS and MCS scores of the SF-12, compared to the Low class, patients in the Very High class had significantly lower scores.

#### **5.3.4 Latent Classes for Evening Fatigue**

The fit indices and details regarding selection of the three class model for evening fatigue are shown in Table 8. The trajectories for evening fatigue differed among the latent classes (Figure 7). For the Moderate class (44.7%), their scores remained relatively constant across the six assessments. In contrast, for the Low class (24.9%), severity scores decreased from assessment 1 to assessment 4. For the Very High class (30.4%), severity scores increased at assessment 2, decreased at assessment 3, and increased slightly over assessments 4, 5, and 6.

#### **5.3.5 Differences in Demographic and Clinical Characteristics Among Evening Fatigue Classes**

Compared to the Low class, patients in the Moderate and Very High classes were significantly younger, more likely to be White, and reported a higher SCQ score (Table 11). Compared to the Low and Moderate classes, patients in the Very High class were more likely to be female and reported having childcare responsibilities. In addition, significant differences were found among the three classes for their KPS scores (i.e., Low > Moderate > Very High) and the occurrence of depression (i.e., Low < Moderate < Very High). Compared to the Low class, patients in the Very High class had a higher number of prior cancer treatments.

**Table 11: Differences in Demographic and Clinical Characteristics Among the Evening Fatigue Classes**

Characteristic	Low	Moderate	Very High	Statistics
	PM Fatigue (0)	PM Fatigue (1)	PM Fatigue (2)	
	24.9% (n=101)	44.7% (n=181)	30.4% (n=123)	
	Mean (SD)	Mean (SD)	Mean (SD)	
Age (years)	60.6 (11.5)	58.4 (11.7)	55.1 (11.6)	F=6.52, p=.002 0 > 1 and 2
Education (years)	15.7 (3.1)	16.2 (3.1)	16.2 (3.0)	F=0.92, p=.398
Body mass index (kg/m <sup>2</sup> )	25.6 (5.0)	26.0 (5.1)	25.4 (5.4)	F=0.63, p=.536
Karnofsky Performance Status score	85.9 (11.0)	81.2 (11.6)	75.4 (12.5)	F=21.99, p<.001 0 > 1 > 2
Number of comorbidities	2.2 (1.4)	2.3 (1.2)	2.5 (1.4)	F=0.89, p=.411
Self-administered Comorbidity Questionnaire score	4.7 (2.7)	5.2 (2.6)	6.1 (3.4)	F=6.47, p=.002 0 < 1 and 2
Time since cancer diagnosis (years)	1.0 (1.7)	1.8 (3.6)	1.3 (2.3)	KW=0.13, p=.935
Time since diagnosis (median; years)	0.44	0.42	0.44	
Number of prior cancer treatments	1.1 (1.2)	1.5 (1.3)	1.6 (1.4)	F=4.18, p=.016 0 < 2
Number of metastatic sites including lymph node involvement	1.5 (1.1)	1.5 (1.1)	1.5 (1.1)	F=0.05, p=.949
Number of metastatic sites excluding lymph node involvement	1.0 (1.0)	0.9 (0.9)	0.9 (1.0)	F=0.40, p=.669
AUDIT score	3.5 (3.2)	3.4 (2.8)	3.1 (2.9)	F=0.44, p=.646
Hemoglobin (gm/dl)	11.8 (1.5)	12.1 (1.6)	11.8 (1.5)	F=1.24, p=.291
Hematocrit (%)	35.7 (3.9)	36.1 (4.6)	35.4 (3.8)	F=1.22, p=.296
MAX-2 score	0.14 (0.06)	0.14 (0.06)	0.14 (0.06)	F=0.08, p=.919
	% (n)	% (n)	% (n)	
Gender (% female)	42.6 (43)	38.1 (69)	59.3 (73)	X <sup>2</sup> =13.82, p=.001 0 and 1 < 2

Characteristic	Low	Moderate	Very High	Statistics
	PM Fatigue (0) 24.9% (n=101)	PM Fatigue (1) 44.7% (n=181)	PM Fatigue (2) 30.4% (n=123)	
	% (n)	% (n)	% (n)	
Ethnicity				$X^2=14.42$ , $p=.025$
White	56.6 (56)	71.9 (128)	69.7 (85)	0 < 1 and 2
Asian or Pacific Islander	16.2 (16)	11.8 (21)	9.8 (12)	NS
Black	17.2 (17)	6.7 (12)	6.6 (8)	0 > 1
Hispanic Mixed or Other	10.1 (10)	9.6 (17)	13.9 (17)	NS
Married or partnered (% yes)	74.0 (74)	66.7 (120)	63.1 (77)	$X^2=3.05$ , $p=.218$
Lives alone (% yes)	14.0 (14)	21.2 (38)	18.9 (23)	$X^2=2.21$ , $p=.332$
Childcare responsibilities (% yes)	12.9 (13)	16.6 (29)	33.3 (40)	$X^2=17.25$ , $p<.001$
				0 and 1 < 2
Adult care responsibilities (% yes)	8.6 (8)	6.0 (10)	8.1 (9)	$X^2=0.77$ , $p=.682$
Currently employed (% yes)	35.7 (35)	36.3 (65)	29.8 (36)	$X^2=1.52$ , $p=.468$
Income				KW=2.17, $p=.339$
< \$30,000+	18.2 (16)	20.7 (34)	20.0 (22)	
\$30,000 to <\$70,000	26.1 (23)	18.9 (31)	15.5 (17)	
\$70,000 to < \$100,000	22.7 (20)	13.4 (22)	18.2 (20)	
> \$100,000	33.0 (29)	47.0 (77)	46.4 (51)	
Specific comorbidities (% yes)				
Heart disease	8.9 (9)	3.9 (7)	3.3 (4)	$X^2=4.58$ , $p=.101$
High blood pressure	35.6 (36)	35.9 (65)	27.6 (34)	$X^2=2.58$ , $p=.276$
Lung disease	5.0 (5)	6.1 (11)	6.5 (8)	$X^2=0.25$ , $p=.881$
Diabetes	10.9 (11)	14.9 (27)	12.2 (15)	$X^2=1.05$ , $p=.592$
Ulcer or stomach disease	5.0 (5)	5.0 (9)	7.3 (9)	$X^2=0.89$ , $p=.642$
Kidney disease	2.0 (2)	0 (0)	3.3 (4)	$X^2=5.54$ , $p=.063$
Liver disease	9.9 (10)	15.5 (28)	8.9 (11)	$X^2=3.54$ , $p=.170$
Anemia or blood disease	6.9 (7)	8.3 (15)	13.0 (16)	$X^2=2.87$ , $p=.238$
Depression	6.9 (7)	12.2 (22)	23.6 (29)	$X^2=13.78$ , $p=.001$
				0 < 1 < 2
Osteoarthritis	7.9 (8)	7.2 (13)	12.2 (15)	$X^2=2.43$ , $p=.297$

Characteristic	Low	Moderate	Very High	Statistics
	PM Fatigue (0) 24.9% (n=101)	PM Fatigue (1) 44.7% (n=181)	PM Fatigue (2) 30.4% (n=123)	
	% (n)	% (n)	% (n)	
Back pain	22.8 (23)	18.2 (33)	26.0 (32)	$X^2=2.70$ p=.260
Rheumatoid arthritis	2.0 (2)	2.2 (4)	1.6 (2)	$X^2=0.13$ , p=.938
Exercise on a regular basis (% yes)	73.3 (74)	67.6 (121)	60.3 (73)	$X^2=4.24$ , p=.120
Current or history of smoking (% yes)	32.0 (32)	30.5 (53)	32.5 (39)	$X^2=0.15$ , p=.926
Type of prior cancer treatment				$X^2=10.73$ , p=.097
No prior treatment	41.1 (39)	27.3 (48)	22.3 (27)	
Only surgery, CTX, or RT	30.5 (29)	37.5 (66)	43.0 (52)	
Surgery & CTX, or Surgery & RT, or CTX & RT	21.1 (20)	22.7 (40)	22.3 (27)	
Surgery & CTX & RT	7.4 (7)	12.5 (22)	12.4 (15)	
Colon and rectal cancer (% yes)	61.6 (61)	60.6 (109)	67.2 (82)	$X^2=1.47$ , p=.481
CTX regimen				$X^2=5.48$ , p=.484
FOLFIRI	13.4 (13)	14.7 (26)	13.9 (17)	
FOLFOX	41.2 (40)	40.7 (72)	48.4 (59)	
FOLFIRINOX	8.2 (8)	14.1 (25)	8.2 (10)	
Other	37.1 (36)	30.5 (54)	29.5 (36)	
CTX cycle length				$X^2=6.65$ , p=0.155
14 day	78.2 (79)	83.9 (151)	85.4 (105)	
21 day	20.8 (21)	12.2 (22)	13.0 (16)	
28 day	1.0 (1)	3.9 (7)	1.6 (2)	
Emetogenicity of CTX				$X^2=0.14$ , p=0.998
Minimal/low	15.0 (15)	14.4 (26)	14.8 (18)	
Moderate	81.0 (81)	82.3 (149)	82.0 (81)	
High	4.0 (4)	3.3 (6)	3.3 (4)	

Characteristic	Low	Moderate	Very High	Statistics
	PM Fatigue (0) 24.9% (n=101)	PM Fatigue (1) 44.7% (n=181)	PM Fatigue (2) 30.4% (n=123)	
	% (n)	% (n)	% (n)	
Antiemetic regimen				$\chi^2=5.11, p=0.530$
None	3.0 (3)	5.6 (10)	6.7 (8)	
Steroid alone or serotonin antagonist alone	11.1 (11)	10.7 (19)	11.8 (14)	
Serotonin receptor antagonist and steroid	68.7 (68)	62.7 (111)	65.9 (66)	
NK-1 receptor antagonist and two other antiemetics	17.2 (17)	20.9 (37)	26.1 (31)	

Abbreviations: AUDIT = Alcohol Use Disorders Identification Test, CTX = chemotherapy, dl = deciliter, FOLFIRI = leucovorin/5-fluorouracil/irinotecan, FOLFIRINOX = leucovorin/5-fluorouracil/irinotecan/oxaliplatin, FOLFOX = leucovorin/5-fluorouracil/oxaliplatin, gm = grams, kg = kilograms, KW = Kruskal Wallis test, m<sup>2</sup> = meter squared, NK-1 = neurokinin-1, NS = not significant, RT = radiation therapy, SD = standard deviation

### **5.3.6 Differences in Symptom Scores and QOL Outcomes Among Evening Fatigue Classes**

As shown in Table 12, significant differences were found among the three classes for trait anxiety, state anxiety, depression, sleep disturbance, morning fatigue, and evening fatigue scores (i.e., Low < Moderate < Very High). For attentional function, the pattern was as expected (i.e., Low > Moderate > Very High). For morning energy, compared to the Moderate class, patients in the Very High evening fatigue class had lower scores. For evening energy, compared to the other two classes, patients in the Very High class had lower scores. In terms of the occurrence of pain, compared to the Low class, a higher percentage of patients in the Very High class reported non-cancer pain. For patients who had pain, compared to the Low class, patients in the Moderate and Very High classes had higher worst pain intensity and pain interference scores.

Except for the spiritual well-being subscale, significant differences were found among the three classes for the QOL-PV subscales and total scores (i.e., Low > Moderate > Very High). For the PCS scores of the SF-12, compared to the other two classes, patients in the Very High evening fatigue class had significantly lower scores. Significant differences were found among the three evening fatigue classes for the MCS scores (i.e., Low > Moderate > Very High).

**Table 12: Differences in Symptoms Scores and QOL Outcomes Among the Evening Fatigue Classes**

	Low PM Fatigue (0) 24.9% (n=101)	Moderate PM Fatigue (1) 44.7% (n=181)	Very High PM Fatigue (2) 30.4% (n=123)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	
<b>Symptoms scores</b>				
Trait anxiety ( $\geq 31.8$ )	28.8 (7.8)	33.2 (8.7)	39.1 (10.8)	F=33.71, p<.001 0 < 1 < 2
State anxiety ( $\geq 32.2$ )	27.5 (9.2)	32.8 (10.1)	38.9 (13.5)	F=29.17, p<.001 0 < 1 < 2
Depressive symptoms ( $\geq 16$ )	7.2 (6.5)	10.8 (7.0)	17.3 (10.2)	F=45.59, p<.001 0 < 1 < 2
Sleep disturbance ( $\geq 43$ )	37.0 (16.9)	49.7 (17.5)	61.8 (20.3)	F=48.63, p<.001 0 < 1 < 2
Attentional function ( $\leq 7.5$ )	7.5 (1.6)	6.7 (1.6)	5.6 (1.9)	F=36.17, p<.001 0 > 1 > 2
Morning fatigue ( $\geq 3.2$ )	1.5 (1.7)	2.5 (1.8)	4.3 (2.5)	F=54.00, p<.001 0 < 1 < 2
Evening fatigue ( $\geq 5.6$ )	2.7 (1.8)	4.7 (1.4)	7.3 (1.4)	F=250.45, p<.001 0 < 1 < 2
Morning energy ( $\leq 6.2$ )	4.6 (2.7)	4.8 (2.2)	3.9 (2.3)	F=5.83, p=.003 1 > 2
Evening energy ( $\leq 3.5$ )	4.1 (2.4)	4.0 (1.7)	2.3 (1.8)	F=32.09, p<.001 0 and 1 > 2
	% (n)	% (n)	% (n)	
<b>Pain type</b>				
No pain	39.4 (39)	34.3 (61)	21.3 (26)	X <sup>2</sup> =16.42, p=.012 0 and 1 > 2
Only non-cancer pain	19.2 (19)	23.6 (42)	34.3 (42)	0 < 2
Only cancer pain	19.2 (19)	15.7 (28)	11.5 (14)	NS
Both cancer and non-cancer pain	22.2 (22)	26.4 (47)	32.8 (40)	NS
<b>For patients with pain</b>				
Worst pain intensity score	Mean (SD) 5.2 (2.8)	Mean (SD) 5.5 (2.5)	Mean (SD) 6.6 (2.5)	F=5.85, p=.003 0 < 1 and 2
Pain interference score	1.9 (2.1)	2.8 (2.2)	4.0 (2.7)	F=13.70, p<.001 0 < 1 and 2
<b>Multidimensional Quality of Life Scale- Patient Version</b>				
Physical well-being	7.9 (1.5)	6.7 (1.6)	5.8 (1.8)	F=45.67, p<.001 0 > 1 > 2
Psychological well-being	7.0 (1.7)	5.8 (1.5)	4.9 (1.7)	F=46.18, p<.001 0 > 1 > 2

	Low PM Fatigue (0) 24.9% (n=101)	Moderate PM Fatigue (1) 44.7% (n=181)	Very High PM Fatigue (2) 30.4% (n=123)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	
Social well-being	7.0 (1.8)	5.7 (1.8)	4.9 (1.8)	F=37.24, p<.001 0 > 1 > 2
Spiritual well-being	5.6 (2.2)	5.2 (2.1)	5.0 (2.1)	F=2.25, p=.107
Total QOL score	7.0 (1.3)	5.8 (1.2)	5.1 (1.3)	F=58.26, p<.001 0 > 1 > 2
Medical Outcomes Study- Short Form 12				
Physical Component Summary score	44.5 (9.7)	42.5 (10.0)	37.5 (10.7)	F=13.39, p<.001 0 and 1 > 2
Mental Component Summary score	54.4 (7.7)	50.2 (8.4)	44.7 (11.0)	F=29.41, p<.001 0 > 1 > 2

Abbreviations: LFS = Lee Fatigue Scale, NS = not significant, QOL = quality of life, SD = standard deviation

## 5.4 Discussion

This study is the first to identify subgroups of patients with GI cancers with distinct morning and evening fatigue severity profiles. Given the paucity of research on diurnal variations in fatigue severity in these patients, one focus of this discussion will be on a comparison of our findings with average fatigue severity scores in patients with these types of cancer. In addition, to evaluate for common and distinct risk factors associated with a more severe morning or evening fatigue profile, as well as for consistency across cancer types, comparisons of these characteristics are made between the patients with GI cancers (i.e., current sample) and our previous reports of the total sample of patients with heterogenous cancer diagnoses (Table 13) (Wright et al., 2017; Wright et al., 2019).

**Table 13: Comparisons of Demographic, Clinical, and Symptom Characteristics Associated with Membership in the Higher Morning and Evening Fatigue Latent Classes**

Characteristics (All comparisons done to the Low class)	Very High AM Fatigue GI Sample	Very High AM Fatigue Total Sample <sup>a</sup>	Very High PM Fatigue GI Sample	Very High PM Fatigue Total Sample <sup>b</sup>
<b>Demographic Characteristics</b>				
Younger age	♦	♦	♦	♦
Being female	♦		♦	♦
Being White			♦	♦
Higher BMI		♦		
Not being married or partnered	♦	♦		
Living alone	♦	♦		
Having childcare responsibilities	♦		♦	♦
Not being employed	♦	♦		
Lower income	♦	♦		
Not exercising on a regular basis	♦	♦		
<b>Clinical Characteristics</b>				
Lower KPS score	♦	♦	♦	♦
Higher number of comorbidities	♦	♦		
Higher SCQ score	♦	♦	♦	♦
Higher number of prior cancer treatments	♦		♦	
Not having high blood pressure				♦
Having a diagnosis of anemia or blood disease	♦	♦		
Having a diagnosis of depression	♦	♦	♦	♦
Having back pain		♦		
<b>Symptoms</b>				
Higher trait anxiety	♦	♦	♦	♦
Higher state anxiety	♦	♦	♦	♦
Higher depressive symptoms	♦	♦	♦	♦
Higher sleep disturbance	♦	♦	♦	♦
Lower attentional function	♦	♦	♦	♦
Higher morning fatigue	♦	♦	♦	♦
Higher evening fatigue	♦	♦	♦	♦
Lower morning energy	♦	♦		
Lower evening energy	♦	♦	♦	♦
Having pain	♦	♦	♦	♦

Abbreviations: AM = morning, BMI = body mass index, KPS = Karnofsky Performance Status, PM = evening, SCQ = Self-administered Comorbidity Questionnaire

a. Wright, F., Dunn, L. B., Paul, S. M., Conley, Y. P., Levine, J. D., Hammer, M. J., Cooper, B. A., Miaskowski, C., & Kober, K. M. (2019). Morning fatigue severity profiles in oncology outpatients receiving chemotherapy. *Cancer Nurs*, 42(5), 355-364.  
<https://doi.org/10.1097/ncc.0000000000000626>

b. Wright, F., Cooper, B. A., Conley, Y. P., Hammer, M. J., Chen, L. M., Paul, S. M., Levine, J. D., Miaskowski, C., & Kober, K. M. (2017). Distinct evening fatigue profiles in oncology outpatients receiving chemotherapy. *Fatigue*, 5(3), 131-144. <https://doi.org/10.1080/21641846.2017.1322233>

While four distinct morning and evening fatigue classes were identified in the total sample (Wright et al., 2017; Wright et al., 2019), for both the current and total sample, two common classes were identified for both morning and evening fatigue (i.e., Low, Very High). The severity scores for the Low morning fatigue classes (range = 1.5 to 2.8) were comparable across the two samples. However, for the patients with GI cancers, the fatigue severity scores for the Very High morning fatigue class were ~1.5 points lower across the six assessments. For evening fatigue, the severity scores for the Low (range = 1.9 to 2.8) and Very High (range = 6.9 to 7.6) classes were comparable across both samples. These findings suggest that while evening fatigue severity is similar across cancer types, patients with GI cancers may be at decreased risk for higher levels of morning fatigue. One potential explanation for this finding is that the MAX2 score (a measure of chemotherapy-induced toxicity) was lower (0.14) in the current sample compared to the total sample (0.17). In addition, given that previous studies found that women reported more severe symptoms during chemotherapy (Lin et al., 2020a), the lower morning fatigue scores may be related to the lower percentage of women (45.5%)

in the current sample compared to the total sample (77.9%). In addition, our findings are consistent with a previous report that found that patients with GI cancers experienced less severe fatigue than patients with breast and lung cancers (Batra et al., 2020).

Given that most of the studies of oncology patients did not evaluate for diurnal variations in fatigue severity, associations with various risk factors will be described in relationship to previously reported mean fatigue severity scores. As shown in Table 13, across our two samples, four common risk factors for higher levels of morning and evening fatigue were identified, namely: younger age, a higher comorbidity burden, a lower performance status, and a self-reported diagnosis of depression. Age-related differences in inflammatory responses, perceptions of the symptom experience, and dose adjustments in chemotherapy regimens may explain the relationships between younger age and higher levels of fatigue (Bower et al., 2008; Sprangers & Schwartz, 1999). Previous studies have found that a higher level of comorbidity is associated with increases in fatigue severity (Poort et al., 2020). Given that a higher number of comorbidities contribute to decrements in functional status (Petrick et al., 2014), it is not surprising that a common risk factor for higher levels of morning and evening fatigue was a lower KPS score. Of note, for both samples, the differences in KPS scores between the patients in the Very High classes compared to the Low classes, represent not only statistically significant but clinically meaningful differences (i.e.,  $d = 0.9$ ). Equally important, our associations between more severe morning and evening fatigue and a

clinical diagnosis of depression may all be related to a shared biological pathway (i.e., activation of the immune-inflammatory pathways) (Chaves-Filho et al., 2019). Clinicians can use these four common characteristics to identify oncology patients who are at increased risk for severe levels of both morning and evening fatigue. Clinician can refer patients for psychological care or physical therapy depending on their risk profile.

For both samples, the common risk factors for higher levels of evening fatigue were: being female, being White, and having childcare responsibilities (Table 13). Our findings suggest that the additional burden of childcare responsibilities, primarily for women, contributes to higher levels of evening fatigue. Given that 25.8% of the women in the current sample reported having childcare responsibilities compare to 16.4% of the men ( $p = 0.025$ ), future studies need to evaluate the linkages between these two risk factors. Findings regarding ethnic differences in the severity of evening fatigue in oncology patients are inconsistent. While gender and race are not modifiable risk factors, clinicians can identify support services for female patients and those patients with childcare responsibilities. While the number of prior cancer treatments was comparable across the two samples, this characteristic was the only risk factor associated with higher levels of morning and evening fatigue in the patients with GI cancers. This association may be partially explained by the cumulative effects of various cancer treatments or differences in the sequence of these treatments (Tantoy et al., 2016).

For both samples, the common risk factors for higher levels of morning fatigue included: being unmarried, living alone, being unemployed, having a lower annual household income, lack of regular exercise, and a self-reported diagnosis of anemia or blood disease (Table 13). Lower incomes and lack of social support may exacerbate the financial burden of cancer treatment and increase psychological distress (Wright et al., 2019). These worries may disrupt sleep and result in higher levels of morning fatigue. While these characteristics are not easily modifiable, particularly in patients who are socioeconomically disadvantaged, referrals to social workers or social services may be warranted. Lack of regular exercise was the only modifiable risk factor for higher levels of morning fatigue. While the effects of exercise on diurnal variations in fatigue severity have not been investigated, regular exercise results in decreases in average fatigue severity (Thong et al., 2020). Therefore, clinicians need to encourage patients to exercise during and following chemotherapy. While a self-reported diagnosis of anemia was associated with higher morning fatigue severity, for both the current and total sample, no between group differences in hemoglobin and hematocrit levels were found. While previous studies found associations between average fatigue severity and anemia (Lanser et al., 2020), additional research is warranted to confirm or refute this association.

A growing body of evidence suggests that patients with GI cancers experience multiple co-occurring symptoms (Lin et al., 2020a, 2020b; Pettersson et al., 2014). In fact,

the patients with GI cancers in the current study reported an average of 13 symptoms prior to their second or third cycle of chemotherapy (Tantoy et al., 2018). Except for morning energy, across both samples, patients in the Very High morning and evening fatigue classes reported higher symptom severity scores for trait and state anxiety, depressive symptoms, sleep disturbance, and pain as well as lower levels of attentional function and evening energy. In both samples, all of the symptom severity scores reported by the Very High morning and evening fatigue classes were above the clinically meaningful cutoff scores for the various instruments. In addition, for both samples, the differences between the Low and Very High fatigue classes represent not only statistically significant but clinically meaningful differences in symptom severity scores (i.e., effect sizes ranged from 0.4 [morning and evening energy] to 1.1 [sleep disturbance, depressive symptoms, and attentional function]).

Psychoneurological symptoms including fatigue, anxiety, depression, sleep disturbance, cognitive dysfunction, and pain are known to co-occur as a symptom cluster (George et al., 2020). The initiation of a series of inflammatory processes, as well as dysregulation of the hypothalamic-pituitary-adrenal axis, circadian rhythms, and the serotonin system that occur following the administration of chemotherapy, are the commonly hypothesized mechanisms for these co-occurring psychoneurological symptoms (Kim et al., 2012). Future research needs to determine the common and distinct mechanisms for the co-occurrence of these symptoms and diurnal variations in

fatigue severity. For example, in one study (Dhruva et al., 2015), while higher levels of average fatigue were associated with increased evening cortisol levels and increased overall cortisol secretion, they were not associated with morning cortisol levels.

In the current sample, but not in the total sample, lower levels of energy were associated with higher levels of morning and evening fatigue. Energy is defined as a person's potential to perform physical and mental activities (Wright et al., 2017) and decrements in energy is a distinct symptom from fatigue (Lerdal, 1998). Because diurnal variations in levels of energy are not routinely evaluated in oncology patients, future studies need to evaluate for the common and distinct molecular mechanisms associated with the co-occurrence of morning and evening fatigue, morning and evening energy, and sleep disturbance.

In terms of QOL outcomes, except for the spiritual well-being subscale of the disease specific QOL measure and the PCS score of the generic QOL measure, statistically and clinically meaningful decrements in QOL outcomes were found among the distinct morning and evening fatigue profiles ( $d = 0.2$  to  $1.3$ ). Of note, across all of the morning and evening fatigue latent classes, patients in the current sample reported PCS scores of  $<50$  which is lower than the normative score for the general population (Padilla et al., 1990).

### **5.4.1 Limitations**

Several limitations warrant consideration. Because patients were not recruited prior to the initiation of chemotherapy, risk profiles for fatigue from its initiation through completion were not evaluated. Given that the majority of the patients were White and well-educated, our findings may not generalize to more diverse and socioeconomically disadvantaged patients. In addition, given the heterogeneity in GI cancers in this study, future studies need to perform similar evaluations of patients with specific GI cancers (e.g., gastric, pancreatic).

### **5.5 Conclusion**

Despite these limitations, this study is the first to identify subgroups of patients with GI cancers with distinct morning and evening fatigue profiles and identify risk factors associated with higher levels of morning and evening fatigue. Based on the high occurrence and severity of both morning and evening fatigue, clinicians need to assess for the four common risk factors, as well as associated co-occurring symptoms and initiate personalized symptom management interventions and referrals.

## **6. Distinct Sleep Disturbance Profiles in Patients with Gastrointestinal Cancers Receiving Chemotherapy**

### ***6.1 Introduction***

Sleep disturbance is a frequent and distressing symptom in patients receiving chemotherapy that has detrimental effects on their cognitive and functional status, quality of life (QOL), and disease progression (Chen et al., 2018). While sleep disturbance in patients with breast (Carroll et al., 2019), lung (Chen et al., 2008), prostate (Liu et al., 2020), and gynecologic (Evans et al., 2016) cancer has been documented, less is known about the occurrence of, risk factors for, and impact of this symptom in patients with gastrointestinal (GI) cancers. In previous studies of patients with GI cancers, occurrence rates for sleep disturbance ranged from 38% (Sun et al., 2020) to 63% (Tantoy et al., 2017) and severity scores were in the moderate range (Rohrl et al., 2016; Tantoy et al., 2017). In a longitudinal study of 361 patients with colorectal cancer (Innominato et al., 2015), sleep disturbance was reported by 56% of patients prior to and by 52% during chemotherapy. These findings suggest that a significant number of patients with GI cancers report moderate to high levels of sleep disturbance during chemotherapy.

In terms of risk factors, two studies of patients with colorectal cancer found that higher rates of sleep disturbance were associated with pain, anxiety, fatigue, retirement, and the existence of multiple comorbid conditions (Coles, Bennett, et al., 2018; Coles,

Tan, et al., 2018). In another cross-sectional study of 434 patients with colorectal cancer (Sun et al., 2020), the occurrence of sleep disturbance was positively correlated with pain and anxiety. In addition, compared to patients with liver cancer who did not experience sleep disturbance (Chung et al., 2017), those who reported this symptom had higher rates and severity of co-occurring symptoms. In terms of patient outcomes, sleep disturbance was associated with a poor treatment response (Innominato et al., 2015), worse QOL (Tantoy et al., 2018), higher risk of earlier death (Innominato et al., 2015), and lower overall survival (Palesh et al., 2017).

While these studies provide important information on sleep disturbance in patients with GI cancers, several limitations warrant consideration. First, only one study described changes over time in sleep disturbance in these patients (Innominato et al., 2015). Second, only four studies examined risk factors for higher levels of sleep disturbance (Chung et al., 2017; Coles, Bennett, et al., 2018; Coles, Tan, et al., 2018; Sun et al., 2020). In addition, little information is available on specific sleep characteristics (e.g., sleep quality, sleep maintenance) in these patients. Finally, none of these studies used a person-centered analytic approach (e.g., latent variable modeling) to evaluate for distinct sleep disturbance profiles in patients with GI cancers. Therefore, the purposes of this study were to identify subgroups of patients with GI cancers with distinct sleep disturbance profiles and evaluate for differences among these subgroups in

demographic, clinical, and sleep characteristics, as well as co-occurring symptoms and QOL outcomes.

## **6.2 Methods**

### **6.2.1 Patients and Settings**

This study is part of a prospective longitudinal study of symptom clusters in oncology outpatients receiving chemotherapy that used the Theory of Symptom Management as its theoretical framework (Humphreys et al., 2014). The methods for this study were described in detail in our previous publications (Papachristou et al., 2018; Wright et al., 2017; Wright et al., 2019). In brief, eligible patients for the parent study: were  $\geq 18$  years of age; had a diagnosis of breast, GI, gynecological, or lung cancer; had received chemotherapy within the preceding 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 Veteran's Affairs hospital, and four community-based oncology programs. A total of 2,234 patients were approached and 1,343 consented to participate (60.1% response rate) in the parent study. The major reason for refusal was being overwhelmed with their cancer treatment. For this study, only patients with GI cancers who had complete data for sleep disturbance ( $n = 405$ ) were included.

## 6.2.2 Instruments

Patients completed a demographic questionnaire, the Karnofsky Performance Status (KPS) scale (Karnofsky et al., 1977), and the Self-administered Comorbidity Questionnaire (SCQ) (Sangha et al., 2003). Patients' medical records were reviewed for disease and treatment information.

*Assessment of sleep disturbance.* The 21-item General Sleep Disturbance Scale (GSDS) was designed to assess seven aspects of sleep disturbance (i.e., excessive daytime sleepiness, medications for sleep, sleep quality, sleep quantity, sleep onset latency, mid-sleep awakenings, early awakenings) in the past week. Each item was rated on a 0 (never) to 7 (everyday) numeric rating scale (NRS). The GSDS total score can range from 0 (no disturbance) to 147 (extreme disturbance). Each mean subscale score ranges from 0 to 7. A mean subscale score of  $\geq 3$  or a total GSDS score of  $\geq 43$  indicate a significant level of sleep disturbance that warrants clinical evaluation and management (Fletcher et al., 2008). The GSDS has well-established validity and reliability (Lee & DeJoseph, 1992; Miaskowski & Lee, 1999). In our study, the Cronbach's alpha for the GSDS total score was 0.83.

*Assessment of common co-occurring symptoms.* All of the instruments that were used to assess common co-occurring symptoms are valid and reliable. The symptoms that were assessed included: state and trait anxiety (Spielberger State-Trait Anxiety Inventories [STAI-T] and [STAI-S] (Spielberger et al., 1983)); depressive symptoms

(Center for Epidemiological Studies-Depression scale [CES-D] (Radloff, 1977)); morning and evening fatigue and morning and evening energy (Lee Fatigue Scale [LFS] (Lee et al., 1991)); cognitive dysfunction (Attentional Function Index [AFI] (Cimprich et al., 2011)); and pain (Brief Pain Inventory [BPI] (Daut et al., 1983)).

*Assessment of QOL.* QOL was evaluated using disease-specific (i.e., Quality of Life Scale-Patient Version [QOL-PV]) and generic (i.e., Medical Outcomes Study-Short Form-12 [SF-12]) measures. The 41-item QOL-PV evaluated four dimensions of QOL (i.e., physical, psychological, social, and spiritual well-being) in oncology patients, as well as a total QOL score (Padilla et al., 1990). The SF-12 was scored into two components (i.e., physical component summary (PCS) and mental component summary (MCS) scores). Higher PCS and MCS scores indicate a better QOL (Ware et al., 1996).

### **6.2.3 Study Procedures**

The parent study was approved by the Committee on Human Research at the University of California, San Francisco, by the Institutional Review Board (IRB) at each of the study sites, and by the IRB of Duke University. Patients were approached by a research staff member in the infusion unit, during their first or second cycle of chemotherapy, to discuss participation in the study. Written informed consent was obtained from all patients. Depending on the length of their chemotherapy cycles, patients completed questionnaires in their home, a total of six times over two cycles of chemotherapy including recovery from previous chemotherapy cycle (i.e., assessments 1

and 4), approximately 1 week after chemotherapy administration (i.e., acute symptoms, assessments 2 and 5), and approximately 2 weeks after chemotherapy administration (i.e., potential nadir, assessments 3 and 6).

#### **6.2.4 Data Analysis**

Latent profile analysis (LPA) was used to identify subgroups of patients with distinct sleep disturbance profiles over the six assessments. 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. To determine the best fitting model to characterize the latent class structure, multiple information criteria were used. Lower values for the Akaike Information Criteria (AIC) and Bayesian Information Criterion (BIC) represent better fitting models. Entropy values classify the quality of the model, in which values close to 1 indicate good classification. When using the Vuong-Lo-Mendell-Rubin likelihood ratio test (VLMR) to compare the models, a significant p-value suggests that one estimated model fits the data better than another model with one fewer group (Kim, 2014; Nylund et al., 2007). Estimation of model fit was conducted with Mplus Version 8.0 with 800 to 2,000 random starts.

Descriptive statistics and frequency distributions were calculated for demographic and clinical characteristics using SPSS, version 27 (IBM Corporations, Armonk, NY). Differences in demographic, clinical, and sleep characteristics, as well as co-occurring symptoms and QOL outcomes, among the latent classes, were evaluated

using parametric and non-parametric tests. Post hoc contrasts were calculated using the Bonferroni procedure. A p-value of  $< 0.05$  was considered statistically significant.

## **6.3 Results**

### **6.3.1 Latent Classes for Sleep Disturbance**

The three-class solution was selected for sleep disturbance because the BIC for that solution was lower than the BIC for the 2-class solution (Table 14). 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 were extracted.

The trajectories for sleep disturbance differed among the latent classes (Figure 8). Using the clinically meaningful total GSDS score of  $\geq 43$ , the sleep disturbance classes were named Low (35.8%), High (48.6%), and Very High (15.6%). For the High and Very High classes, sleep disturbance scores increased slightly in the weeks following the administration of chemotherapy (i.e., assessment 2 and 4). In contrast, for the Low class, sleep disturbance scores increased slightly at assessment 2, decreased at assessment 3, and then remained relatively constant across assessments 4 through 6.

**Table 14: General Sleep Disturbance Scale Latent Profile Solutions and Fit Indices for One through Four Classes for Patients with Gastrointestinal Cancers**

Model	LL	AIC	BIC	Entropy	VLMR
1 Class	-8539.59	17121.19	17205.27	n/a	n/a
2 Class	-8406.77	16869.54	16981.65	0.75	265.64 <sup>+</sup>
3 Class <sup>a</sup>	-8331.34	16732.68	16872.81	0.80	150.87 <sup>*</sup>
4 Class	-8290.61	16665.22	16833.38	0.798	81.46 <sup>ns</sup>

Baseline Entropy and VLMR are not applicable for the one-class solution

\*p < .05; +p = .0004

<sup>a</sup>The three-class solution was selected because the BIC for that solution was lower than the BIC for the 2-class solution. 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 were extracted. Although the BIC for the 4-class solution was smaller than the BIC for the 3-class solution, one predicted class in the 4-class solution was small (43 predicted cases; less than 11% of the sample), raising the concern that the solution would not generalize to other samples.

Abbreviations: AIC = Akaike's 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

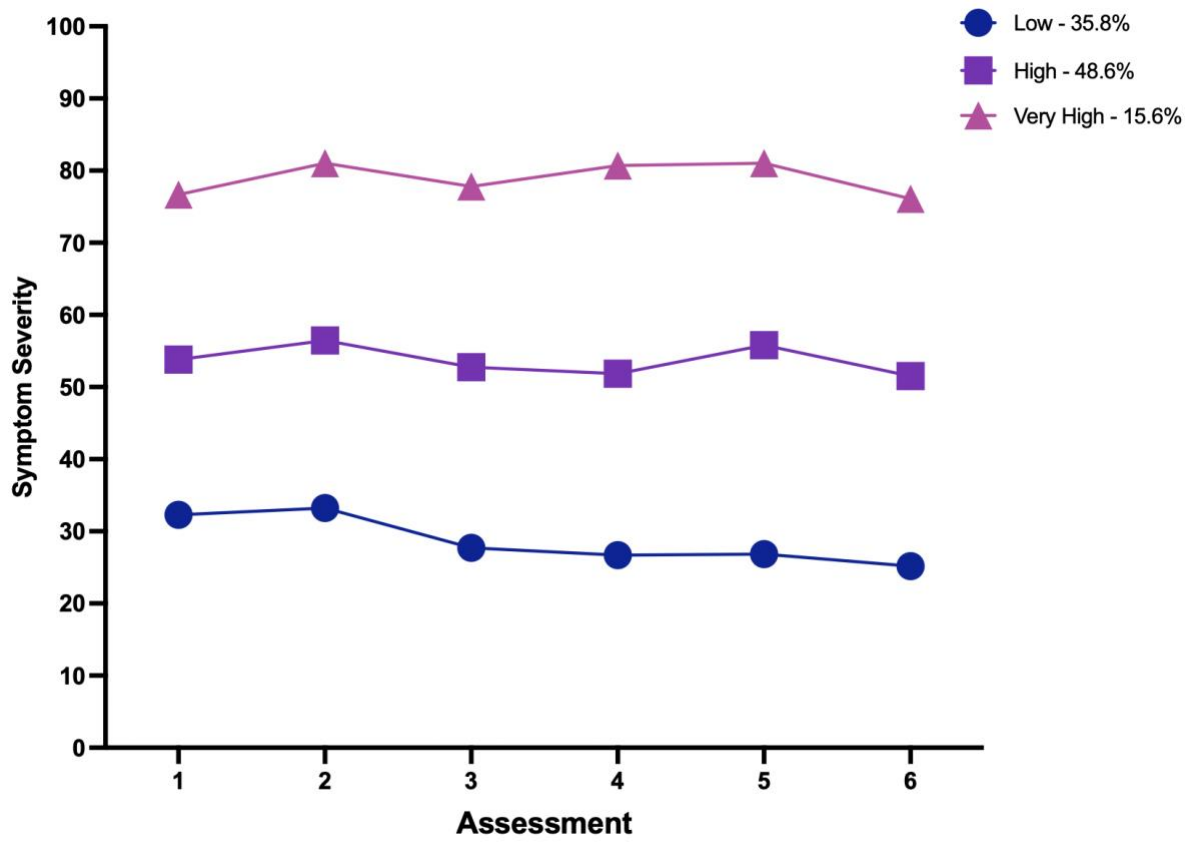


Figure 8: Sleep Disturbance Trajectories for Patients in Each of the Latent Classes

### **6.3.2 Differences in Demographic and Clinical Characteristics**

As shown in Table 15, compared to the Low class, patients in the High class were more likely to be female. Compared to the Low class, patients in the Very High class were less likely to be employed and had a diagnosis of back pain. Compared to the Low class, patients in the High and Very High classes were significantly younger, had a higher number of comorbidities, had a higher number of prior cancer treatments, were less likely to be married/partnered, and were less likely to exercise on a regular basis. Compared to the Low and High classes, patients in the Very High class were more likely to report having childcare responsibilities. In addition, significant differences were found among the three classes for the KPS scores (i.e., Low > High > Very High), as well as SCQ scores and occurrence of self-reported depression (i.e., Low < High < Very High).

**Table 15: Differences in Demographic and Clinical Characteristics Among the Sleep Disturbance Classes**

Characteristic	Low	High	Very High	Statistics
	Sleep Disturbance	Sleep Disturbance	Sleep Disturbance	
	(0) 35.8% (n=145)	(1) 48.6% (n=197)	(2) 15.6% (n=63)	
	Mean (SD)	Mean (SD)	Mean (SD)	
Age (years)	60.4 (10.3)	57.1 (12.3)	55.0 (12.6)	F=5.79, p=.003 0 > 1 and 2
Education (years)	16.1 (2.9)	16.0 (3.2)	16.0 (3.1)	F=0.04, p=.958
Body mass index (kg/m <sup>2</sup> )	25.3 (4.5)	25.6 (5.4)	26.8 (5.4)	F=1.90, p=.151
Karnofsky Performance Status score	87.4 (9.4)	78.6 (11.6)	71.2 (12.4)	F=52.56, p<.001 0 > 1 > 2
Number of comorbidities	2.0 (1.1)	2.5 (1.5)	2.7 (1.4)	F=8.39, p<.001 0 < 1 and 2
Self-administered Comorbidity Questionnaire score	4.4 (2.3)	5.6 (2.9)	6.8 (3.7)	F=17.86, p<.001 0 < 1 < 2
Time since cancer diagnosis (years)	1.1 (1.9)	1.8 (3.6)	1.2 (2.1)	KW=5.57, p=.062
Time since diagnosis (median; years)	0.39	0.46	0.43	
Number of prior cancer treatments	1.1 (1.2)	1.5 (1.3)	1.8 (1.5)	F=7.92, p<.001 0 < 1 and 2
Number of metastatic sites including lymph node involvement	1.4 (1.1)	1.5 (1.2)	1.5 (1.0)	F=0.20, p=.816
Number of metastatic sites excluding lymph node involvement	1.0 (0.9)	1.0 (1.0)	0.9 (0.9)	F=0.34, p=.713
AUDIT score	3.6 (2.8)	3.3 (3.1)	3.0 (2.8)	F=0.84, p=.433
Hemoglobin (gm/dl)	11.9 (1.4)	12.0 (1.6)	11.9 (1.6)	F=0.28, p=.760
Hematocrit (%)	35.7 (3.7)	35.9 (4.5)	35.5 (4.3)	F=0.34, p=.715
MAX-2 score	0.14 (0.06)	0.14 (0.06)	0.13 (0.05)	F=0.46, p=.632

Characteristic	Low Sleep Disturbance (0)	High Sleep Disturbance (1)	Very High Sleep Disturbance (2)	Statistics
	35.8% (n=145)	48.6% (n=197)	15.6% (n=63)	
	% (n)	% (n)	% (n)	
Gender (% female)	34.5 (50)	53.3 (105)	49.2 (31)	$\chi^2=12.23$ , $p=.002$ $0 < 1$
Ethnicity				$\chi^2=7.86$ , $p=.248$
White	64.1 (91)	71.1 (138)	65.1 (41)	
Asian or Pacific Islander	14.8 (21)	9.8 (19)	12.7 (8)	
Black	12.0 (17)	8.8 (17)	4.8 (3)	
Hispanic Mixed or Other	9.2 (13)	10.3 (20)	17.5 (11)	
Married or partnered (% yes)	78.9 (112)	61.4 (121)	58.7 (37)	$\chi^2=13.81$ , $p=.001$ $0 > 1$ and $2$
Lives alone (% yes)	15.5 (22)	20.3 (40)	22.6 (14)	$\chi^2=1.87$ , $p=.392$
Childcare responsibilities (% yes)	16.6 (24)	18.5 (35)	37.1 (23)	$\chi^2=12.22$ , $p=.002$ $0$ and $1 < 2$
Adult care responsibilities (% yes)	7.2 (10)	6.8 (12)	8.6 (5)	$\chi^2=0.21$ , $p=.900$
Currently employed (% yes)	42.1 (59)	32.1 (63)	21.0 (13)	$\chi^2=9.14$ , $p=.010$ $0 > 2$
Income				KW=4.18, $p=.124$
< \$30,000+	13.9 (17)	19.1 (34)	35.5 (22)	
\$30,000 to <\$70,000	20.5 (25)	20.8 (37)	14.5 (9)	
\$70,000 to < \$100,000	22.1 (27)	15.7 (28)	11.3 (7)	
> \$100,000	43.4 (53)	44.4 (79)	38.7 (24)	
Specific comorbidities (% yes)				
Heart disease	5.5 (8)	5.1 (10)	4.8 (3)	$\chi^2=0.06$ , $p=.970$
High blood pressure	33.8 (49)	37.1 (73)	22.2 (14)	$\chi^2=4.71$ , $p=.095$
Lung disease	2.8 (4)	7.1 (14)	9.5 (6)	$\chi^2=4.57$ , $p=.102$
Diabetes	9.7 (14)	13.2 (26)	20.6 (13)	$\chi^2=4.66$ , $p=.097$
Ulcer or stomach disease	3.4 (5)	7.6 (15)	4.8 (3)	$\chi^2=2.82$ , $p=.244$
Kidney disease	0.7 (1)	1.5 (3)	3.2 (2)	$\chi^2=1.86$ , $p=.394$

Characteristic	Low Sleep Disturbance (0)	High Sleep Disturbance (1)	Very High Sleep Disturbance (2)	Statistics
	35.8% (n=145) % (n)	48.6% (n=197) % (n)	15.6% (n=63) % (n)	
Liver disease	11.7 (17)	13.2 (26)	9.5 (6)	$X^2=0.64$ , $p=.728$
Anemia or blood disease	5.5 (8)	10.2 (20)	15.9 (10)	$X^2=5.81$ , $p=.055$
Depression	4.1 (6)	16.2 (32)	31.7 (20)	$X^2=28.44$ , $p<.001$ $0 < 1 < 2$
Osteoarthritis	4.8 (7)	11.2 (22)	12.7 (8)	$X^2=5.19$ , $p=.075$
Back pain	15.2 (22)	22.8 (45)	33.3 (21)	$X^2=8.80$ , $p=.012$ $0 < 2$
Rheumatoid arthritis	2.1 (3)	2.0 (4)	3.2 (2)	$X^2=0.31$ , $p=.856$
Exercise on a regular basis (% yes)	77.9 (113)	60.9 (120)	59.3 (35)	$X^2=12.67$ , $p=.002$ $0 > 1$ and $2$
Current or history of smoking (% yes)	30.1 (43)	31.1 (59)	36.1 (22)	$X^2=0.74$ , $p=.690$
Colon and rectal cancer (% yes)	59.7 (86)	64.1 (125)	66.7 (42)	$X^2=1.13$ , $p=.569$
Type of prior cancer treatment				$X^2=19.51$ , $p=.003$ $0 > 1$ and $2$
No prior treatment	42.0 (58)	23.3 (45)	19.4 (12)	
Only surgery, CTX, or RT	31.9 (44)	39.9 (77)	41.9 (26)	NS
Surgery & CTX, or Surgery & RT, or CTX & RT	18.1 (25)	25.4 (49)	21.0 (13)	NS
Surgery & CTX & RT	8.0 (11)	11.4 (22)	17.7 (11)	NS
CTX regimen				$X^2=6.79$ , $p=.341$
FOLFIRI	15.0 (21)	10.8 (21)	22.6 (14)	
FOLFOX	41.4 (58)	44.3 (86)	43.5 (27)	
FOLFIRINOX	12.1 (17)	11.3 (22)	6.5 (4)	
Other	31.4 (44)	33.5 (65)	27.4 (17)	
CTX cycle length				$X^2=3.84$ , $p=.428$
14 day	80.7 (117)	84.2 (165)	84.1 (53)	
21 day	17.9 (26)	12.2 (24)	14.3 (9)	
28 day	1.4 (2)	3.6 (7)	1.6 (1)	

Characteristic	Low	High	Very High	Statistics
	Sleep Disturbance (0)	Sleep Disturbance (1)	Sleep Disturbance (2)	
	35.8% (n=145)	48.6% (n=197)	15.6% (n=63)	
	% (n)	% (n)	% (n)	
Emetogenicity of CTX				$\chi^2=3.62, p=.460$
Minimal/low	11.7 (17)	17.9 (35)	11.1 (7)	
Moderate	84.8 (123)	79.0 (154)	84.1 (53)	
High	3.4 (5)	3.1 (6)	4.8 (3)	
Antiemetic regimen				$\chi^2=4.78, p=.572$
None	3.5 (5)	5.2 (10)	9.8 (6)	
Steroid alone or serotonin antagonist alone	11.9 (17)	11.5 (22)	8.2 (5)	
Serotonin receptor antagonist and steroid	65.0 (93)	61.3 (117)	57.4 (35)	
NK-1 receptor antagonist and two other antiemetics	19.6 (28)	22.0 (42)	24.6 (15)	

Abbreviations: AUDIT = Alcohol Use Disorders Identification Test, CTX = chemotherapy, dl = deciliter, FOLFIRI = leucovorin/5-fluorouracil/irinotecan, FOLFIRINOX = leucovorin/5-fluorouracil/irinotecan/oxaliplatin, FOLFOX = leucovorin/5-fluorouracil/oxaliplatin, gm = grams, kg = kilograms, KW = Kruskal Wallis test, m<sup>2</sup> = meter squared, NK-1 = neurokinin-1, NS = not significant, RT = radiation therapy, SD = standard deviation

### **6.3.3 Differences in Symptom Scores**

As shown in Table 16, significant differences were found among the three sleep disturbance classes for all of the GSDS subscale and total sleep disturbance scores at enrollment (i.e., Low < High < Very High).

As shown in Table 17, significant differences were found among the three classes in trait anxiety, state anxiety, depressive symptoms, morning fatigue, and evening fatigue scores (i.e., Low < High < Very High). Differences in attentional function scores followed the expected pattern (i.e., Low > High > Very High). For morning and evening energy, compared to the Low class, patients in the High and Very High classes had lower scores. In terms of the occurrence of pain, compared to the Low class, a higher percentage of patients in the High and Very High classes reported both cancer and non-cancer pain. For patients who had pain, compared to the Low class, patients in the High and Very High classes had higher worst pain intensity and pain interference scores.

### **6.3.4 Differences QOL Outcomes**

As shown in Figure 9, except for the spiritual well-being subscale, significant differences were found among the three classes for the QOL-PV subscales and total scores (i.e., Low > High > Very High). In addition, significant differences were found among the three sleep disturbance classes for the PCS and the MCS scores (i.e., Low > High > Very High).

**Table 16: Differences in the General Sleep Disturbance Subscale and Total Scores Among the Sleep Disturbance Classes at Enrollment**

Subscales and Total GSDS Scores <sup>a</sup>	Low Sleep Disturbance (0)	High Sleep Disturbance (1)	Very High Sleep Disturbance (2)	Statistics
	35.8% (n=145)	48.6% (n=197)	15.6% (n=63)	
	Mean (SD)	Mean (SD)	Mean (SD)	
Excessive daytime sleepiness ( $\geq 3$ )	1.4 (1.0)	2.9 (1.2)	4.1 (1.2)	F=139.20, p<.001 0 < 1 < 2
Medications for sleep ( $\geq 3$ )	0.3 (0.6)	0.6 (0.7)	1.0 (1.1)	F=21.00, p<.001 0 < 1 < 2
Sleep quality ( $\geq 3$ )	1.7 (1.4)	3.5 (1.4)	5.2 (1.4)	F=150.74, p<.001 0 < 1 < 2
Sleep quantity ( $\geq 3$ )	3.9 (1.3)	4.7 (1.5)	5.7 (1.8)	F=32.47, p<.001 0 < 1 < 2
Sleep onset latency ( $\geq 3$ )	1.2 (1.5)	2.7 (1.9)	4.6 (2.4)	F=73.48, p<.001 0 < 1 < 2
Mid-sleep awakenings ( $\geq 3$ )	3.9 (2.4)	5.0 (2.0)	6.2 (1.3)	F=29.94, p<.001 0 < 1 < 2
Early awakenings ( $\geq 3$ )	2.1 (2.0)	3.9 (2.2)	5.6 (1.8)	F=70.63, p<.001 0 < 1 < 2
Total GSDS scores ( $\geq 43$ )	31.5 (11.6)	54.5 (12.4)	78.2 (14.6)	F=324.05, p<.001 0 < 1 < 2

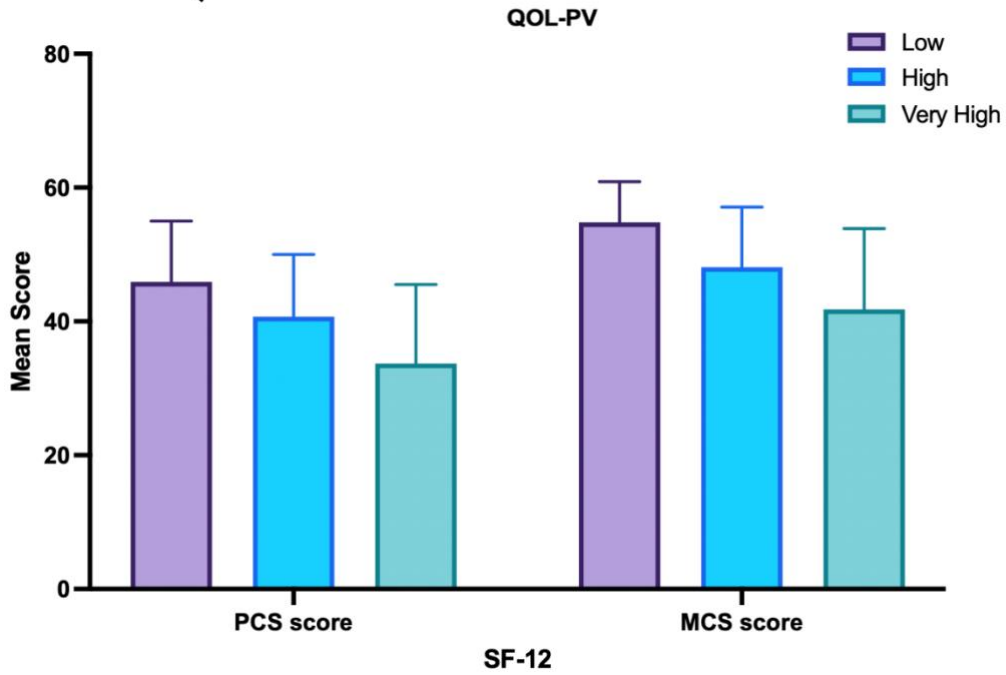
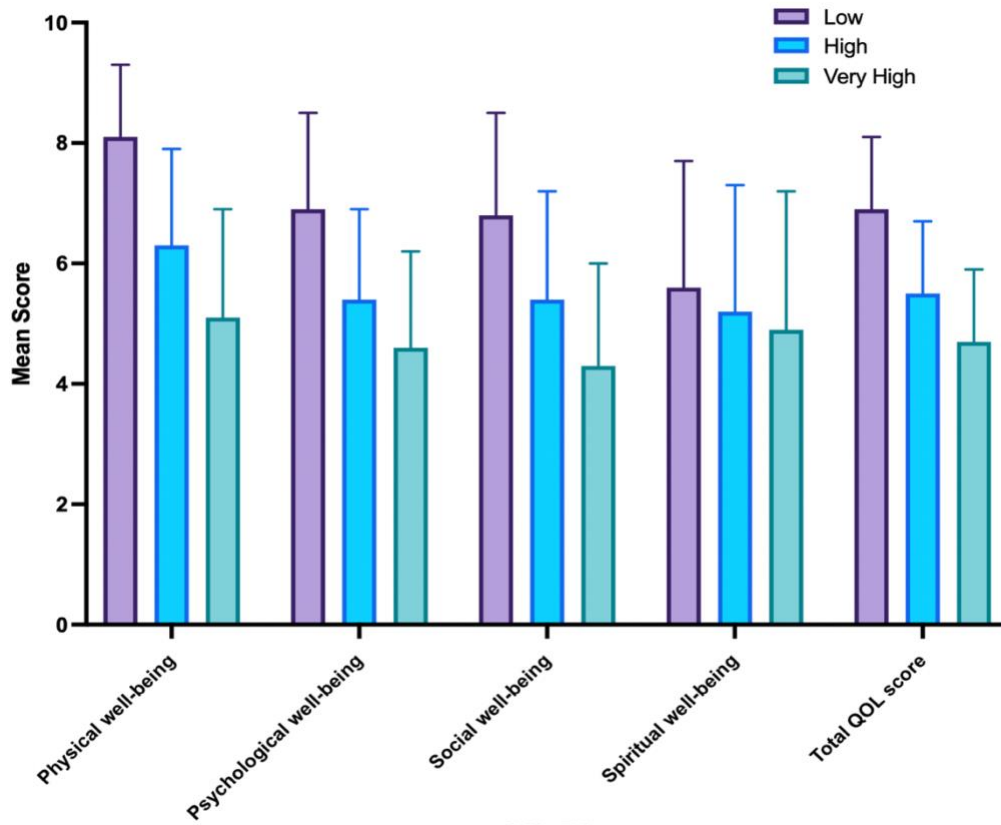
Abbreviations: GSDS = General Sleep Disturbance Scale, SD = standard deviation  
<sup>a</sup> Numbers in parenthesis indicate clinical meaningful cutoff scores.

**Table 17: Differences in Co-occurring Symptoms Scores Among the Sleep Disturbance Classes at Enrollment**

Symptoms <sup>a</sup>	Low Sleep Disturbance (0) 35.8% (n=145)	High Sleep Disturbance (1) 48.6% (n=197)	Very High Sleep Disturbance (2) 15.6% (n=63)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	
Symptoms scores				
Trait anxiety ( $\geq 31.8$ )	28.3 (6.4)	35.2 (9.0)	42.8 (11.6)	F=64.17, p<.001 0 < 1 < 2
State anxiety ( $\geq 32.2$ )	26.8 (7.6)	35.1 (10.9)	42.4 (14.4)	F=52.60, p<.001 0 < 1 < 2
Depressive symptoms ( $\geq 16$ )	6.3 (5.4)	13.4 (7.7)	19.5 (10.7)	F=74.21, p<.001 0 < 1 < 2
Attentional function ( $\leq 7.5$ )	7.7 (1.5)	6.2 (1.6)	5.2 (1.9)	F=59.68, p<.001 0 > 1 > 2
Morning fatigue ( $\geq 3.2$ )	1.2 (1.0)	3.2 (2.1)	5.3 (2.2)	F=120.20, p<.001 0 < 1 < 2
Evening fatigue ( $\geq 5.6$ )	3.6 (2.0)	5.5 (2.1)	6.7 (1.7)	F=58.71, p<.001 0 < 1 < 2
Morning energy ( $\leq 6.2$ )	5.2 (2.5)	4.2 (2.3)	3.7 (2.1)	F=10.74, p<.001 0 > 1 and 2
Evening energy ( $\leq 3.5$ )	4.2 (2.0)	3.2 (1.9)	2.9 (2.1)	F=12.74, p<.001 0 > 1 and 2
	% (n)	% (n)	% (n)	
Pain type				X <sup>2</sup> =27.86, p<.001
No pain	45.1 (64)	25.8 (50)	19.0 (12)	0 > 1 and 2
Only non-cancer pain	23.9 (34)	27.3 (53)	25.4 (16)	NS
Only cancer pain	15.5 (22)	16.0 (31)	12.7 (8)	NS
Both cancer and non-cancer pain	15.5 (22)	30.9 (60)	42.9 (27)	0 < 1 and 2
For patients with pain	Mean (SD)	Mean (SD)	Mean (SD)	
Worst pain intensity score	4.7 (2.5)	6.0 (2.4)	7.3 (2.5)	F=12.89, p<.001 0 < 1 < 2
Pain interference score	1.8 (1.9)	3.1 (2.2)	4.9 (2.8)	F=26.35, p<.001 0 < 1 < 2

Abbreviations: NS = not significant, SD = standard deviation

<sup>a</sup> Numbers in parenthesis indicate clinical meaningful cutoff scores.



**Figure 9: Qualitive of Life Outcomes for the Latent Classes**

Abbreviations: MCS = mental component summary, PCS = physical component summary, QOL-PV = Quality of Life Scale-Patient Version, SF-12 = Medical Outcomes Study-Short Form-12

## **6.4 Discussion**

This study is the first to identify subgroups of patients with GI cancers with distinct sleep disturbance profiles. Consistent with previous studies of patients with GI cancers (Innominato et al., 2015; Sun et al., 2020; Tantoy et al., 2017), almost 65% of our patients reported high levels of sleep disturbance across all six assessments (i.e., the mean total GSDS scores were above the clinically meaningful cutoff score of  $\geq 43$ ). Similar to the findings from our previous report of the total sample of patients with heterogenous cancer diagnoses (Tejada et al., 2019), the mean total GSDS score for the patients with GI cancers (i.e., 50.2) suggests a high overall level of sleep disturbance. However, in the LPA analysis for the total sample that identified the same three sleep disturbance profiles, compared to the patients with the other types of cancer (i.e., breast, lung, gynecological), a higher percentage of patients with GI cancers were classified in the Low class. Our current analysis of only patients with GI cancers suggests that within cancer type analyses are warranted to identify the characteristics associated with membership in the higher classes even when a specific type of cancer may have a lower overall symptom burden compared to other cancer types. While the relative proportions of patients in the High and Very High classes were slightly higher in the total sample (i.e., 74.8%) compared to the patients with GI cancers (i.e., 64.8%), for both samples, their total GSDS scores were almost identical. It should be noted that total GSDS scores of

approximately 60 are indicative of significant sleep disturbance as reported in studies of shift workers (Lee, 1992) and mothers and fathers of newborn infants (Gay et al., 2004).

The GSDS subscale scores provide specific information about differences in a number of sleep characteristics among the patient subgroups. As shown in Table 16, for all of the GSDS subscales, scores increased in a stepwise fashion among the three classes. However, across the three classes, insufficient quantity of sleep and a high number of mid-sleep awakenings were the only two subscales that had scores above the clinically meaningful cutoff, which suggests that the problem occurs on three or more days per week.

In addition, the scores on the GSDS subscales allow for an evaluation of two common problems associated with sleep disturbance, namely: difficulty with the initiation of sleep (i.e., sleep onset latency) and difficulty with the maintenance of sleep (i.e., early awakenings and mid-sleep awakenings). The relatively high mid-sleep awakening (i.e., 3.9) score in the Low class as well as the relatively high mid-sleep awakening (i.e., 5.0) and early awakening (i.e., 3.9) scores in the High class suggest that both groups have problems with sleep maintenance. In contrast, patients in the Very High class had problems with both sleep initiation and maintenance. Consistent with previous studies of patients undergoing radiation therapy (Garrett et al., 2011) and treatment for breast cancer (Van Onselen et al., 2013), the use of sleep medications was extremely low. Taken together, these findings suggest that sleep disturbance is a

significant problem in patients with GI cancers. Clinicians need to determine the underlying processes for these sleep disturbances and teach patients effective sleep hygiene interventions (e.g., increases in daytime activity, establishment of a regular bedtime) (Chung et al., 2018; Zengin & Aylaz, 2019).

One goal of this study was to identify common and distinct risk factors associated with higher levels of sleep disturbance within and across cancer types. To achieve this goal, as summarized in Table 18, we identified characteristics associated with membership in the Very High sleep disturbance class compared to the Low sleep disturbance class in both the current sample of patients with GI cancers and the total sample with heterogeneous types of cancer (Tejada et al., 2019). For both samples, the common risk factors associated with membership in the Very High class were: younger age, not being married/partnered, being unemployed, having childcare responsibilities, lack of regular exercise, having a lower performance status, and having a higher comorbidity burden. Findings regarding age differences in sleep disturbance are inconsistent with some finding associations with younger (Miaskowski et al., 2011; Van Onselen et al., 2012) and others with older (Lai et al., 2018; Rogers et al., 2008) age. These inconsistencies may be related to specific types of cancer and/or the timing of the assessments.

**Table 18: Demographic, Clinical, and Symptom Characteristics Associated with Higher Levels of Sleep Disturbance**

Characteristics (the comparisons done to the Low class)	Very High Sleep Disturbance Class GI Sample	Very High Sleep Disturbance Class Total Sample <sup>a</sup>
<b>Demographic Characteristics</b>		
Younger age	♦	♦
Being female		♦
Being not married or partnered	♦	♦
Living alone		♦
Being not currently employed	♦	♦
Lower income		♦
Having childcare responsibilities	♦	♦
Lack of exercise on a regular basis	♦	♦
<b>Clinical Characteristics</b>		
Higher body mass index		♦
Lower KPS score	♦	♦
Higher number of comorbidities	♦	NE
Higher SCQ score	♦	♦
Having a diagnosis of back pain	♦	NE
Having a diagnosis of depression	♦	NE
Having prior cancer treatments	♦	
Higher number of prior cancer treatments	♦	
<b>Symptom Characteristics</b>		
Higher trait anxiety	♦	♦
Higher state anxiety	♦	♦
Higher depressive symptoms	♦	♦
Higher sleep disturbance	♦	♦
Lower attentional function	♦	♦
Higher morning fatigue	♦	♦
Higher evening fatigue	♦	♦
Lower morning energy	♦	♦
Lower evening energy	♦	♦
Having pain	♦	♦
Having only non-cancer pain		♦
Having both cancer and non-cancer pain	♦	♦

Abbreviations: KPS = Karnofsky Performance Status, NE = not evaluated, SCQ = Self-administered Comorbidity Questionnaire

<sup>a</sup> Reference: Tejada, M., Viele, C., Kober, K. M., Cooper, B. A., Paul, S. M., Dunn, L. B., Hammer, M. J., Wright, F., Conley, Y. P., Levine, J. D., & Miaskowski, C. (2019). Identification of subgroups of chemotherapy patients with distinct sleep disturbance profiles and associated co-occurring symptoms. *Sleep*, 42(10), zsz151. <https://doi.org/10.1093/sleep/zsz151>

The added stress associated with some of the other demographic risk factors may explain their associations with very high levels of sleep disturbance. For example, patients who are not married or partnered may experience higher levels of loneliness which is associated with sleep disturbance (Griffin et al., 2020). The added stress of caring for children while receiving chemotherapy may contribute to a lack of sleep or poorer quality of sleep (Palesh et al., 2013). In addition, being unemployed may be associated with an increased financial burden and associated with sleep problems (Zhang et al., 2014). While these characteristics are not modifiable, clinicians can provide referrals to social services and/or psychological counseling to help patients manage their stress.

Lack of regular exercise is the only modifiable risk factor associated with membership in the Very High sleep disturbance class. The benefits of exercise to decrease sleep problems are well documented (Coles et al., 2018; Medysky et al., 2017). For example, a meta-analysis found that patients who participated in an aerobic exercise program (i.e., 4 to 8 week, 80 to 149 minutes per week) experienced significant reductions in sleep disturbance (i.e., medium to large effects) (Fang et al., 2019). Therefore, clinicians need to encourage patients to increase aerobic exercise during and following chemotherapy.

Consistent with prior studies (Chen et al., 2008; Van Onselen et al., 2013), higher levels of sleep disturbance were associated with a higher comorbidity burden and lower

functional status in our patients with GI cancers. Of note, the differences in SCQ and KPS scores between the patients in the Low and Very High classes represent not only statistically significant but clinically meaningful differences (i.e.,  $d = 0.8$  and  $1.3$ , respectively). It is reasonable to hypothesize and is supported by studies of patients with other chronic conditions (e.g., hypertension, diabetes) that higher comorbidity burden contributes to sleep disturbance (Katz & McHorney, 1998; Mokhlesi et al., 2016). In addition, findings from this study suggest that a low functional status may contribute to a lack of regular exercise and associated sleep disturbance.

In terms of the distinct factors that were associated with membership in the Very High class, in the patients with GI cancers, three factors were identified, namely: having received prior cancer treatments, having a higher total number of prior cancer treatments, and having higher number of comorbidities. While not assessed in the total sample, a higher percentage of patients in the Very High class self-reported diagnoses of back pain and depression. Compared to the 58% of patients in the Low class, 80.6% of the patients with GI cancers in the Very High class had received at least one additional treatment prior to chemotherapy. While the timing between the previous and current treatments was not evaluated, this finding supports previous research that suggests that the effects of cancer treatments on sleep disturbance may be cumulative (Tantoy et al., 2017). The high occurrence rates for self-reported back pain (33.3%) and depression (31.7%) in the Very High class of patients with GI cancers provide some insights into the

associations between sleep disturbance and comorbidity burden. For example, in the general population both back pain (Nijs et al., 2018) and depression (Asarnow, 2020) are associated with sleep disturbance.

In our previous studies (Lin et al., 2021; Lin et al., 2020a), we found that patients with GI cancers experienced an average of 10 to 15 multiple co-occurring symptoms. Similar to the GSDS subscale scores, levels of trait and state anxiety, depressive symptoms, cognitive dysfunction, morning and evening fatigue, and pain intensity and interference were significantly different among the three sleep disturbance classes of patients with GI cancers (Table 17). It is interesting to note that for all three sleep disturbance classes, morning energy scores were below the clinically meaningful cutoff score. However, only patients in the Very High class had scores that were well above the clinically meaningful cutoff for all of the other symptoms listed in Table 17.

When comparisons were done between the current sample and the total sample (Table 18), our findings suggest that very high levels of sleep disturbance are associated with multiple co-occurring symptoms. It should be noted that in both samples, the differences in all of the symptom severity scores, between the Low and Very High classes represent not only statistically significant but clinically meaningful differences (i.e., effect sizes ranged from 0.6 [morning energy] to 1.8 [morning fatigue]). While previous studies have reported on positive associations between sleep disturbance and fatigue (Medysky et al., 2017), anxiety (Battle, 2013), depression (Irwin et al., 2013), and

pain (Loh et al., 2018) in oncology patients, none of these studies assessed all of these co-occurring symptoms in the same sample of patients. The hypothesized mechanisms for the co-occurrence of sleep disturbance and other symptoms include: increases in proinflammatory cytokine activity; dysregulation of the hypothalamic-pituitary-adrenal axis; and misaligned circadian rhythms (Irwin et al., 2013; Miaskowski et al., 2011). Future studies need to determine the common and distinct mechanisms for the co-occurrence of these symptoms.

In terms of generic and disease-specific QOL outcomes, except for the spiritual well-being subscale of the QOL-PV, significant differences were found among the three sleep disturbance classes. Compared to the Low class, all of the differences across the various domains of QOL in the Very High class represent not only statistically significant but clinically meaningful differences ( $d = 1.3$  to  $1.7$ ). Of note, across all three classes, patients with GI cancers reported PCS scores of  $<50$  which is lower than the normative score for the general population (Padilla et al., 1990). Consistent with previous studies in patients with lung (Chen et al., 2008) and ovarian (Clevenger et al., 2013) cancer, high levels of sleep disturbance were associated with poorer QOL outcomes.

#### **6.4.1 Limitations**

Several limitations warrant consideration. While a valid and reliable measure was used to evaluate sleep disturbance, future studies need to evaluate for similar

associations using objective measures such as actigraphy and/or polysomnography. Because patients were not recruited prior to the initiation of chemotherapy, risk profiles for sleep disturbance from its initiation through completion were not evaluated. Given that the majority of the patients were White and well educated, our findings may not generalize to more diverse samples. In addition, given the heterogeneity in GI cancers in this study, future studies need to consider similar evaluations of patients with specific GI cancers (e.g., pancreatic, gastric).

## **6.5 Conclusion**

This study is the first to identify subgroups of patients with GI cancers with distinct sleep disturbance profiles and identify risk factors associated with higher levels of sleep disturbance. Additional research is warranted to explore underlying molecular mechanisms that contribute to the development of sleep disturbance and the co-occurrence of other common symptoms during chemotherapy. Clinicians need to assess for the common risk factors and associated co-occurring symptoms, as well as initiate personalized symptom management interventions and referrals.

## 7. Conclusion

The purpose of this dissertation was to identify and describe multiple co-occurring symptoms in patients with GI cancers. This purpose was achieved through 1) an integrative literature review (Chapter 2) to describe common and co-occurring symptoms in patients with gastric cancer; 2) a qualitative descriptive study (Chapter 3) to describe the symptom experience and self-management for multiple co-occurring symptoms in patients with gastric cancer; and 3) three quantitative studies using a person-centered approach (Chapter 4, 5, and 6) to identify subgroups of patients with GI cancers with distinct profiles of symptom experiences (i.e., multiple co-occurring symptoms, morning and evening fatigue, sleep disturbance) and then determine a number of demographic and clinical characteristics, as well as co-occurring symptoms and QOL outcomes among these subgroups.

Findings from this dissertation can help patients and their families to better understand the disease- and treatment-related multiple co-occurring symptoms that present in GI cancers, as well as assist researchers and clinicians to identify patients with GI cancers who are at the highest risk for a higher symptom burden and develop innovative methods to recognize and treat those symptoms. This dissertation is the first step in my program of research and provides a solid foundation to explore the underlying biologic mechanisms of multiple co-occurring symptoms and develop personalized symptom management interventions for future work.

## **7.1 Summary**

We synthesized four key findings from this dissertation that add depth and breadth to our understanding for and contribute to the literature of multiple co-occurring symptoms in patients with GI cancers.

The first key finding was the unique symptom experiences and self-management strategies for multiple co-occurring symptoms in patients with gastric cancer. We used gastric cancer as an exemplar. Our findings from Chapter 2 (i.e., integrative review) provided a solid foundation for the later chapters and helped us identify the gaps in this field. To address one of the gaps, in Chapter 3, we used a descriptive qualitative design to deeply understand the symptom experiences and self-management strategies among patients with gastric cancer during treatment, especially in American patients. The findings were consistent with most of the physical symptoms that were identified in Chapter 2 but did not include affective/cognitive symptoms. Possible explanations for this difference include 1) patients with cancer overlooked affective/cognitive symptoms in favor of physical symptoms when they were asked what symptoms they experienced; 2) a number of patients underwent surgery and/or chemotherapy and/or radiation therapy in Chapter 2, while all patients received chemotherapy in Chapter 3. Different treatment modalities may result in distinct symptom experiences. In addition, a large amount of inter-individual variability and dynamic nature in the experiences of multiple co-occurring symptoms were described by our participants, which led us to use a

person-centered approach (i.e., latent class/profile analysis) and longitudinal designs in later chapters. Four symptom self-management strategies were identified: medications for symptoms, information-seeking from the clinician team, lifestyle modifications, and psychosocial and spiritual support. The findings provide insights into the basis for the development of patient-centered symptom self-management interventions that consider patients' preferences, needs, and distinct symptom experiences. Consistent with a review of guideline-recommended symptom management strategies that cross over two or more cancer symptoms (Kwekkeboom et al., 2020), our findings suggest that clinicians should develop and test symptom management interventions in the context of multiple co-occurring symptoms and apply the guidelines to addressing these symptoms.

The second key finding was the identification of subgroups of patients with GI cancers with distinct symptom profiles. In the era of precision health (Collins & Varmus, 2015), it is critical that we understand the significant inter-individual variability in patients' symptom experiences through identifying subgroups of patients with similar symptom experiences. Two to three classes/profiles were identified for multiple co-occurring symptoms, morning and evening fatigue, and sleep disturbance. The subgroups we identified were inconsistent in patients with heterogeneous cancer diagnoses (Miaskowski et al., 2015; Wright et al., 2019). The inconsistency may be attributed to differences in sample sizes and heterogeneity in cancer diagnoses and

treatments. While the number of subgroups is different, our findings suggest that regardless of symptom type and number and cancer diagnosis, a subgroup of patients with GI cancers is at higher risk for an extremely high symptom burden. Clinicians should identify patients with GI cancers at higher risk for the worst symptom profiles or highest symptom burden and develop effective methods to recognize and treat these high-risk subgroups. In addition, our current analysis of patients with GI cancers also suggests that analyses within cancer type are warranted. Future research needs to perform similar evaluations of patients with specific GI cancers (e.g., pancreatic, gastric).

The third key finding was the identification of common and distinct risk factors as well as modifiable and non-modifiable risk factors associated with a more severe symptom profile across cancer types. One of the major advantages of using a person-centered approach in this dissertation is that we identified salient demographic and clinical characteristics that place patients at increased risk for a higher symptom burden. The comparisons are made between the current sample of patients with GI cancers and our previous reports of the total sample of patients with heterogenous cancer diagnoses. Our findings suggest that most of the risk factors were identical in patients with GI cancers and heterogenous cancer diagnoses. Clinicians should take advantage of these common risk factors associated with higher symptom profiles to treat patients with a wide range of cancer diagnoses. For non-modifiable risk factors (e.g., younger age, unemployment, having childcare responsibilities), clinicians can identify support

services (e.g., social workers) and initiate appropriate referrals (e.g., physical therapy, psychological counseling) for these patients. Lack of regular exercise is the only modifiable risk factor identified for a higher symptom burden. The evidence has shown the medium to large effect of exercises on symptom relief (Fang et al., 2019). These findings suggest that clinicians need to encourage patients to increase exercise (e.g., 8-week aerobic exercise program) during and following chemotherapy. The inconsistencies with the distinct risk factors may be related to specific types of cancer and/or the differences in chemotherapy-induced toxicity and gender proportions. Additional research is warranted to determine the phenotypic and molecular characteristics that contribute to a higher symptom burden in these patients.

The fourth key finding was the associations of morning and evening fatigue and sleep disturbance with other co-occurring symptoms including anxiety, depressive symptoms, pain, and cognitive dysfunction as well as the associations of multiple co-occurring symptoms with QOL outcomes. We found that higher levels of morning and evening fatigue and sleep disturbance were associated with not only statistically significant but clinically meaningful increases in trait and state anxiety, depressive symptoms, pain, and cognitive dysfunction (i.e., medium to high effect sizes). These findings were consistent with previous studies on co-occurring psychoneurological symptoms (Kim et al., 2012; Starkweather et al., 2017). Future research could determine the common and distinct mechanisms for the co-occurrence of these symptoms. In

addition, our findings showed that except for spiritual well-being, a higher symptom burden was associated with statistically significant and clinically meaningful decrements in QOL outcomes that include physical, psychological, and social wellbeing (i.e., medium to high effect sizes). Consistency was found in higher levels of multiple co-occurring symptoms, morning and evening fatigue, and sleep disturbance being associated with poorer QOL outcomes in this population. Clinicians need to develop symptom interventions targeting multiple co-occurring symptoms to improve QOL for patients with GI cancers.

In summary, this dissertation is the first to identify the subgroups of patients with GI cancers with distinct symptom experience profiles and determine common and distinct risk factors associated with more severe symptom profiles, as well as describe symptom experiences and self-management strategies for multiple co-occurring symptoms. Additional research is warranted to explore underlying molecular mechanisms that contribute to the development of multiple co-occurring symptoms during chemotherapy. Clinicians need to assess for common risk factors and associated co-occurring symptoms, as well as initiate personalized symptom management interventions and referrals.

## **7.2 Limitations**

The limitations of the dissertation are summarized. First, given that the majority of the patients were White and well educated, our findings may not generalize to more

diverse and socioeconomically disadvantaged patient samples. Second, there was heterogeneity and different proportions of GI cancer types in the samples (e.g., 45.6% colon, 19.8% rectal, 18.3% pancreatic, 5.3% esophageal, and 4.9% gastric cancer). Third, because patients were not recruited prior to the initiation of chemotherapy, risk profiles of symptom experiences from initiation through completion were not evaluated. Fourth, the Memorial Symptom Assessment Scale utilized in the study was developed to evaluate symptoms experienced by oncology patients not specific to patients with GI cancers. It did not include some GI specific symptoms (e.g., acid reflux, flatulence, early satiety). Finally, while we evaluated a number of demographic and clinical characteristics, we did not include psychological, social, and environmental variables (e.g., stress, uncertainty, social support, living conditions). We only evaluated the QOL outcomes, and other outcomes such as response to treatment, mortality, health care utilization, and costs were not included.

### ***7.3 Implications***

While this dissertation contributed knowledge about multiple co-occurring symptoms in patients with GI cancers, research on multiple co-occurring symptoms is still in early stages. Findings from this dissertation have several implications for future research, clinical practice, and policy.

### 7.3.1 Implications for Research

While advances have been made in the identification of subgroups of patients with distinct symptom experiences using grouping techniques (e.g., latent class/profile analysis) and the evaluation of multiple co-occurring symptom experiences, a number of areas warrant investigation to advance the field of symptom science research. Future research should focus on identification of subgroups of patients with distinct symptom profiles present in specific GI cancers (e.g., gastric, pancreatic). Additional studies are needed to identify the symptom experience among ethnic and racial minorities and socioeconomically disadvantaged patients. In addition, more research should focus on multiple co-occurring symptoms by the distress and frequency dimensions. Other clinical and treatment characteristics (e.g., time since cancer diagnosis, MAX2 scores, chemotherapy regimens) associated with a higher symptom burden and the effects of multiple co-occurring symptoms on outcomes such as cost, emotional status, and self-care should be studied. While social determinants of health (e.g., socioeconomic conditions, social support) are known to influence risk of and treatment for GI cancer (Carethers & Doubeni, 2020), additional research is warranted on how these characteristics individually and collectively influence the symptom burden of these patients. Longitudinal trajectories in both qualitative and quantitative studies should also be incorporated in multiple co-occurring symptom research to capture the dynamic nature of symptom experiences. More importantly, using new analytic techniques on

multiple co-occurring symptoms (e.g., machine learning, evolutionary algorithms, latent transition analysis, risk stratification) promises the growth of symptom science research (Miaskowski et al., 2017).

The findings from this dissertation emphasize the need for further investigations into the common and distinct underlying mechanisms or etiologies of multiple co-occurring symptoms. The primary hypothesized mechanisms for the co-occurrence of these symptoms include the initiation of a series of inflammatory processes (e.g., increases in proinflammatory cytokine activity), dysregulation of the hypothalamic-pituitary-adrenal axis, activation of the sympathetic nervous system (e.g., misaligned circadian rhythms), and immune responses (e.g., eosinophils, viral antibody) that occur following the administration of chemotherapy (Bower & Lamkin, 2013; Irwin et al., 2013; Kim et al., 2012; Starkweather et al., 2017). Such findings also suggest that additional research is warranted to determine if only one mechanism works, or multiple mechanisms interact and work together. Future studies need to determine the best approaches to evaluate the underlying genetic, epigenetic, or biobehavioral mechanisms for multiple co-occurring symptoms and utilizing omics methodologies to discover biomarkers for symptom science research. Understanding the underlying mechanisms is essential to developing effective treatments across cancer types and even chronic conditions.

In this era of precision health, it is imperative that we develop personalized interventions that consider the significant inter-individual variability in patients' symptom experiences and their treatment preferences and personal needs. The number of studies on symptom interventions is still limited; much more must be done before we effectively identify and intervene to reduce multiple co-occurring symptoms present in this population. A personalized symptom intervention allows for the identification of patients with a higher risk for more severe symptom burden and then the implementation of aggressive interventions for these high-risk patients. With a focus on personalized care, future research is needed to determine the most efficacious interventions for multiple co-occurring symptoms and evaluate the use of technology in symptom self-management research. In addition, mechanistic-based studies hold great promise to identify new biological and behavioral targets that will form the basis for interventional studies. Overall, the development of personalized symptom interventions in these patients supports the potential for reducing their symptom burden and improving their capacity to live well over their entire lives.

### **7.3.2 Implications for Practice and Policy**

Findings from this dissertation may increase awareness among clinicians about multiple co-occurring symptoms experienced by patients with GI cancers and may also inform clinical symptom assessment in practice. Increasing awareness among clinicians about multiple co-occurring symptoms that patients experience may not only

underscore the importance of symptom assessments on a regular basis in clinical practice, but also be used to inform anticipatory guidance provided to patients with GI cancers and their caregivers about what to expect when receiving chemotherapy. The knowledge from these findings may be used to further target symptom assessment to address multiple co-occurring symptoms, rather than individual symptoms in isolation, which is consistent with the experience of patients with GI cancers receiving chemotherapy.

In addition, our findings suggest that clinicians can guide an initial and focused assessment based on 10 most frequently co-occurring symptoms. For example, fatigue was the first or second most common symptom among the patients with a worse symptom profile. High rates of worrying and feeling sad warrant evaluation by clinicians. Morning and evening fatigue, sleep disturbance, anxiety, depression, pain, and cognitive dysfunction that occur concurrently need to be assessed at the same time. Findings from this dissertation also suggest that clinicians need to evaluate additional symptoms as warranted using a comprehensive instrument such as the Memorial Symptom Assessment Scale, and the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events and Measurement Information System. Given the prevalence, range, and severity of symptoms in patients with GI cancers, assessing for these multiple co-occurring symptoms will assist oncology nurses to well support their patients.

By knowing that multiple symptoms have a tendency to occur together, clinicians could prevent and better manage these symptoms. Clinicians should recognize patients' risks of having multiple co-occurring symptoms and provide personalized prevention or treatment. The risk information could also be presented to patients and their caregivers, which would provide them more support in terms of relevant knowledge and better prepare them to self-manage for multiple co-occurring symptoms. Clinicians can target more intense symptom management interventions and initiate appropriate referrals for patients who are at risk for a worse symptom profile. For example, patients with high levels of comorbidity and substantial decrements in physical function would benefit from referrals to physical therapy. Patients who are in lower socioeconomic status or have childcare responsibilities should be referred to social workers or support services, and patients who self-report depression should be referred to psychological counseling.

A national Cancer Moonshot initiative was launched to accelerate efforts in cancer prevention, diagnosis, and treatment in 2016. The Blue Ribbon Panel was established to produce a report on the recommendations and priorities for cancer research (Jaffee et al., 2017). Of note, one of ten recommendations is symptom management research. Findings from this dissertation could be used to develop interventions targeting multiple co-occurring symptoms to advance symptom management research. In addition, one priority in the report is to understand and

eliminate cancer disparities. Risk factors identified in our study (e.g., lower income, having childcare responsibilities, lack of exercise, higher comorbidity burden) may contribute to cancer disparities. Our findings suggest that future research needs to incorporate minorities and socioeconomically disadvantaged populations. In terms of health policy, medical services should be enhanced for health insurance, access to health care, social resources, staffing, and clinician workload in underserved and impoverished areas to reduce cancer disparities. With the Cancer Moonshot 2.0 launch (Agus et al., 2021), clinicians, researchers, stakeholders, patients, and advocates need to work together and develop and update policies and guidelines to prevent and treat multiple co-occurring symptoms to support patients with GI cancers as well as their family members when undergoing treatment and during survivorship.

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## Biography

Yufen Lin joined the PhD program at Duke University School of Nursing in 2017. She received her Bachelor of Medicine in Nursing from Central South University and Master of Medicine in Nursing from Fudan University in China. She is a registered nurse and has worked at different cancer centers. Her research interests focus on symptom science and oncology nursing. She has 13 peer-reviewed publications and 13 abstracts that were presented at the national and international conferences. She was a recipient of the American Cancer Society doctoral grant, the Oncology Nursing Foundation Research Doctoral Scholarship and Congress Scholarship, the Duke University School of Nursing pilot study funds, and the Duke Summer Research Fellowship. She was also awarded as the “Rising Star” at the Sigma Theta Tau International Nursing Research Congress and the outstanding trainee at the Duke Cancer Institute Retreat. She is a member of several professional organizations, such as the Oncology Nursing Society, the Sigma Theta Tau International Honor Society of Nursing, and the Multinational Association of Supportive Care in Cancer. In addition, she is in the peer review board of several high-impact journals (e.g., Oncology Nursing Forum, Biological Research for Nursing). She has received a College Teaching Certificate at Duke University Graduate School and a U.S. GRADE Network Guideline Development Certificate.

### **Publications during doctoral training:**

1. **Lin, Y.**, Docherty, S. L., Porter, L. S., & Bailey, D. E. (2020). Common and co-occurring symptoms experienced by patients with gastric cancer. *Oncology Nursing Forum*, 47(2), 187-202. doi: 10.1188/20.onf.187-202
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3. **Lin, Y.**, Docherty, S.L., Porter, L.S., & Bailey, D.E. (2020). Symptom experience and self-management for multiple co-occurring symptoms in patients with gastric cancer: A qualitative study. *European Journal of Oncology Nursing*, 49, 101860. doi: 10.1016/j.ejon.2020.101860
4. **Lin, Y.**, Bailey, D.E., Docherty, S.L, Porter, L.S., Cooper, B.A. Paul, S.M., Kober, K.M., Hammer, M.J., Wright, F., Dunn, L.B., Conley, Y.P., Levine, J.D., & Miaskowski, C. (2021). Distinct profiles of multiple co-occurring symptoms in patients with gastrointestinal cancers receiving chemotherapy. *Supportive Care in Cancer*. Advance online publication. doi: 10.1007/s00520-020-05946-4
5. Wei, S., Kang, B., Bailey, D. E., Caves, K., **Lin, Y.**, McConnell, E. S., Thurow, M., Woodward, A., Wright-Freeman, K., Xue, T. M., & Corazzini, K. N. (2021). Using technology to measure older adults' social networks for health and well-being: A scoping review. *The Gerontologist*. Advance online publication. doi: 10.1093/geront/gnab039
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### **Under review:**

1. **Lin, Y.**, Bailey, D.E., Docherty, S.L, Porter, L.S., Cooper, B.A., Paul, S.M., Kober, K.M., Hammer, M.J., Wright, F., Conley, Y.P., Levine, J.D., & Miaskowski, C. Distinct morning and evening fatigue profiles in patients with gastrointestinal cancers receiving chemotherapy. *BMJ Supportive & Palliative Care* (Minor Revision)

2. Molloy, M., Zhao, Y., Leonard, C., Chen, Y., Cadavero, A., Xing, W., Vaughn, J., **Lin, Y.**, Min, H., Oermann, M., & Hu, Y. Nursing students from China and United States: Learning together through virtual simulation. *Nursing Education Perspectives* (Minor Revision)
3. Li, H., Schlaeger, J.M., Min, K.J., **Lin, Y.**, Park, C., Liu, T., Sun, M., & Doorenbos, A.Z. Acupuncture improves multiple symptoms in breast cancer survivors: A systematic review and meta-analysis. *Journal of Alternative and Complementary Medicine*
4. Bechard, E., Evans, J., Cho, E., **Lin, Y.**, Kozhumam, A., Jones, J., Grob, S., & Glass, O. Feasibility, acceptability, and potential effectiveness of expressive writing for COVID-19 resilience. *Complementary Therapies in Clinical Practice*