ONLINE EXCLUSIVE ARTICLE

Symptom Clusters in Patients With Pancreatic Cancer Undergoing Surgical Resection: Part II

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OBJECTIVES: To explore the relationship between 16 symptom clusters (SCs), clinical and demographic influencing factors, and clinical outcomes over time in patients with pancreatic cancer (PC) undergoing surgical resection.

SAMPLE & SETTING: 143 patients with stage II PC undergoing surgical resection were recruited to participate in this longitudinal, exploratory study conducted at Thomas Jefferson University Hospital, a National Cancer Institute–designated cancer center.

METHODS & VARIABLES: Quality of life was measured preoperatively and at three, six, and nine months postoperatively. Statistical methods included simple linear and Cox proportional hazard regression.

RESULTS: Preoperative pain was significantly associated with the pain–gastrointestinal SC, and preoperative worry was significantly associated with the mood SC. The strongest negative association with emotional well-being across all study time points was found with the preoperative mood SC. The insomnia–digestive problems SC and the nutritional problems SC demonstrated a trend toward poor survival.

IMPLICATIONS FOR NURSING: Findings provide evidence that preoperative worry and pain are associated with SC severity and that SCs may have a detrimental effect on quality of life and survival in patients with PC undergoing surgical resection.

KEYWORDS pancreatic cancer; symptom clusters; quality of life; survival; surgery

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Patients with pancreatic cancer (PC) experience a wide range of symptoms as a result of the cancer itself and its treatments. Commonly reported PC symptoms include fatigue, pain, weight loss, nausea, anorexia, constipation, diarrhea, trouble digesting food, insomnia, depression, anxiety, and symptoms of diabetes (Huang et al., 2000; Noquez, 2008; Reyes-Gibby et al., 2007; Sun et al., 2008; Yeo et al., 2012). Patients with PC were found to experience some of the highest levels of psychological distress, fatigue, and pain when compared to patients with other cancer types (Carlson et al., 2004; Noquez, 2008; Zabora, BrintzenhofeSzoc, Curbow, Hooker, & Piantadosi, 2001). Evidence suggests that symptoms rarely occur alone; in fact, patients undergoing surgical resection for PC experience, on average, 5–10 symptoms simultaneously (Yeo et al., 2012).

The presence of two or more interrelated, concurrent symptoms that may or may not have a common causative mechanism is called a symptom cluster (SC) (Dodd, Miaskowski, & Lee, 2004; Kim, McGuire, Tulman, & Barsevick, 2005). SCs have been identified in patients with virtually every cancer type, including patients with breast (Sullivan et al., 2018), ovarian (Huang et al., 2016), prostate (Dirksen, Belyea, Wong, & Epstein, 2016), lung (Franceschini, Jardim, Fernandes, Jamnik, & Santoro, 2013), colorectal (Agasi-Idenburg, Thong, Punt, Stuiver, & Aaronson, 2017), and PC (Yeo et al., 2012). Patients with cancer experience SCs before (Browall et al., 2017; Kim, Barsevick, & Tulman, 2009), during (Kim, Barsevick, Tulman, & McDermott, 2008; Sullivan et al., 2018), and even years after treatment (Zucca, Boyes, Linden, & Girgris, 2012).

The presence or severity of SCs has been found to be influenced by several demographic and clinical factors: age, gender, race/ethnicity, marital status,

FIGURE 1. Previously Identified Symptom Clusters Using Exploratory and Confirmatory Factor Analysis: Preoperative

Factor 1
Pain–gastrointestinal
- Nausea[a], back pain, abdominal pain/cramping, poor appetite, constipation, trouble digesting food[a]

Factor 2
Mood
- Anxiety, depression

Factor 3
Digestive problems
- Loss of bowel control, trouble digesting food[a]

Factor 4
Fatigue–nutritional problems
- Weight loss, change in taste, dry mouth, fatigue

Factor 5
Jaundice
- Nausea[a], jaundice

[a] Symptom that loaded onto more than one factor

tobacco use, cancer stage, treatment type, and comorbid conditions in patients with cancer (Cheville et al., 2011; Kim et al., 2009; Nho, Reul Kim, & Nam, 2017; Reyes-Gibby, Aday, Anderson, Mendoza, & Cleeland, 2006; Xiao et al., 2012). A relationship has also been observed between poor quality of life (QOL) and a higher number (Lin, Chen, Yang, & Zhou, 2013) and greater severity of SCs (Franceschini et al., 2013; Nho et al., 2017; Sanford et al., 2014). Certain SCs were also found to be predictors of poor QOL in specific cohorts, including older adults with cancer (Cheng & Lee, 2011), newly diagnosed patients undergoing active treatment (Pirri et al., 2013), and patients with advanced cancers (Dong et al., 2016). Likewise, an association has been observed between SCs and reduced survival in patients with lung (Cheville et al., 2011), esophageal (Wikman, Johar, & Lagergren, 2014), and advanced cancers (Aktas, Walsh, & Rybicki, 2012). Given these important relationships, SCs have become a priority focus of oncology nursing research (Knobf et al., 2015).

The body of research regarding factors that influence SCs and the relationship between SCs and clinical outcomes in many cancer types is rapidly growing: however, research focused on these phenomena in patients with PC remains limited. To date, only three studies have examined the factors that influence the SC experience or the effect of SCs on clinical outcomes in patients with various cancer types, including patients with PC. Gender, cancer type, and marital status were found to be significantly associated with SC intensity (Noquez, 2008), whereas age, race and C-reactive protein levels were found to not be significantly related to SCs (Laird et al., 2011; Noquez, 2008). SCs were found to be associated with poor clinical outcomes, including decreased physical functioning (Laird et al., 2011) and reduced median survival (Yeo et al., 2012).

The management of SCs is a concern for oncology nurses and for patients with cancer and their family members, who must assume responsibility for the day-to-day management of symptoms. Understanding factors that influence SCs is not only critical to ensure that appropriate symptom management strategies are implemented, but also to enhance counseling and anticipatory guidance provided to patients with PC and their family members. Gaining an understanding of the clinical and demographic factors that influence SC severity may also help explain causative mechanisms of SCs and assist clinicians in identifying patients at increased risk for more severe SCs postoperatively (Kim et al., 2009). In addition, understanding the factors that influence the severity of SCs and their relationship to QOL and survival may enable clinicians to identify high-risk patients and implement earlier SC interventions, which may

FIGURE 2. Previously Identified Symptom Clusters Using Exploratory and Confirmatory Factor Analysis: 3 Months Postoperative

Factor 1
Mood–pain–anorexia–fatigue
- Depression, anxiety, nausea[a], back pain, abdominal pain/cramping, poor appetite, fatigue

Factor 2
Insomnia–digestive problems
- Loss of bowel control, trouble digesting food, trouble sleeping

Factor 3
Gastrointestinal sickness
- Diarrhea, itching[a], nausea[a]

Factor 4
Nutritional problems
- Weight loss, change in taste, dry mouth, itching[a]

[a] Symptom that loaded onto more than one factor

FIGURE 3. Previously Identified Symptom Clusters Using Exploratory and Confirmatory Factor Analysis: 6 Months Postoperative

Factor 1
Mood–pain–insomnia–gastrointestinal
- Depression, anxiety, back pain[a], constipation, trouble sleeping

Factor 2
Bowel–digestive problems
- Loss of bowel control, trouble digesting food, diarrhea

Factor 3
Fatigue–anorexia–nutritional problems
- Weight loss, change in taste, dry mouth, fatigue, poor appetite

Factor 4
Pain–itching
- Itching, abdominal pain/cramping, back pain[a]

[a] Symptom that loaded onto more than one factor

reduce the severity or prevent the occurrence of SCs entirely, therefore improving clinical outcomes in this population (Sanford et al., 2014).

No research has examined factors that influence SCs or the effect of SCs on clinical outcomes over time in patients with PC undergoing surgical resection. Therefore, the purpose of this article is to describe the relationship between the severity of 16 previously identified SCs (Burrell et al., 2018) and (a) demographic and clinical influencing factors and (b) clinical outcomes of QOL and survival over time in patients with stage II PC undergoing surgical resection.

Theoretical Framework

The Theory of Unpleasant Symptoms (TOUS) served as the theoretical framework for this study (Lenz, Pugh, Milligan, Gift, & Suppe, 1997). The TOUS is comprised of three major concepts: (a) the singular or multiple symptoms that the patient is experiencing, (b) the clinical and demographic variables that influence the patient's perception of symptoms (the physiologic, psychological, and situational influencing factors), and (c) the effect that symptoms have on clinical outcomes (performance). The relationship among these three concepts is viewed as dynamic, interactive, and reciprocal in nature. The TOUS was used to conceptualize SCs, determine influencing and performance variables to include in this study, and explore the relationships among these variables.

Methods

Design, Sample, and Setting

This nested, longitudinal, descriptive study was conducted within a randomized, controlled trial (the parent study) at a National Cancer Institute–designated comprehensive cancer center at Thomas Jefferson University Hospital in Philadelphia, Pennsylvania. The parent study (Lavu et al., 2015) evaluated the effectiveness of an intraoperative celiac alcohol nerve block, a pain-relieving intervention, in 485 patients undergoing surgical resection of pancreas and periampullary cancers.

The current article adds to previously reported findings of a descriptive, longitudinal study that explored self-reported symptom profiles to identify the (a) presence of and changes in SCs, (b) factors that influence patients' perceptions of the SCs, and (c) effect of SCs on QOL and survival over time in patients with stage II PC undergoing surgical resection. Because of the large volume of data generated in the study, the findings are being presented in two parts. Self-reported symptom profiles and SCs identified in the study were previously reported (Burrell et al., 2018). This article describes the relationship between 16 previously identified SCs, demographic and clinical influencing factors, and clinical outcomes over time in patients with PC undergoing surgical resection, and serves as a follow-up article that extends the analysis from the prior report (Burrell et al., 2018).

The current study examined a sub-sample of patients with stage IIa or IIb PC undergoing surgical resection with or without adjuvant therapy recruited

FIGURE 4. Previously Identified Symptom Clusters Using Exploratory and Confirmatory Factor Analysis: 9 Months Postoperative

Factor 1
Mood–insomnia–pain–nausea
- Depression, anxiety, nausea, back pain[a], abdominal pain/cramping, trouble sleeping

Factor 2
Digestive–weight loss–bowel problems
- Loss of bowel control, trouble digesting food, diarrhea, weight loss, constipation[a]

Factor 3
Fatigue–pain–nutritional problems
- Dry mouth, change in taste, fatigue, back pain[a], constipation[a]

[a] Symptom that loaded onto more than one factor

TABLE 1. Mean Quality-of-Life Component Scores Over Time: Preoperative

Component	M	$\bar{X}$	SD	Range
Physical well-being (total range = 0–28)	24	22.04	5.53	2–28
Social well-being (total range = 0–28)	26	24.59	3.99	7–28
Emotional well-being (total range = 0–24)	17	16.45	4.97	4–24
Functional well-being (total range = 0–28)	19	18.23	6.86	0–28
FACT-G (total range = 0–108)	83.5	81.16	16.09	26–108
FACT-Hep (total range = 0–180)	140	135.28	23.68	72–176

FACT-G—Functional Assessment of Cancer–General; FACT-Hep—Functional Assessment of Cancer–Hepatobiliary; M—median

through convenience sampling techniques used in the parent study (Lavu et al., 2015). Of the 143 patients who participated in the current study, 17% (n = 24) did not complete the final nine-month questionnaire. Twenty-three patients died, and one patient declined continued participation. Participant response rates were 76% (n = 109) at three months, 64% (n = 92) at six months, and 62% (n = 89) at nine months postoperatively. Based on the use of factor analyses to identify SCs in this study, subject-to-variable guidelines requiring at least five participants for each variable were followed to determine an adequate sample size (Gorsuch, 1983). Therefore, a sample size of 85 participants at each study time point was deemed adequate to conduct a reliable factor analysis. The all-available data approach was used to address missing data to preserve patient variation in the data set and to ensure that inferences are representative of patients with stage II PC undergoing surgery (Nakai & Ke, 2011).

As previously described in greater detail (Burrell et al., 2018), most patients in this study were male (n = 82, 57%) and married (n = 107, 75%), with a mean age of 67.3 (SD = 10.4) years. Most were White (n = 129, 90%), non-Hispanic/non-Latino (n = 134, 94%) with at least one comorbid condition (n = 140, 98%). All patients were diagnosed with stage IIa (n = 28, 20%) or IIb (n = 115, 80%) PC. All patients underwent surgical resection for PC, with the most common surgical procedure being the pylorus-preserving pancreaticoduodenectomy (n = 92, 64%); 38% (n = 54) experienced postoperative complications. Following surgical resection, 82% (n = 117) received adjuvant treatment.

Measures and Variables

Patient-reported QOL was measured by the Functional Assessment of Cancer Therapy–Hepatobiliary (FACT-Hep), a patient-reported instrument designed to measure QOL in patients with hepatobiliary cancers (Heffernan et al., 2002). The FACT-Hep consists of the FACT–General (FACT-G), which assesses generic QOL, and a hepatobiliary-specific subscale, which assesses disease-specific QOL. The 27-item FACT-G assesses four dimensions of QOL: physical, social, emotional, and functional well-being. The hepatobiliary-specific subscale includes an additional 18 questions that assess symptoms and issues pertinent to patients with hepatobiliary cancer. All FACT-Hep items are assessed on a five-point severity scale ranging from 0 (not at all) to 4 (very much). FACT-Hep has demonstrated high internal consistency (Cronbach alpha range = 0.72–0.94), good test-retest reliability (Spearman correlation range = 0.84–0.91), and divergent and convergent validity (Heffernan et al., 2002).

TABLE 2. Mean Quality-of-Life Component Scores Over Time: 3 Months Postoperative

Component	M	$\bar{X}$	SD	Range
Physical well-being (total range = 0–28)	22	21.39	5.08	3–28
Social well-being (total range = 0–28)	25	24.31	4.24	8–28
Emotional well-being (total range = 0–24)	19	18.53	4.45	5–24
Functional well-being (total range = 0–28)	18	17.66	6.37	3–28
FACT-G (total range = 0–108)	85	81.78	16.09	30–108
FACT-Hep (total range = 0–180)	140	137.15	24.21	61–178

FACT-G—Functional Assessment of Cancer–General; FACT-Hep—Functional Assessment of Cancer–Hepatobiliary; M—median

TABLE 3. Mean Quality-of-Life Component Scores Over Time: 6 Months Postoperative

Component	M	$\bar{X}$	SD	Range
Physical well-being (total range = 0–28)	22	21.53	5.16	5–28
Social well-being (total range = 0–28)	25	23.66	4.4	12–28
Emotional well-being (total range = 0–24)	19	18.77	3.67	6–24
Functional well-being (total range = 0–28)	20	19.15	5.79	5–28
FACT-G (total range = 0–108)	84	83.21	14.55	46–108
FACT-Hep (total range = 0–180)	141	140	20.9	81–178

FACT-G—Functional Assessment of Cancer–General; FACT-Hep—Functional Assessment of Cancer–Hepatobiliary; M—median

Procedures

QOL data were collected through mailed questionnaires at four points in time: preoperatively (T1) and at three (T2), six (T3), and nine months (T4) postoperatively. Survival outcome data were collected at T2, T3, and T4 and again at the time of data analysis. Survival outcome data included date of death, as reported by the Social Security Administration's online death index, obituaries, or through family reports. Demographic and clinical data were obtained from electronic health records. Study questionnaires and supportive documentation of patient demographic and clinical data were copied, de-identified, given a unique identification number, and stored in individual patient study folders. Institutional review board approval was obtained for this study from Thomas Jefferson University Hospital and Villanova University.

Data Analysis

As previously described by the authors (Burrell et al., 2018), exploratory factor analysis and confirmatory factor analysis (CFA) were used to identify SCs in the current study. SCs at each study time point were determined by the following criteria (a) at least two symptoms with absolute factor loadings greater than or equal to 0.4 (Kim et al., 2008) and (b) congruence between the exploratory factor analysis and confirmatory factor analysis structures. If the same symptom loaded to two different factors (SCs), both symptom loadings were retained to enhance the clinical meaningfulness of SC findings. See Figures 1–4 for a summary of the 16 previously identified SCs. Multiple sets of SC scores were generated, and SAS Proc MIANALYZE was used to combine estimates from the multiple sets for each of the analyses used.

Simple linear regression (SLR) was used to determine if selected physiologic, psychological, and situational factors influenced the severity of the 16 SCs and to examine the relationship between each of the identified SCs and QOL. In the SLR models examining influencing factors, the selected influencing factor served as the independent variable and SC severity served as the dependent variable. In the SLR models examining QOL, SC severity was the independent variable and FACT-Hep physical, social, emotional, and functional well-being subscale scores and total scores (general and disease-specific QOL) were the outcome variables. Both unadjusted models and models adjusted for adjuvant treatment were tested to examine the relationship between SC severity and QOL.

Cox proportional-hazards regression was used to determine if the severity of the identified SCs was predictive of survival after surgery alone or in conjunction with adjuvant therapy. For these models,

TABLE 4. Mean Quality-of-Life Component Scores Over Time: 9 Months Postoperative

Component	M	$\bar{X}$	SD	Range
Physical well-being (total range = 0–28)	23	21.69	5.26	4–28
Social well-being (total range = 0–28)	25	24.09	4.56	0–28
Emotional well-being (total range = 0–24)	19.5	18.57	4.26	5–24
Functional well-being (total range = 0–28)	20	19.69	6.02	0–28
FACT-G (total range = 0–108)	85	83.94	16.13	34–108
FACT-Hep (total range = 0–180)	139.5	138.15	23.4	64–180

FACT-G—Functional Assessment of Cancer–General; FACT-Hep—Functional Assessment of Cancer–Hepatobiliary; M—median

CFA final factor scores were divided at the median to obtain a high symptom severity and a low severity group for each SC identified at each study time point (T1–T4). Two proportional hazard regression models were constructed: unadjusted model and a model adjusted for variables found to be significantly associated with survival, including neoadjuvant therapy, adjuvant therapy, grade of PC, surgery type, and cancer antigen (CA) 19-9 serum levels.

Given the substantial number of regression models that were tested in this study, p values were adjusted for multiplicity using the method of Benjamini and Hochberg (1995) to control the overall false discovery rate at each study time point at 5%.

Results

Influencing Factors

Two of the 25 physiologic, psychological, and situational influencing factors examined were found to be significantly associated with SC severity. These were preoperative pain and preoperative worry. Preoperative pain status demonstrated a statistically significant relationship with the pain–gastrointestinal SC (factor 1), consisting of nausea, back pain, abdominal pain/cramping, poor appetite, constipation, and trouble digesting food, preoperatively (T1) (slope = 0.71, 95% confidence interval [CI] [0.31, 1.11], p = 0.036). Because SCs have a standard deviation (SD) of 1 by design, for every 1-point increase in pain severity patients with PC reported preoperatively, there was a 0.71 SD increase in severity of the pain–gastrointestinal SC. Similarly, preoperative worry (an affective reaction to cancer) was significantly related to the mood SC (factor 2), consisting of anxiety and depression, at T1 (slope = 0.34, 95% CI [0.2, 0.48], p = 0.001). Therefore, for every 1-point increase in worry severity that patients with PC reported preoperatively, there was a 0.34 SD increase in severity of the mood SC.

Quality of Life

As shown in Tables 1–4, mean physical and functional well-being scores followed a similar trajectory over time. Physical and functional well-being mean scores decreased from T1 to T2, then gradually increased postoperatively at T3 and T4. Mean functional well-being improved postoperatively. Mean social well-being scores at T1 (24.59 [SD = 3.99]) slightly decreased at T2 (24.31 [SD = 4.24]) and T3 (23.66 [SD = 4.4]) and then slightly increased at T4 (24.09 [SD = 4.56]), but never reached preoperative scores. Mean emotional well-being scores increased from T1 at T2 and T3, then slightly decreased at T4. General QOL total mean scores (FACT-G) gradually increased from T1 at all three postoperative time points. Mean disease-specific QOL scores (FACT-Hep) increased from T1 at T2 and T3, then slightly decreased at T4, with all postoperative mean scores exceeding preoperative scores.

TABLE 5. Relationship Between SCs and QOL Adjusted for Type of Adjuvant Treatment: Preoperative

Component	Est	95% CI	FDR p
Factor 1			
Physical well-being	–3.3	[–4.43, –2.16]	< 0.001
Social well-being	–1.12	[–1.99, –0.25]	0.024
Emotional well-being	–1.22	[–2.27, –0.17]	0.042
Functional well-being	–3.27	[–4.64, –1.9]	< 0.001
FACT-G score	–9.1	[–12.28, –5.92]	< 0.001
FACT-Hep score	–15.54	[–20.19, –10.89]	< 0.001
Factor 2			
Physical well-being	–1.95	[–3.33, –0.56]	0.013
Social well-being	–1.25	[–2.08, –0.43]	0.007
Emotional well-being	–3.24	[–4.07, –2.41]	< 0.001
Functional well-being	–2.85	[–4.29, –1.4]	0.000
FACT-G score	–9.25	[–12.58, –5.92]	< 0.001
FACT-Hep score	–11.86	[–17.26, –6.46]	< 0.001
Factor 3			
Physical well-being	0.00	[–1.64, 1.64]	0.998
Social well-being	–0.32	[–1.19, 0.56]	0.561
Emotional well-being	0.75	[–0.51, 2.01]	0.298
Functional well-being	0.28	[–1.39, 1.94]	0.804
FACT-G score	0.54	[–3.71, 4.78]	0.844
FACT-Hep score	–1.11	[–7.24, 5.02]	0.8
Factor 4			
Physical well-being	–3.23	[–4.46, –2.01]	< 0.001
Social well-being	–1.01	[–1.84, –0.19]	0.031
Emotional well-being	–0.67	[–1.65, 0.31]	0.246
Functional well-being	–3.69	[–5.17, –2.2]	< 0.001
FACT-G score	–8.61	[–12.13, –5.09]	< 0.001
FACT-Hep score	–16	[–21.05, –10.95]	< 0.001
Factor 5			
Physical well-being	–1.39	[–2.81, 0.03]	0.085
Social well-being	–0.32	[–1.12, 0.49]	0.532
Emotional well-being	–0.1	[–1.29, 1.09]	0.89
Functional well-being	–1	[–2.68, 0.67]	0.298
FACT-G score	–2.88	[–6.91, 1.16]	0.229
FACT-Hep score	–5.7	[–11.93, 0.53]	0.107

CI—confidence interval; est—estimate of the slope; FACT-G—Functional Assessment of Cancer–General; FACT-Hep—Functional Assessment of Cancer–Hepatobiliary; FDR—false discovery rate; QOL—quality of life; SC—symptom cluster

Increased severity of 13 SCs was found to be associated with disease-specific QOL (FACT-Hep scores) in the unadjusted models (results not shown) and models adjusted for adjuvant treatment (see Tables 5–8). Physical well-being scores were most adversely affected by increased severity of the fatigue–pain–nutritional problems SC (factor 3), consisting of a change in taste, dry mouth, fatigue, back pain, and constipation at T4 (adjusted estimate = –3.54, 95% CI [–4.66, –2.42], p < 0.001). Social well-being (adjusted estimate = –1.71, 95% CI [–2.82, –0.61], p = 0.005); general QOL (FACT-G) (adjusted estimate = –11.65, 95% CI [–15.06, –8.23], p < 0.001); and disease-specific QOL (FACT-Hep) were most negatively affected by increased severity of the mood–insomnia–pain–nausea SC (factor 1), consisting of depression, anxiety, nausea, back pain, abdominal pain/cramping, and trouble sleeping at T4. Emotional well-being scores (adjusted estimate = –3.24, 95% CI [–4.07, –2.41], p < 0.001) were most adversely affected by the mood SC (factor 2) at T1. The insomnia–digestive problems SC consisting of loss of bowel control, trouble digesting food, and trouble sleeping (factor 2) at T2 most negatively affected functional well-being scores (adjusted estimate = –4.16, 95% CI [–5.47, –2.84], p < 0.001).

Survival

Increased severity of two SCs three months postoperatively was associated with survival in the unadjusted models. These two SCs were the insomnia–digestive problems SC and nutritional problems SC. Postoperative patients who experienced high severity of the insomnia–digestive problems SC had a 60% higher hazard of death (hazard ratio [HR] = 1.6, 95% CI [1.08, 2.36]) when compared to those with low severity of this SC (p = 0.048). Postoperative patients who experienced high severity of the nutritional problems SC, consisting of weight loss, change in taste, dry mouth and itching, had a 53% higher hazard of death (HR = 1.53, 95% CI [1.06, 2.2]) than those who experienced low severity of this SC (p = 0.048).

A second set of Cox proportional-hazards regression survival models were then constructed adjusting for neoadjuvant therapy, adjuvant therapy, grade of PC, surgery type, and CA 19-9 levels (see Table 9). In these adjusted models, insomnia–digestive problems SC and the nutritional problems SC did not achieve statistical significance (p = 0.149). The magnitude of the HRs between survival and the insomnia–digestive problems SC (HR = 1.64, 95% CI [0.96, 2.81]) and the nutritional problems SC (HR = 1.53, 95% CI [0.91, 2.58]) at three months postoperatively was essentially unchanged.

Discussion

The TOUS served as a useful framework to examine the relationship between SC severity and influencing factors and clinical outcomes (performance) in resected patients with stage II PC. The TOUS provided a theoretical perspective to conceptualize SCs, determine influencing factors and performance variables to include in this study, and explore the relationships among concepts. Findings from this study

TABLE 6. Relationship Between SCs and QOL Adjusted for Type of Adjuvant Treatment: 3 Months Postoperative

Component	Est	95% CI	FDR p
Factor 1			
Physical well-being	–3.3	[–4.38, –2.22]	< 0.001
Social well-being	–1.34	[–2.27, –0.4]	0.007
Emotional well-being	–3.02	[–3.83, –2.22]	< 0.001
Functional well-being	–4	[–5.37, –2.64]	< 0.001
FACT-G score	–11.64	[–14.66, –8.61]	< 0.001
FACT-Hep score	–16.66	[–21.26, –12.06]	< 0.001
Factor 2			
Physical well-being	–3.41	[–4.44, –2.37]	< 0.001
Social well-being	–1.14	[–2.13, –0.15]	0.032
Emotional well-being	–1.56	[–2.64, –0.49]	0.007
Functional well-being	–4.16	[–5.47, –2.84]	< 0.001
FACT-G score	–10.18	[–13.6, –6.76]	< 0.001
FACT-Hep score	–17.92	[–22.7, –13.14]	< 0.001
Factor 3			
Physical well-being	–1.48	[–3.29, 0.33]	0.121
Social well-being	–0.49	[–1.68, 0.71]	0.434
Emotional well-being	–0.41	[–1.81, 1]	0.565
Functional well-being	–1.66	[–3.85, 0.54]	0.15
FACT-G score	–3.99	[–9.42, 1.44]	0.156
FACT-Hep score	–7.31	[–15.96, 1.34]	0.113
Factor 4			
Physical well-being	–2.32	[–3.35, –1.29]	< 0.001
Social well-being	–1.22	[–2.15, –0.28]	0.015
Emotional well-being	–1.6	[–2.53, –0.68]	0.001
Functional well-being	–3.72	[–4.89, –2.54]	< 0.001
FACT-G score	–8.81	[–11.93, –5.69]	< 0.001
FACT-Hep score	–14.17	[–18.66, –9.68]	< 0.001

CI—confidence interval; est—estimate of the slope; FACT-G—Functional Assessment of Cancer–General; FACT-Hep—Functional Assessment of Cancer–Hepatobiliary; FDR—false discovery rate; QOL—quality of life; SC—symptom cluster

provide important insight into the SC experience in patients with PC undergoing surgery.

Influencing Factors

Physiologic influencing factors: Of the 15 physiologic influencing factors examined, only preoperative pain status was significantly related to a SC. Preoperative pain status has not been previously reported to be an influencing factor for SC occurrence or severity; however, it has been found to be a predictor of reduced survival in patients with PC (Lillemoe et al., 1993) and advanced cancers (Bernhard et al., 2010).

TABLE 7. Relationship Between SCs and QOL Adjusted for Type of Adjuvant Treatment: 6 Months Postoperative

Component	Est	95% CI	FDR p
Factor 1			
Physical well-being	−2.81	[−3.94, −1.69]	< 0.001
Social well-being	−1.51	[−2.45, −0.57]	0.003
Emotional well-being	−2.47	[−3.27, −1.68]	0.001
Functional well-being	−3.62	[−4.9, −2.34]	< 0.001
FACT-G score	−10.43	[−13.25, −7.6]	< 0.001
FACT-Hep score	−14.91	[−19.07, −10.74]	< 0.001
Factor 2			
Physical well-being	−0.94	[−2.18, 0.3]	0.146
Social well-being	−0.86	[−1.93, 0.2]	0.128
Emotional well-being	−0.48	[−1.39, 0.42]	0.301
Functional well-being	−1.58	[−2.95, −0.2]	0.036
FACT-G score	−3.88	[−7.38, −0.37]	0.042
FACT-Hep score	−7.05	[−12.08, −2.03]	0.01
Factor 3			
Physical well-being	−3.23	[−4.38, −2.08]	< 0.001
Social well-being	−0.85	[−1.95, 0.26]	0.146
Emotional well-being	−0.9	[−1.82, 0.02]	0.069
Functional well-being	−2.71	[−4.07, −1.35]	0.000
FACT-G score	−7.69	[−11.2, −4.18]	< 0.001
FACT-Hep score	−13.27	[−17.88, −8.65]	< 0.001
Factor 4			
Physical well-being	−2.07	[−3.63, −0.5]	0.016
Social well-being	−0.34	[−1.62, 0.94]	0.599
Emotional well-being	−0.93	[−2.01, 0.15]	0.113
Functional well-being	−1.6	[−3.53, 0.33]	0.121
FACT-G score	−4.94	[−9.76, −0.11]	0.06
FACT-Hep score	−9.02	[−15.75, −2.29]	0.015

CI—confidence interval; est—estimate of the slope; FACT-G—Functional Assessment of Cancer–General; FACT-Hep—Functional Assessment of Cancer–Hepatobiliary; FDR—false discovery rate; QOL—quality of life; SC—symptom cluster

These findings are consistent with several studies that failed to find a relationship in cancer populations between SCs and physiologic influencing factors of age, gender, race and ethnicity, comorbid conditions, and type of treatment (Agasi-Idenburg et al., 2017; Kim et al., 2008; Maliski, Kwan, Elashoff, & Litwin, 2008; Noquez, 2008; Tsai, Wu, Chiu, & Chen, 2010). However, Noquez (2008) reported an association between female gender and increased severity of a SC consisting of anxiety, depression, somatization, pain, and fatigue in patients with various cancer types, including PC.

Psychological influencing factors: A history of a mental health disorder, cancer acceptance, and coping were not significantly related to SCs in this study; however, preoperative disease (cancer) worry had a statistically significant relationship with the mood SC (anxiety and depression) at T1. Although the relationship between affective reactions to cancer and SCs has not been previously reported, this finding is not surprising given that increased cancer-related worry has been found to predict depression and anxiety in long-term cancer survivors (Deimling, Bowman, Sterns, Wagner, & Kahana, 2006).

Situational influencing factors: None of the six situational factors examined demonstrated a statistically significant relationship with any of the SCs identified in this study. These findings were consistent with previous research that failed to demonstrate a significant relationship between the identified SCs and social support (So et al., 2009) and marital status (Kim et al., 2009; Maliski et al., 2008). However, Noquez (2008) found that widowed, single, and divorced patients experienced a higher severity of a SC consisting of pain, fatigue, depression, anxiety, and somatization in a large sample of heterogeneous cancer types, including patients with PC. The lack of a significant association between SCs and marital status may also be related to a lack of variability in this study (75% were married or living as married). Previous studies also identified a significant relationship between tobacco use and SCs in patients with lung cancer (Cheville et al., 2011) and head and neck cancers (Xiao et al., 2012). No relationship was noted between tobacco use and SC severity in the current study, which may be because respiratory-related symptoms were not examined.

Clinical Outcomes (Performance)

Quality of life: The current article's findings suggest a significant relationship between the severity of 13 SCs and disease-specific QOL in patients with stage

II PC undergoing surgical resection regardless of type of adjuvant treatment. These findings are consistent with several previous research studies (Ferreira et al., 2008; Franceschini et al., 2013; Pirri et al., 2013; Sanford et al., 2014). The strongest negative association with emotional well-being across all study time points was found with preoperative mood SC (anxiety and depression). The highest prevalence and severity of anxiety and depression occurred in the preoperative period. Therefore, it was not surprising that the mood SC had the strongest relationship to emotional well-being at that time. Several other studies have identified a distinct SC of depression and anxiety (Breen et al., 2009; Cheung, Le, Gagliese, & Zimmermann, 2011); however, none of these studies examined the relationship between this SC and QOL.

Compared to other SCs, the insomnia–digestive problems SC had the strongest negative association with functional well-being scores at T2. The fact that this SC has not been previously identified in the literature is not unexpected given the limited research to date on SCs in patients with PC. Of note is the finding that the unique combination of digestive problems (trouble digesting food and loss of bowel control) and trouble sleeping had a large negative effect on functional well-being. Digestive difficulties are, in part, related to pancreatic enzyme insufficiency preoperatively and postoperatively (Coleman, 2010).

The strongest negative association with social well-being and QOL (general and disease-specific) across all study time points was found with the mood–insomnia–pain–nausea SC at T4. This clustering of symptoms has not been reported in the literature. Of the SCs identified, the mood–insomnia–pain–nausea SC had the strongest negative effect on close personal relationships with friends and family members. Given that family members and friends provide key social support to patients with cancer, it is not surprising that this SC also had the greatest negative relationship with QOL.

Severity of the fatigue–pain–nutritional problems SC had the greatest negative relationship with physical well-being at T4. This distinct SC has not been previously reported in cancer populations. Laird et al. (2011) identified a similar SC consisting of fatigue, pain, and depression associated with reduced physical functioning in a large heterogeneous sample of patients with advanced gastrointestinal, lung, and PC who also experienced cachexia. The relationship identified between physical well-being and the fatigue–pain–nutritional problems SC was not unexpected given that fatigue and pain are the most physically incapacitating symptoms reported by patients with cancer (Hoffman, Given, von Eye, Gift, & Given, 2007; Shute, 2013).

Survival: The current study was the first to explore the prognostic value of SCs over time in patients with stage II PC undergoing surgical resection. SCs identified in this investigation were not found to be significantly associated with overall survival after adjusting for relevant clinical variables. The magnitude of the HR between the insomnia–digestive problems and nutritional problems SCs and survival at T2 were essentially the same in the adjusted and unadjusted models, therefore suggesting that additional study of these relationships is warranted. The absence of a statistically significant association between SCs and survival in patients with PC undergoing surgical resection is not consistent with previous findings in the literature. One possible explanation for lack of statistically significant findings may be the relatively small sample size in the current study. Several studies that

TABLE 8. Relationship Between SCs and QOL Adjusted for Type of Adjuvant Treatment: 9 Months Postoperative

Component	Est	95% CI	FDR p
Factor 1			
Physical well-being	–3.21	[–4.39, –2.03]	< 0.001
Social well-being	–1.71	[–2.82, –0.61]	0.005
Emotional well-being	–2.86	[–3.78, –1.94]	< 0.001
Functional well-being	–3.86	[–5.2, –2.52]	< 0.001
FACT-G score	–11.65	[–15.06, –8.23]	< 0.001
FACT-Hep score	–18.02	[–22.79, –13.24]	< 0.001
Factor 2			
Physical well-being	–1.24	[–2.57, 0.09]	0.097
Social well-being	–1.28	[–2.4, –0.16]	0.04
Emotional well-being	–0.86	[–1.82, 0.1]	0.109
Functional well-being	–1.63	[–3.08, –0.19]	0.041
FACT-G score	–5.02	[–8.83, –1.21]	0.017
FACT-Hep score	–10.34	[–15.8, –4.89]	0.001
Factor 3			
Physical well-being	–3.54	[–4.66, –2.42]	< 0.001
Social well-being	–0.53	[–1.77, 0.71]	0.537
Emotional well-being	–1.61	[–2.71, –0.52]	0.007
Functional well-being	–2.54	[–4.11, –0.97]	0.003
FACT-G score	–8.22	[–12.33, –4.11]	< 0.001
FACT-Hep score	–14.6	[–20.35, –8.85]	< 0.001

CI—confidence interval; est—estimate of the slope; FACT-G—Functional Assessment of Cancer–General; FACT-Hep—Functional Assessment of Cancer–Hepatobiliary; FDR—false discovery rate; QOL—quality of life; SC—symptom cluster

controlled for the presence of potentially influencing clinical and demographic factors have found a significant relationship between a greater symptom burden and reduced survival (Teunissen, de Graeff, de Haes, & Voeset, 2006) and that SCs were predictors of decreased survival in cohorts of patients with cancer (Aktas et al., 2012; Wikman et al., 2014).

Limitations

The main limitations of this study were the limited generalizability of findings related to patient recruitment using convenience sampling techniques from a single high-volume PC center, as well as the lack of sample racial and ethnic diversity and the relatively small sample size.

Implications for Nursing

Nursing Theory

These findings provide empirical support that may be used to refine the concepts and propositions of the TOUS. SCs are not explicitly included in the TOUS; however, findings from several studies allowed for an expansion of the TOUS's conceptualization of multiple, concurrent symptoms to include SCs (Fox & Lyon, 2006; Hoffman et al., 2007; Kim et al., 2009). The findings provide additional support for the explicit inclusion of SCs in the TOUS. In addition, increased severity of two SCs were significantly related to physiologic (preoperative pain status) and psychological (cancer-related worry) influencing factors and 13 SCs were significantly related to QOL performance measures, therefore supporting key TOUS propositions.

Nursing Practice

The findings from this study may be used in oncology nursing practice to enhance the anticipatory guidance and counseling of patients and their family members about what to expect after PC surgery, guide patient and caregiver decision-making regarding treatment options, and inform SC assessment and management in patients with PC undergoing surgical resection. Understanding factors that influence SC severity may assist clinicians in identifying patients at increased risk for experiencing more severe SCs during the postoperative period and help to explain underlying causative SC mechanisms (Kim et al., 2009). Increased attention should be focused on designing management strategies that address clusters rather than isolated symptoms. In addition, understanding the factors that influence the severity of SCs and the SCs associated with poor clinical outcomes may enable clinicians to implement earlier interventions to prevent SCs or reduce their severity, thereby improving QOL and possibly survival outcomes (Sanford et al., 2014).

Several findings from this study have practical applications for current oncology nursing practice.

TABLE 9. Effect of Symptom Cluster Severity on Survival: Adjusted Model

	Preoperative			3 Months Postoperative			6 Months Postoperative			9 Months Postoperative		
Factor	HR[a]	95% CI	FDR p (Adj)	HR[a]	95% CI	FDR p (Adj)	HR[a]	95% CI	FDR p (Adj)	HR[a]	95% CI	FDR p (Adj)
1	1.16	[0.64, 2.12]	0.79	1.58	[0.95, 2.64]	0.149	0.81	[0.48, 1.37]	0.572	0.76	[0.4, 1.47]	0.704
2	1.25	[0.76, 2.06]	0.79	1.64	[0.96, 2.81]	0.149	0.67	[0.39, 1.17]	0.572	0.72	[0.37, 1.38]	0.704
3	1.08	[0.63, 1.85]	0.79	1.31	[0.75, 2.3]	0.341	0.77	[0.45, 1.32]	0.572	1.06	[0.56, 1.98]	0.867
4	1.24	[0.7, 2.19]	0.79	1.53	[0.91, 2.58]	0.149	0.96	[0.52, 1.75]	0.883	–	–	–
5	1.14	[0.66, 1.98]	0.79	–	–	–	–	–	–	–	–	–

[a] Cox proportional hazards regression categorized factors: high versus low symptom cluster severity risk of death according to symptom cluster severity adjusted for adjuvant treatment, neoadjuvant treatment, surgery type, grade, and CA19-9.
adj—adjusted; CI—confidence interval; FDR—false discovery rate; HR—hazard ratio

Greater severity of pain and cancer worry during the preoperative period were found to be associated with increased severity of the pain–gastrointestinal SC and mood SC, respectively. These findings underscore the importance of assessing patients for the presence of pain and worry to reduce the severity of or even prevent the presence of SCs in patients prior to surgery. In addition, increased severity of the mood SC, consisting of anxiety and depression, demonstrated a significant association with poor QOL in the current study. This relationship suggests that oncology nursing professionals should also increase attention on screening patients with PC for common affective reactions to cancer, such as anxiety and depression, during the preoperative period. Similarly, given that pain has been found to be an independent predictor of reduced survival (Lillemoe et al., 1993) and that increased severity of several pain-related SCs in this study were associated with poor QOL, it is reasonable to conclude that implementing early, appropriate pain management strategies may improve QOL outcomes in this population.

Increased severity of the insomnia–digestive problems SC and nutritional problems SC demonstrated a significant relationship with QOL. Although the relationship between these SCs and survival did not achieve statistical significance, the trend toward significance is promising. These findings highlight the importance of managing digestive problems and nutrition, which are critical factors in preventing malnutrition and withstanding surgery and subsequent adjuvant therapy in patients beginning at the time of diagnosis. Oncology nurses can play an important role in counseling and educating PC survivors and their caregivers about the importance of adequate nutrition and collaborating with the oncology team in recommending referrals to a nutritional specialist to maximize their QOL and survival potential.

Nursing Research

Future research should explore factors that influence SC severity and the effect that SCs have on QOL and survival in patients with PC undergoing surgical resection. The magnitude of the relationship between increased severity of the insomnia–digestive SC and nutritional problems SC and poor survival warrants additional research and clinical awareness by oncology nurses. This study provides a framework for future interprofessional investigations into the role of SCs in QOL and survival in preoperative and postoperative patients with PC.

KNOWLEDGE TRANSLATION

- This study provides evidence of factors that influence patients' perceptions of symptom cluster (SC) severity on clinical outcomes in postoperative patients with pancreatic cancer.
- Findings from this study provide evidence that preoperative worry and pain are associated with SC severity and that increased SC severity may have a negative effect on quality of life and survival.
- SC assessments are an important nursing tool for identifying preoperative and postoperative patients with pancreatic cancer who are at increased risk for adverse clinical outcomes.

Conclusion

Findings from this study provide the first data-driven evidence of factors that influence patients' perceptions of SC severity and the adverse effects of SC severity on QOL and perhaps even survival in patients with stage II PC followed from the time of surgery to nine months after surgical resection. Although causality cannot be determined between the SCs and clinical outcomes in this study, these potentially important associations warrant additional investigation.

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