Online Exclusive Article

Symptom Clusters in Chinese Patients With Primary Liver Cancer

Yixin Wang, PhD, Margaret O'Connor, DN, RN, FRCNA, Yan Xu, PhD, RN, and Xiaohong Liu, MS, RN

Primary liver cancer (PLC) is an increasingly critical healthcare issue throughout the world, in part because of widespread hepatitis B and C virus (HBV and HCV) infections, excessive alcohol consumption, and continuing obesity (Sherman, 2004). Globally, PLC ranks sixth and third on the lists of cancer morbidity and mortality, respectively, with an estimated 748,000 patients newly diagnosed with PLC in 2008 and 696,000 deaths occurring, 85% of which were found in lesser-developed countries (Jemal, Center, DeSantis, & Ward, 2010). Of note, more than 50% of the worldwide cases of PLC occur in China (Jemal et al., 2010), where PLC ranks third in cancer incidence and is the second-leading cause of cancer death (Ministry of Health of the People's Republic of China, 2011). These dismal statistics mirror the reality that PLC often is diagnosed at an advanced stage with a poor prognosis. Patients with PLC suffer from an array of symptoms caused by the cancer itself and its treatments, such as pain, fever, anorexia, mood disorders, and fatigue (Bianchi et al., 2003; Zhu, 2003). In clinical practice, these symptoms seldom occur individually but usually appear in groups or clusters. The co-occurrence of multiple symptoms, in comparison to that of a single symptom, may lead to a prolonged delay in scheduled treatments and effectiveness of treatment protocols and a more rapid decline in a patient's quality of life (QOL). However, only a limited number of studies in the literature have addressed symptom clusters in patients with PLC; therefore, this area should be further explored to develop more efficient and effective approaches to symptom management for patients with PLC.

Considering the large population of patients with PLC in China and the benefits of alleviating their multiple symptoms, the authors conducted a study to explore symptom cluster profiles in Chinese patients with PLC. The main objectives of this study were to identify symptom clusters and their clinical meanings in Chinese patients with PLC, to examine the factors related

Purpose/Objectives: To derive symptom clusters and their clinical meanings in Chinese patients with primary liver cancer (PLC), to examine the factors related to the identified symptom clusters, and to validate the impact of the identified symptom clusters on patients' quality of life (QOL).

Design: Cross-sectional.

Setting: Inpatient departments at a medical center for hepatobiliary disease in China.

Sample: 277 patients with PLC, aged 18–77 years.

Methods: Data were collected from a number of measures, including demographic and disease characteristics, the MD Anderson Symptom Inventory, six additional symptom items specific to PLC, and the Functional Assessment of Cancer Therapy–Hepatobiliary questionnaire. Factor analysis was used to derive symptom clusters, independent-samples t test or one-way analysis of variance was performed to identify the factors related to each symptom cluster, and multivariate regression models were applied to examine the predictive impact of the identified symptom clusters on PLC.

Main Research Variables: Demographic and medical variables, symptom clusters, and QOL.

Findings: Three symptom clusters were identified: gastrointestinal sickness, neuropsychological, and liver dysfunction. Patients who received liver protection treatment, received more than one kind of treatment, and had poorer physical performance, worse liver function, and more advanced cancer scored higher in severity across all three symptom clusters. All of the symptom clusters explained 48% of the QOL variance, and the liver dysfunction symptom cluster (adjusted $R^2 = 0.425$) showed a superior influence.

Conclusions: The liver dysfunction symptom cluster may be unique to Chinese patients with PLC. Patients with certain demographic and disease characteristics could be at risk for experiencing severe symptom clusters. In addition, a differential impact of the symptom clusters on QOL was noted in these patients.

Implications for Nursing: The factors related to severity should be considered when managing symptom clusters. Because the predictive impacts of the three individual symptom clusters on QOL were varied and ordered in magnitude, healthcare providers should first alleviate the primary symptom cluster. This approach could be cost-effective and improve QOL.

to the identified symptom clusters, and to validate the impact of these symptom clusters on patients' QOL.

Literature Review

In general, patients with PLC experience symptoms of tumor growth such as abdominal pain and distension (Heffernan et al., 2002; Sun et al., 2008; Yount et al., 2002); jaundice, itching, and dehydration caused by malignant biliary obstruction (Heffernan et al., 2002); and, frequently, common symptoms of liver dysfunction such as abdominal distension, weight loss, weakness, loss of appetite, nausea, jaundice, diarrhea, and unexplained fever (Curley, 1998; Wong & Fielding, 2008). In addition, treatment for PLC may lead to morbidity and symptom burden. Lai et al. (2007) and Shun et al. (2005) reported that fatigue and fever were common symptoms in patients with PLC after undergoing transcatheter hepatic arterial chemoembolization (TACE) and stereotactic radiation. In addition, patients with PLC tend to exhibit reactive emotional symptoms such as sadness and distress about their poor prognosis and treatment side effects (Steel et al., 2010; Steel, Geller, Gamblin, Olek, & Carr, 2007; Tsay, Chen, Chen, Lin, & Lin, 2008). These multiple symptoms, either disease-related or treatment-related, physical or psychological, or both, may occur concurrently in clusters and have a deleterious effect on the QOL of patients with PLC (Steel et al., 2010; Sun et al., 2008; Tsai, Wu, Chiu, & Chen, 2010; Yount et al., 2002).

Dodd, Miaskowski, and Paul (2001) first called for awareness of the presence of symptom clusters in patients with cancer and their possible synergistic negative influence on patients' outcomes. Dodd et al. (2001) defined a symptom cluster as three or more concurrent symptoms that are related to each other but are not required to share the same etiology. Kim, McGuire, Tulman, and Barsevick (2005) then refined the definition by proposing that a symptom cluster could consist of two or more symptoms that are related to each other and occur together. Whether the definition accepted is two, three, or more symptoms, the key to the concept is that symptoms occur in groups and are related to each other within a cluster (Barsevick, Whitmer, Nail, Beck, & Dudley, 2006). Miaskowski, Dodd, and Lee (2004) suggested that this relationship could be achieved through a common mechanism or etiology, a shared common variance, or the production of different outcomes than individual symptoms. Since then, the study of symptom clusters has become a new frontier in cancer symptom management research and drawn considerable attention from researchers and clinicians (Miaskowski et al., 2004).

A number of investigations of symptom clusters have been conducted in either heterogeneous (i.e., patients with a variety of cancer diagnoses and/or cancer stages) or homogeneous patient groups (i.e., patients in a particular care setting, with a certain cancer stage, a specific metastatic site, or a single cancer site) (Fan, Filipczak, & Chow, 2007; Kim, Dodd, Aouizerat, Jahan, & Miaskowski, 2009; Xiao, 2010). Regarding studies of a single cancer site, the literature has shed much light on breast and lung cancers (Fan et al., 2007; Kim, Dodd, et al., 2009; Xiao, 2010)—which are the most common malignancies in developed countries—with prostate, ovarian, and brain cancers noted to some extent (Fan et al., 2007; Kim, Dodd, et al., 2009; Xiao, 2010); however, limited studies to date have addressed PLC. Huang and Lin (2009) found, in a group of 77 patients with hepatocellular carcinoma, that fatigue, sleep disturbance, and depression coexisted and depression played a completely mediating role between the other

Table 1. Patient Characteristics

Characteristic	n	%
Gender		
Male	240	87
Female	37	13
Age (years)		
18–44	82	30
45–59	156	56
60 or older	39	14
Religious affiliation		
No	225	81
Yes	52	19
Marital status		
Married	262	95
Single, divorced, or widowed	15	5
Education		
Primary school	27	10
Junior high school	94	34
Senior high school	76	27
College or university	80	29
Employment status		
Unemployed or retired	165	60
Employed	112	40
Family monthly income (CNY)[a]		
Less than 1,000	47	17
1,000–2,999	117	42
3,000–4,999	61	22
5,000 or higher	52	19
Perceived disease-related financial burden		
Heavy	220	79
Moderate	34	12
Mild	23	8
Insurance coverage ratio		
None	70	25
Less than 30	35	13
30–49	63	23
50–79	86	31
80–100	23	8

N = 277

[a] 1,000 CNY is equivalent to about $160 U.S.

CNY—Chinese yuan currency

Note. Because of rounding, not all percentages total 100.

Table 2. Patients' Medical Characteristics

Characteristic	n	%
Time since diagnosis		
Less than 1 month	70	25
1 month	94	34
6 months	43	16
1 year	58	21
3 years	12	4
Child-Pugh status[a]		
A	228	82
B	44	16
C	5	2
ECOG PSR		
0	74	27
1	178	64
2	25	9
Cancer stage		
I	70	25
II	59	21
III	121	44
IV	27	10
Current treatment[b]		
Surgery	46	16
TACE	125	45
Percutaneous local ablation	14	5
Traditional Chinese medicine	57	21
Liver protection treatment	114	41
Amount of current treatments		
One	206	74
Two	63	23
Three	8	3

N = 277

[a] The Child-Pugh status classifies liver function for patients with liver disease and is determined by the Child-Pugh score, which employs five clinical measures of liver disease. Each measure is scored 1–3, with 3 indicating most severe derangement. Combined scores of 5–6 indicate Child-Pugh status A, scores of 7–9 indicate status B, and 10–15 indicate status C.

[b] Multiple treatments may be selected.

ECOG PSR—Eastern Cooperative Oncology Group Performance Status Rating; TACE—transcatheter hepatic arterial chemoembolization

Note. Because of rounding, not all percentages total 100.

two symptoms. Although this was the first study to explore the phenomenon of symptom clustering in patients with PLC, selecting only the three symptoms in symptom cluster identification is questionable without controlling for other variables like age and pain, which may have an effect on symptom cluster profiles and the relationship within a cluster. Ryu et al. (2010) identified four symptom clusters in 180 Korean patients with hepatocellular carcinoma: pain-appetite, fatigue-related, gastrointestinal, and itching-constipation. However, the antecedents and outcomes of the symptom clusters were not investigated. Therefore, studies on symptom clusters in patients with PLC need additional examination, as the knowledge of whether or how different symptoms of patients with PLC may be grouped in clusters, what factors may influence the symptom clusters, and how a symptom cluster's impact on a patient's QOL could facilitate the development of more cost-effective symptom interventions and the improvement of QOL in patients with PLC.

Methods

Participants

A cross-sectional study design was used with a convenience sample of inpatients from a medical center for hepatobiliary disease in Shanghai, China, from October 2010 to March 2011. Participants selected for this study met the following inclusion criteria: at least 18 years of age, diagnosed with PLC, receiving active and/or supportive treatment for PLC, and had the ability to give written informed consent. Participants who could not understand and communicate in Chinese or who showed evidence of a psychiatric disorder were excluded. A total of 400 inpatients who met the criteria were approached and asked to participate. Of these, 78 (20%) refused to participate and 45 (11%) returned incomplete questionnaires. Therefore, the study's statistical analysis was based on the remaining 277 (69%) participants.

Measures

Demographic and disease characteristics: Demographic and socioeconomic data regarding age, gender, religious affiliation, marital status, education level, employment status, total family monthly income, perceived disease-related financial burden, and health insurance coverage were collected though a face-to-face interview tool. Disease data were obtained from patients' doctors and verified by a researcher who was in charge of reviewing medical records. The data items included which hospital departments provided treatment, time elapsed since diagnosis, cancer stage, current treatment, physical performance status (measured through the Eastern Cooperative Oncology Group Performance Status Rating [ECOG PSR]) (Sorensen, Klee, Palshof, & Hansen, 1993), liver function status (Child-Pugh status, which is determined by the presence of ascites, encephalopathy, serum albumin, total bilirubin, and prothrombin time) (Pugh, Murray-Lyon, Dawson, Pietroni, & Williams, 1973), whether hospital readmission occurred and whether HBV and cirrhosis were present.

The MD Anderson Symptom Inventory: The MD Anderson Symptom Inventory (MDASI) is well established as a validated and reliable tool for assessing cancer-related symptoms regardless of therapy or specific cancer diagnosis (Cleeland et al., 2000). Because one of the aims of the current study was to explore symptom clusters in patients with PLC, the first part of

the MDASI, which focuses on 13 symptom items, was chosen for assessing the severity of the most common symptoms across most cancer types and treatments—pain, fatigue, nausea, sleep disturbance, distress, shortness of breath, difficulty remembering, poor appetite, drowsiness, dry mouth, sadness, vomiting, and numbness. These 13 symptoms are rated on an 11-point numeric scale from 0 (not present) to 10 (as bad as you can imagine). A Chinese version of the MDASI has been developed with sound psychometric properties in Chinese patients with cancer (Wang et al., 2004). In the current study, the internal consistency Cronbach alpha was 0.92 for this part of the MDASI.

Additional symptom items: Considering that some symptoms specific for patients with PLC are not included in the MDASI, six additional items assessing the severity of abdominal distention, diarrhea, jaundice, pruritus, weight loss, and fever were added to the first part of the MDASI to further expand the possibilities of these symptoms being included in symptom clusters. These symptoms had been identified before the current study through a pilot study, including a literature review, and expert panel and patient surveys. The symptoms emerged as the most common. For the convenience of statistical analysis, the six items were rated in the same format as the first part of the MDASI.

Functional Assessment of Cancer Therapy–Hepatobiliary: The Functional Assessment of Cancer Therapy–Hepatobiliary (FACT-Hep) questionnaire, which is used specifically for measuring the QOL of patients with hepatobiliary cancers (Heffernan et al., 2002), was developed into a Chinese version through a standard translation/back-translation procedure with good validity, reliability, and sensitivity (Zhu, Lang, Chen, Li, & Ling, 2008). FACT-Hep consists of the original FACT–General (FACT-G) scales and the hepatobiliary cancer subscale (HCS). The FACT-G is comprised of 27 items assessing four primary QOL domains: physical well-being ([PWB], seven items, range = 0–28), social and family well-being ([SFWB], seven items), emotional well-being ([EWB], six items), and functional well-being ([FWB], seven items). The HCS includes 18 items assessing specific concerns and issues in patients with hepatobiliary cancers. All items are scored from 0–4, but the item "I am satisfied with my sex life" in the SFWB domain was removed from the scale in this study because previous studies reported low response rates in Chinese patients (Wang, Shen, & Xu, 2011; Zheng et al., 2007). Therefore, the possible total scores in this sample ranged from 0–176, with higher scores indicating better QOL. Cronbach alpha for PWB, SFWB, EWB, FWB, HCS, and overall FACT-Hep in the current study were 0.8, 0.85, 0.76, 0.84, 0.83, and 0.9, respectively.

Procedures

After receiving university ethics committee and human subject committee approval for this study from Second Military Medical University of the Chinese People's Liberation Army and from the Eastern Hepatobiliary Surgery Hospital in Shanghai, China, the researchers approached patients who met the selection criteria, provided a detailed explanation of the study to them, and then obtained written consent. Participants were asked to independently fill out a questionnaire consisting of the MDASI, the six additional symptom items, and FACT-Hep. If a participant was unable to complete the questionnaire independently, the researchers read the questionnaire items to the participant and recorded his or her answers. The researchers were available onsite during the administration of the questionnaires to provide clarification about questionnaire items.

Statistical Analysis

Descriptive statistics were used to summarize the demographic and clinical variables and the scores on the MDASI, the six additional symptom items, and FACT-Hep. With a Kaiser-Meyer-Oklin value of 0.91 and a Bartlett's Test of Sphericity reaching statistical significance ($p < 0.001$), a principal axis factoring with varimax rotation was conducted on the 19 possible symptoms (13 symptoms from MDASI and 6 additional symptoms) to derive symptom clusters. The number of clusters was determined by the number of factors with eigenvalues greater than 1, and symptoms within a cluster were only retained if their factor loading scores were greater than 0.4. The internal reliability of each derived symptom

Table 3. Descriptive Statistics on Symptom Severity and Prevalence

Symptom	$\bar{X}$	SD	n	%
Fatigue	5.23	2.72	255	92
Distress	4.93	2.69	232	84
Sleep disturbance	4.89	2.39	248	90
Pain	4.85	2.73	225	81
Abdominal distension	4.74	2.26	197	71
Fever	4.48	2.63	168	61
Sadness	4.47	2.39	217	78
Drowsiness	4.4	2.45	204	74
Poor appetite	4.35	2.51	219	79
Dry mouth	4.23	2.34	228	82
Nausea	4.16	2.33	180	65
Vomiting	3.78	2.66	160	58
Shortness of breath	3.74	2.2	174	63
Weight loss	3.7	2.34	209	76
Difficulty remembering	3.61	2.35	192	69
Diarrhea	3.45	2.25	146	53
Numbness	3.21	1.96	146	53
Pruritus	3.14	2.26	158	57
Jaundice	3.11	2.12	163	59

N = 277

Table 4. Principal Factor Analysis With a Varimax Rotation Pattern Matrix of Symptoms and Reliability

	Factor Loading		
Cluster	**Factor 1**	**Factor 2**	**Factor 3**
Gastrointestinal sickness			
Nausea	0.82	–	–
Vomiting	0.71	–	–
Pain	0.69	–	–
Fatigue	0.56	–	–
Dry mouth	0.53	–	–
Fever	0.45	–	–
Poor appetite	0.43	–	0.41
Neuropsychological			
Sadness	–	0.7	–
Distress	–	0.68	–
Difficulty remembering	–	0.54	–
Shortness of breath	–	0.52	–
Sleep disturbance	–	0.46	–
Drowsiness	–	0.46	–
Numbness	–	0.42	–
Liver dysfunction			
Weight loss	–	–	0.61
Jaundice	–	–	0.58
Abdominal distension	–	–	0.57
Pruritus	–	–	0.55
Diarrhea	–	–	0.5
Cronbach alpha	0.87	0.85	0.79
Eigenvalue	3.51	2.98	2.82
Explained variance	18.46	15.7	14.86
Cumulative variance	14.27	34.16	49.02

N = 277
Factor 1—gastrointestinal sickness symptom cluster; Factor 2—neuropsychological symptom cluster; Factor 3—liver dysfunction symptom cluster

cluster was assessed by Cronbach alpha coefficient. The severity scores of all symptoms in a cluster were transformed into normally distributed standardized scores and then summed to obtain a cluster-based score, as proposed by Kim, Barsevick, and Tulman (2009).

The influence of demographic and clinical variables on the severity of each symptom cluster was tested through either independent-samples t test or one-way analysis of variance (ANOVA) followed by the Scheffé t test for post-hoc examinations. Differences were considered significant at $p < 0.05$.

With entry criteria of 0.05 and removal criteria of 0.1, stepwise multivariate linear regression models were performed to examine which symptom clusters were respectively predictive of diminished QOL after controlling for the possible demographic and clinical factors. For the analysis, ordinal and dichotomous independent variables were entered as continuous variables, while two dummy variables were created for the independent variable of hospital departments (an unordered categorical variable): departments of internal medicine versus departments of surgical medicine (department 1) and departments of internal medicine versus departments of invasive technology (department 2). Predicting variables with a threshold of $p < 0.05$ were identified as covariates that were significantly associated with QOL. All statistical analyses were performed using SPSS®, version 13.0.

Results

Participant Characteristics

The sample consisted of 277 patients with PLC. The participants ranged in age from 18–77 years, with a mean age of 50.09 (SD = 10.12). Participants were recruited from three different departments: internal medicine (41%), surgical medicine (30%), and invasive technology (30%). Most were readmitted to the hospital (68%), infected with HBV (91%), or diagnosed with cirrhosis (73%) (see Tables 1 and 2).

Symptom Clusters

Almost all of the participants (99%) presented with at least two concurrent symptoms; the median number of concurrent symptoms reported by each participant was 14. Descriptive statistics on symptom severity and prevalence are displayed in Table 3. Overall, each symptom was experienced by more than 50% of the sample, and the severity score of each symptom was greater than 3 on the 0–10 point scale. The five most common symptoms, ranked in order, were fatigue, sleep disturbance, distress, dry mouth, and pain. Fatigue was perceived to have the most severity, followed by distress, sleep disturbance, pain, and abdominal distention.

An exploratory factor analysis using principal factor analysis and a varimax rotation was employed to understand the latent constructs of the 19 symptoms in this sample (see Table 4). Three factors with eigenvalues greater than 1 were retained and the three derived symptom clusters were labeled gastrointestinal sickness, neuropsychological, and liver dysfunction, all of which accounted for 49% of the total variance. The gastrointestinal sickness symptom cluster included nausea, vomiting, pain, fatigue, dry mouth, fever, and poor appetite. The neuropsychological symptom cluster consisted of sadness, distress, difficulty remembering, shortness of breath, sleep disturbance, drowsiness, and numbness. The liver dysfunction symptom cluster included weight loss, jaundice, abdominal distension, pruritus, diarrhea, and poor appetite. Poor appetite loaded on both gastrointestinal sickness and liver dysfunction symptom clusters. The internal reliabilities were 0.87 for the gastrointestinal sickness symptom cluster, 0.85 for the neuropsychological symptom cluster, and 0.79 for the liver dysfunction symptom cluster.

Factors Related to Symptom Clusters

Significant demographic and disease factors associated with the identified symptom clusters are summarized

in Table 5. In general, patients who received liver protection treatment, who received more than one kind of treatment, who were rated as having relatively poorer physical performance status, who were classified as Child-Pugh C, or who were at advanced cancer stage III or IV tended to report significantly higher severity scores across all the three symptom clusters than did their counterparts. In addition, patients who had undergone TACE scored higher on the gastrointestinal sickness symptom cluster, whereas unemployed patients had more severe symptoms associated with the liver dysfunction symptom cluster. Although statistically meaningful differences in the severity of the liver dysfunction symptom cluster were not found in post-hoc tests for the variable of perceived disease-related financial burden, the ANOVA F-statistic was significant and the clinical findings showed a relationship between higher severity of liver dysfunction symptoms and heavier financial burden.

Effects of Symptom Clusters on Quality of Life

Table 6 demonstrates the descriptive statistics for the FACT-Hep and its subscales—PWB, SFWB, EWB, FWB, and HCS. According to the percentage of total score, the mean scores of all scales were relatively poor. Multiple regression analysis was applied to examine the effect of the three symptom clusters on QOL (see Tables 7 and 8), and the three symptom clusters explained 36% and 48% of the variances of the PWB subscale and the FACT-Hep total score regression models, respectively, after controlling for the relatively small effect of other demographic and disease variables (adjusted $R^2 = 0.096$ and 0.022, respectively). However, the gastrointestinal sickness symptom cluster (adjusted $R^2 = 0.302$) exerted a major effect on PWB, whereas the liver dysfunction symptom cluster (adjusted $R^2 = 0.425$) showed a superior influence on overall QOL. In addition, the gastrointestinal sickness (adjusted $R^2 = 0.012$, mild but not neglected), neuropsychological (adjusted $R^2 = 0.207$), and liver dysfunction (adjusted $R^2 = 0.051$) symptom clusters were identified as unique symptom clusters that were predictive of FWB, EWB, and SFWB, respectively. For the HCS regression model, gastrointestinal sickness and liver dysfunction clusters accounted for 45% of the variance after controlling for the influence of the other two medical variables (hospital readmission and number of current treatments), but liver dysfunction (adjusted $R^2 = 0.431$) played a much greater role than gastrointestinal sickness (adjusted $R^2 = 0.023$).

Discussion

Symptom cluster research is an important topic in oncology nursing. The current study identified three symptom clusters and their related factors, and verified a differential impact of these symptom clusters on the QOL of Chinese patients with PLC. These findings could add value to the literature regarding symptom clusters.

Table 5. Univariate Analyses of the Severity of Symptom Clusters

	Symptom Cluster					
	Gastrointestinal Sickness		Neuropsychological		Liver Dysfunction	
Variable	t/F	Post-Hoc	t/F	Post-Hoc	t/F	Post-Hoc
Perceived disease-related financial burden	–	–	–	–	2.87*	Not found
Employment	–	–	–	–	2.02*	Unemployment > employment
Transcatheter hepatic arterial chemoembolization	3.38**	Yes > no	–	–	–	–
Liver protection treatment	3.49**	Yes > no	3.63***	Yes > no	3.7***	Yes > no
Amount of current treatments	21.89***	2, 3 > 1	17.09***	2, 3 > 1	9.9***	2, 3 > 1
Eastern Cooperative Oncology Group Performance Status Rating	34.86***	2 > 1 > 0	38.28***	2 > 1 > 0	46.22***	2 > 1 > 0
Child-Pugh status[a]	5.33**	C > A, B	4.361*	C > A	14.83***	C > B > A
Cancer stage	6.33***	IV, III > II, I	2.87*	Not found	11.05***	IV, III > II, I

N = 277

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

[a] The Child-Pugh status classifies liver function for patients with liver disease and is determined by the Child-Pugh score, which employs five clinical measures of liver disease. Each measure is scored 1–3, with 3 indicating most severe derangement. Combined scores of 5–6 indicate Child-Pugh status A, scores of 7–9 indicate status B, and 10–15 indicate status C.

Note. The t statistic is a result of the t test and can be used to deduce whether or not the means of two independent groups are equal. The F statistic is a statistic of the results from analysis of variance and can be used to deduce whether or not the means of several groups are all equal.

Table 6. Descriptive Statistics for the FACT-Hep and Subscales

Scale	$\bar{X}$	SD	$\bar{X}$ %	SD %
EWB	16.27	4.13	67.79	17.2
FWB	16.69	5.07	58.88	18.09
HCS	49.8	9.61	69.16	13.34
PWB	16.86	5.04	60.22	17.99
SFWB	18.91	3.76	79.79	15.66
FACT-Hep total	118.33	19.45	67.23	11.05

N = 277

EWB—emotional well-being; FACT-Hep—Functional Assessment of Cancer Therapy–Hepatobiliary; FWB—functional well-being; HCS—hepatobiliary cancer subscale; PWB—physical well-being; SFWB—social and family well-being

Gastrointestinal Sickness

The gastrointestinal sickness symptom cluster included nausea, vomiting, pain, fatigue, dry mouth, fever, and poor appetite. Several plausible explanations exist for this symptom cluster pattern. First, all of these symptoms may be clustering because of an underlying biologic mechanism; it has been noted that proinflammatory cytokines such as interleukin-1, interleukin-6, tumor necrosis factor-α, and interferon-α play a significant role in inducing illness behaviors (Gilbertson-White, Aouizerat, & Miaskowski, 2011). These include physiological responses such as fever, pain, and fatigue, and behavioral responses such as decreased eating and decreased activity. In addition, a patient who is taking medication such as nonsteroidal anti-inflammatory drugs for pain and fever may experience fatigue, dry mouth, and symptoms of gastrointestinal disturbance. Finally, the symptoms in this cluster are all potential side effects of TACE, which 45% of the participants in this study received. Although research in Korea reported a similar symptom cluster consisting of pain, nausea, loss of appetite, fever, and changes in taste in patients with PLC (Ryu et al., 2010), more studies are needed to confirm whether this symptom cluster occurs consistently in varied populations of patients with PLC.

Neuropsychological

A large number of previous investigations have demonstrated that affective symptoms tend to cluster consistently regardless of cancer site, stage, and treatment modality (Xiao, 2010), and the results of the current study are no exception. However, the authors also found that psychological symptoms such as sadness and distress were grouped together with neurologic symptoms such as sleep disturbance, drowsiness, numbness, and difficulty remembering. This can be interpreted by the evidence in clinical settings that patients with psychological discomfort also may experience sleep disorders and sensation changes. Regarding the reason for memory difficulties clustering with sadness and distress, patients with these psychological problems may be more likely to become absent minded when doing ordinary things because they are consumed with thinking about their prognosis. However, the memory difficulties were mostly the patients' self-perception of their cognitive function, which may not necessarily indicate actual cognitive decline. Shortness of breath involved in the neuropsychological symptom cluster is a new finding in this study. Although the causes of shortness of breath are various, patients with PLC experiencing sadness and distress may be more likely to have heightened awareness of their somatic functions and, therefore, develop self-perpetuating symptoms such as tightness in the throat and shortness of breath (American Psychiatric Association, 2000). Healthcare providers should screen and manage psychological symptoms effectively, which may alleviate physiological symptoms to some extent.

Liver Dysfunction

The liver dysfunction symptom cluster consisted of six symptoms that indicate liver function decline—weight loss, jaundice, abdominal distension, pruritus, diarrhea, and poor appetite. This symptom cluster is considered unique to patients with PLC, particularly for Chinese patients with PLC among whom HBV and cirrhosis are the main etiology (Jemal et al., 2010); 91% and 73% of the participants in this study coexisted with HBV or cirrhosis, respectively. In addition, poor appetite was involved in both the liver dysfunction and gastrointestinal sickness symptom clusters—a finding that is different from most other studies where a symptom was put exclusively in one cluster, but similar to Aprile, Ramoni, Keefe, and Sonis (2008) and Francoeur (2005), where certain symptoms were grouped in several clusters. Therefore, whether a symptom can be shared by different clusters has not been agreed on by researchers and additional studies are needed to clearly define this concept in symptom clusters.

Five disease and treatment-related factors were found related to the severity of clustering symptoms across the three identified symptom clusters. As reported in Dodd, Cho, Cooper, and Miaskowski (2010), Kim, Barsevick, et al. (2009), and Pud et al. (2008), the negative relationship between physical performance status (ECOG PSR) and the severity of each symptom cluster was found. Although the cause and effect direction of this relationship is unclear, the possibility exists that a symptom cluster in patients with PLC can be better managed by improving the level of their physical performance status. In addition, the association between cancer stage and individual symptom severity in patients with cancer has been identified in many studies

Table 7. Stepwise Multivariate Regression Model of Quality-of-Life Outcome Variables for PWB, SFWB, and EWB

	Physical Well-Being					Social and Family Well-Being					Emotional Well-Being				
Variable	B	SE	β	t	Adjusted R^2	B	SE	β	t	Adjusted R^2	B	SE	β	t	Adjusted R^2
Factor 1	–0.017	0.007	–0.179	–2.386	0.302	–	–	–	–	–	–	–	–	–	–
Factor 2	–0.019	0.007	–0.193	–2.737	0.014	–	–	–	–	–	–0.038	0.004	–0.469	–8.892	0.207
Factor 3	–0.03	0.008	–0.245	–3.805	0.043	–0.021	0.005	–0.233	–4.022	0.051	–	–	–	–	–
Religious	1.189	0.581	–0.092	–2.045	0.006	–	–	–	–	–	–	–	–	–	–
Burden	1.581	0.374	–0.192	–4.224	0.028	–	–	–	–	–	–	–	–	–	–
DP1	1.148	0.559	–0.104	–2.052	0.008	–	–	–	–	–	–	–	–	–	–
DP2	2.06	0.598	–0.187	–3.446	0.011	–	–	–	–	–	–	–	–	–	–
TCM	2.444	0.591	0.197	4.137	0.043	–	–	–	–	–	–	–	–	–	–
Surgery	–	–	–	–	–	1.71	0.583	0.17	2.933	0.026	–	–	–	–	–
Coverage	–	–	–	–	–	–	–	–	–	–	0.542	0.164	0.174	3.305	0.028
R^2	0.471	–	–	–	–	0.083	–	–	–	–	0.24	–	–	–	–
Adjusted R^2	0.455	–	–	–	–	0.077	–	–	–	–	0.235	–	–	–	–
Model F	29.819*	–	–	–	–	12.458*	–	–	–	–	43.343*	–	–	–	–

N = 277

* $p < 0.001$

Burden—perceived disease-related financial burden; Coverage—insurance coverage ratio; DP1—department 1 (internal medicine versus surgical medicine); DP2—department 2 (internal medicine versus invasive technology); EWB—emotional well-being; Factor 1—gastrointestinal sickness symptom cluster; Factor 2—neuropsychological symptom cluster; Factor 3—liver dysfunction symptom cluster; Religious—religious affiliation; PWB—physical well-being; SE—standard error; SFWB—social and family well-being; TCM—traditional Chinese medicine

(Skaug, Eide, & Gulsvik, 2007; Talcott et al., 2003; Wang et al., 2011), with the current study also finding that patients at advanced stages of PLC had more severe symptom clusters than those at early and middle stages. Liver function status also is a significant factor. According to post-hoc analysis, a significant difference was noted in the severity of the liver dysfunction symptom cluster between patients with Child-Pugh status A, B, and C; however, a significant difference was missing in the gastrointestinal sickness and neuropsychological symptom clusters between patients with Child-Pugh status A and B. This subtly different influence is understandable because the liver dysfunction symptom cluster is more sensitive to the change of liver function in comparison to the other two symptom clusters. Therefore, protection of liver function may bring more substantial benefits to alleviating the liver dysfunction symptom cluster.

In the current study, patients who received liver protection treatment scored higher (i.e., had more severe symptoms) on each symptom cluster than did their counterparts. In relation to the authors' original assumption that liver protection treatment should help reduce the severity of symptom clusters, this was an unexpected result. However, this result may simply imply liver protection treatment may not take effect immediately in patients who often have poorer liver function and/or more severe symptom clusters. In addition, the number of kinds of current treatments might influence the severity of symptom clusters, which may mean that more kinds of treatment cause more

various side effects, and then lead to much more complicated and intense interactions between symptoms in a cluster. Healthcare providers should make note of this when caring for patients who receive more than one kind of treatment during hospitalization.

In addition to these five factors (physical performance status, cancer stage, liver function status, liver protection treatment, and number of current treatments), undergoing TACE was another variable related to the gastrointestinal sickness symptom cluster. The association between undergoing TACE and the more severe gastrointestinal sickness symptom cluster may confirm a presumed etiology of this symptom cluster that side effects of TACE could lead to concurrent symptoms in the gastrointestinal sickness symptom cluster. Because this symptom cluster is TACE-related, healthcare providers should anticipate its rise and decline after treatment in patients undergoing TACE and ensure that corresponding symptom interventions are in place.

Perceived disease-related financial burden and employment status were two other factors related to the liver dysfunction symptom cluster. Similar findings were reported in previous studies (Fu et al., 2009; Skaug et al., 2007; Talcott et al., 2003) in which demographic variables, including employment and financial status, were associated with individual symptoms or a symptom cluster in patients with cancer. As suggested by Gilbertson-White et al. (2011), other variables that could differentiate the patient groups with different employment status or financial burden may be responsible for differences in symptom severity. These variables, including attitudes toward symptoms, access to care for treatment of symptoms, and likeliness to report symptoms should be further explored.

Although the impact of symptom clusters on QOL in patients with cancer has been widely acknowledged (Xiao, 2010), limited studies have explored whether different symptom clusters exert different impacts on QOL. This study not only investigated, but also compared the impact of each symptom cluster on total QOL and its five subdimensions (PWB, SFWB, EWB, FWB, and HCS) in patients with PLC.

Generally, independent of demographic and clinical characteristics, a sole symptom cluster affects each of the three QOL dimensions of SFWB, EWB, and FWB. The liver dysfunction symptom cluster was a significant determinant of patients' rating on SFWB. In China, patients with HBV often experience discrimination and may be a disadvantaged group in many aspects of their social life; as a result, most try to isolate themselves from interactions with other people and, accordingly, perceive less social support from family, friends, and others. Of note, more serious HBV leads to poorer liver function, which causes more critical social isolation and, therefore, less perceived social support (Cui, 1989). This phenomenon could explain why participants in this study (almost all of whom had HBV) reported less social and family well-being when they scored higher on the severity of the liver dysfunction symptom cluster. Also, the neuropsychological symptom cluster was predictive of EWB and is consistent with the authors' assumption that EWB would be negatively influenced by the neuropsychological symptom cluster, mainly because the core symptoms in this cluster are psychological and affective, and their prediction of emotional well-being has been documented in Fan et al. (2007), Kim et al. (2009), and Xiao (2010). In addition, the gastrointestinal sickness symptom cluster showed an impact on FWB. Although this impact was mild compared with the total impact of all of the independent variables, healthcare providers should recognize the importance of managing the gastrointestinal sickness symptom cluster when seeking to improve the functional well-being of patients with PLC, as the relationship between functional status and symptom cluster may be a vicious cycle (Kim et al., 2009).

Regarding HCS, both the gastrointestinal sickness and liver dysfunction symptom clusters were significantly negative determinants, independent of another two clinical variables (i.e., whether hospital readmission occurred or not, and the number and kinds of current treatments), but liver dysfunction exerted a relatively greater impact than gastrointestinal sickness. HCS is a module specific to hepatobiliary cancer (Heffernan et al., 2002; Zhu et al., 2008); the liver dysfunction symptom cluster, which is mostly predictive of HCS, may be the symptom cluster unique to patients with PLC. In addition, for PWB and total QOL, the three symptom clusters each showed a significant impact after the other confounding variables were controlled. Of note, the gastrointestinal sickness and liver dysfunction symptom clusters were highly predictive of the variance of PWB and total QOL, respectively. Knowing the three symptom clusters that impact PWB or overall QOL in order of priority, healthcare providers should attempt to use available but limited resources (i.e., healthcare providers and healthcare funds) to manage symptom clusters according to their importance and urgency—an efficient way to improve QOL in patients with PLC.

Limitations

Several limitations exist with this study. The sample mainly consisted of middle-aged patients (aged 45–59 years; 56% of the sample), and the ratio of men to women was almost 8:1. Although similar or even more pronounced gender disparities have been documented in some literature (Ryu et al., 2010; Science Daily, 2007), the findings of this study cannot be generalized to all

Table 8. Stepwise Multivariate Regression Model of Quality-of-Life Outcome Variables for FWB, HCS, and Total FACT-Hep

	Functional Well-Being Subscale					Hepatobiliary Cancer Subscale					FACT-Hep				
Variable	B	SE	β	t	Adjusted R^2	B	SE	β	t	Adjusted R^2	B	SE	β	t	Adjusted R^2
Factor 1	–0.02	0.006	–0.212	–3.57	0.012	–0.044	0.011	–0.245	–3.972	0.023	–0.052	0.026	–0.144	–2.022	0.046
Factor 2	–	–	–	–	–	–	–	–	–	–	–0.08	0.026	–0.209	–3.09	0.011
Factor 3	–	–	–	–	–	–0.121	0.014	–0.526	–8.858	0.431	–0.183	0.028	–0.394	–6.46	0.425
Employment	1.148	0.575	0.111	1.995	0.008	–	–	–	–	–	–	–	–	–	–
Income	0.538	0.288	0.104	1.87	0.016	–	–	–	–	–	–	–	–	–	–
DP1	1.518	0.597	0.137	2.542	0.008	–	–	–	–	–	–	–	–	–	–
TCM	2.155	0.671	0.172	3.213	0.023	–	–	–	–	–	–	–	–	–	–
PLA	–4.015	1.245	–0.174	–3.225	0.125	–	–	–	–	–	–	–	–	–	–
ECOG	–1.826	0.525	–0.206	–3.476	0.029	–	–	–	–	–	–	–	–	–	–
Readmission	–	–	–	–	–	1.933	0.902	0.094	2.144	0.007	–	–	–	–	–
Number	–	–	–	–	–	1.929	0.885	0.103	2.179	0.007	–	–	–	–	–
Education	–	–	–	–	–	–	–	–	–	–	1.827	0.857	0.092	2.131	0.007
Burden	–	–	–	–	–	–	–	–	–	–	–2.891	1.382	–0.091	–2.092	0.009
DP2	–	–	–	–	–	–	–	–	–	–	–4.821	1.883	–0.113	–2.56	0.006
R^2	0.247	–	–	–	–	0.476	–	–	–	–	0.515	–	–	–	–
Adjusted R^2	0.227	–	–	–	–	0.468	–	–	–	–	0.504	–	–	–	–
Model F	12.594*	–	–	–	–	61.819*	–	–	–	–	47.784*	–	–	–	–

N = 277

* $p < 0.001$

Burden—perceived disease-related financial burden; DP1—department 1 (internal medicine versus surgical medicine); DP2—department 2 (internal medicine versus invasive technology); ECOG—Eastern Cooperative Oncology Group; FACT-Hep—Functional Assessment of Cancer Therapy–Hepatobiliary; Factor 1—gastrointestinal sickness symptom cluster; Factor 2—neuropsychological symptom cluster; Factor 3—liver dysfunction symptom cluster; Income—family monthly income; FWB—functional well-being; HCS—hepatobiliary cancer subscale; Number—the number of kinds of current treatment; PLA—percutaneous local ablation; Readmission—hospital readmission; SE—standard error; TCM—traditional Chinese medicine

patients with PLC, particularly those of female gender. In addition, the study was conducted in an inpatient setting at a medical center, so the authors' findings should be carefully interpreted in other care settings, such as palliative care units or community care centers. Also, this study used a cross-sectional design, indicating that changes in symptom clusters over time were not investigated. Future studies should explore variations in the pattern and severity of symptom clusters along the disease and treatment trajectory. Finally, the factor analysis used in this study is an exploratory statistical procedure; therefore, some unclear issues require future consideration, including whether the identified symptom clusters can be reproduced in a similar sample, whether a symptom can be shared by different symptom clusters, and how symptoms in a symptom cluster interact. These questions can be clarified by confirmatory statistical analysis, such as confirmatory factor analysis, confirmatory network analysis, and structured equation models.

Implications for Nursing

Healthcare providers should be aware that patients with PLC could experience multiple concurrent symptoms. When a patient complains of highly prevalent symptoms within a cluster, healthcare professionals need to assess for other symptoms within this cluster. According to the demographic and clinical factors found in the current study, healthcare providers need to identify the patient groups who are potentially at risk for severe symptom clusters and then provide the symptom interventions as necessary. In addition, the predictive impacts of the three individual symptom clusters on QOL were varied and ordered in magnitude. This finding suggests the need for healthcare providers to alleviate the primary symptom cluster in an approach that is both cost-effective and that leads to improvement in patients' QOL.

Conclusions

The term symptom cluster is attracting more attention in the field of symptom management research (Miaskowski et al., 2004). The current study examined this term in patients with PLC who usually experience multiple concurrent symptoms that have rarely been targeted before. Despite some limitations, findings from this study provide a starting point for investigations into symptom clusters in the PLC population. Of the three identified symptom clusters, the liver dysfunction symptom cluster is assumed to be unique to patients with PLC; however, this assumption needs additional examination and modification. Additional investigations are needed in a more homogeneous PLC sample, such as patients undergoing TACE and patients at an advanced stage. Empirical studies also are needed to find core symptoms in a cluster or to verify how symptoms in a cluster interact. Resolving these issues may increase the understanding of symptom clusters and contribute to effective and efficient management of symptom clusters in patients with PLC.

Yixin Wang, PhD, is a lecturer in the School of Nursing at the Second Military Medical University in Shanghai, China; Margaret O'Connor, DN, RN, FRCNA, is the Vivian Bullwinkel Chair in the Department of Palliative Care Nursing and a professor on the Palliative Care Research Team in the School of Nursing and Midwifery at Monash University in Melbourne, Australia; and Yan Xu, PhD, RN, and Xiaohong Liu, MS, RN, are professors in the School of Nursing at the Second Military Medical University. No financial relationships to disclose. Liu can be reached at xhliu@smmu.edu.cn, with copy to editor at ONFEditor@ons.org. (Submitted December 2011. Accepted for publication February 3, 2012.)

Digital Object Identifier: 10.1188/12.ONF.E468-E479

References

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed., text revision). Washington, DC: Author.

Aprile, G., Ramoni, M., Keefe, D., & Sonis, S. (2008). Application of distance matrices to define associations between acute toxicities in colorectal cancer patients receiving chemotherapy. *Cancer, 112,* 284–292.

Barsevick, A.M., Whitmer, K., Nail, L.M., Beck, S.L., & Dudley, W.N. (2006). Symptom cluster research: Conceptual, design, measurement, and analysis issues. *Journal of Pain and Symptom Management, 31,* 85–95.

Bianchi, G., Loguercio, C., Sgarbi, D., Abbiati, R., Brunetti, N., De Simone, T., . . . Marchesini, G. (2003). Reduced quality of life of patients with hepatocellular carcinoma. *Digestive and Liver Disease, 35,* 46–54.

Cleeland, C.S., Mendoza, T.R., Wang, X.S., Chou, C., Harle, M.T., Morrissey, M., & Engstrom, M.C. (2000). Assessing symptom distress in cancer patients: The MD Anderson Symptom Inventory. *Cancer, 89,* 1634–1646.

Cui, L.L. (1989). Nursing care of the patient with hepatitis B with psychological depression. *Chinese Journal of Nursing, 24,* 413.

Curley, A.S. (1998). *Liver cancer (M.D. Anderson solid tumor oncology series).* New York, NY: Springer.

Dodd, M.J., Cho, M.H., Cooper, B.A., & Miaskowski, C. (2010). The effect of symptom clusters on functional status and quality of life in women with breast cancer. *European Journal of Oncology Nursing, 14,* 101–110.

Dodd, M.J., Miaskowski, C., & Paul, S.M. (2001). Symptom clusters and their effect on the functional status of patients with cancer. *Oncology Nursing Forum, 28,* 465–470.

Fan, G., Filipczak, L., & Chow, E. (2007). Symptom clusters in cancer patients: A review of the literature. *Current Oncology, 14*(5), 173–179.

Francoeur, R.B. (2005). The relationship of cancer symptom clusters to depressive affect in the initial phase of palliative radiation. *Journal of Pain and Symptom Management, 29,* 130–155.

Fu, O.S., Crew, K.D., Jacobson, J.S., Greenlee, H., Yu, G., Campbell, J., . . . Hershman, D.L. (2009). Ethnicity and persistent symptom burden in breast cancer survivors. *Journal of Cancer Survivorship, 3,* 241–250.

Gilbertson-White, S., Aouizerat, B.E., & Miaskowski, C. (2011). Methodologic issues in the measurement of cytokines to elucidate the biological basis for cancer symptoms. *Biological Research for Nursing, 13,* 15–24.

Heffernan, N., Cella, D., Webster, K., Odom, L., Martone, M., Passik, S., . . . Blumgart, L. (2002). Measuring health-related quality of life in patients with hepatobiliary cancers: The Functional Assessment of Cancer Therapy–Hepatobiliary questionnaire. *Journal of Clinical Oncology, 20,* 2229–2239.

Huang, T.W., & Lin, C.C. (2009). The mediating effects of depression on sleep disturbance and fatigue symptom clusters in patients with hepatocellular carcinoma. *Cancer Nursing, 32,* 398–403.

Jemal, A., Center, M.M., DeSantis, C., & Ward, E.M. (2010). Global patterns of cancer incidence and mortality rates and trends. *Cancer Epidemiology, Biomarkers and Prevention, 19,* 1893–1907.

Kim, H.J., Barsevick, A.M., & Tulman, L. (2009). Predictors of the intensity of symptoms in a cluster in patients with breast cancer. *Journal of Nursing Scholarship, 41,* 158–165.

Kim, H.J., McGuire, D.B., Tulman, L., & Barsevick, A.M. (2005). Symptom clusters: Concept analysis and clinical implications for cancer nursing. *Cancer Nursing, 28,* 270–282.

Kim, J.E., Dodd, M.J., Aouizerat, B.E., Jahan, T., & Miaskowski, C. (2009). A review of the prevalence and impact of multiple symptoms in oncology patients. *Journal of Pain and Symptom Management, 37,* 715–736.

Lai, Y.H., Shun, S.C., Hsiao, Y.L., Chiou, J.F., Wei, L.L., Tsai, J.T., . . . Kao, C.Y. (2007). Fatigue experiences in hepatocellular carcinoma patients during six weeks of stereotactic radiotherapy. *Oncologist, 12,* 221–230.

Miaskowski, C., Dodd, M., & Lee, K. (2004). Symptom clusters: The new frontier in symptom management research. *Journal of the National Cancer Institute. Monographs, 32,* 17–21.

Ministry of Health of the People's Republic of China. (2011). *China's health statistics yearbook 2011.* Beijing, China: Peking Union Medical College Press.

Pud, D., Ben Ami, S., Cooper, B.A., Aouizerat, B.E., Cohen, D., Radiano, R., . . . Miaskowski, C. (2008). The symptom experience of oncology outpatients has a different impact on quality-of-life outcomes. *Journal of Pain and Symptom Management, 35,* 162–170. doi:10.1016/j.jpainsymman.2007.03.010

Pugh, R.N., Murray-Lyon, I.M., Dawson, J.L., Pietroni, M.C., & Williams, R. (1973). Transection of the oesophagus for bleeding oesophageal varices. *British Journal of Surgery, 60,* 646–649.

Ryu, E., Kim, K., Cho, M.S., Kwon, I.G., Kim, H.S., & Fu, M.R. (2010). Symptom clusters and quality of life in Korean patients with hepatocellular carcinoma. *Cancer Nursing, 33,* 3–10.

Science Daily. (2007). *Why liver cancer is more prevalent in males than in females.* Retrieved from http://www.sciencedaily.com/releases/2007/07/070705153012.htm

Sherman, M. (2004). Pathogenesis and screening for hepatocellular carcinoma. *Clinics in Liver Disease, 8,* 419–443.

Shun, S.C., Lai, Y.H., Jing, T.T., Jeng, C., Lee, F.Y., Hu, L.S., & Cheng, S.Y. (2005). Fatigue patterns and correlates in male liver cancer patients receiving transcatheter hepatic arterial chemoembolization. *Supportive Care in Cancer, 13,* 311–317.

Skaug, K., Eide, G.E., & Gulsvik, A. (2007). Prevalence and predictors of symptoms in the terminal stage of lung cancer: A community study. *Chest, 131,* 389–394.

Sorensen, J.B., Klee, M., Palshof, T., & Hansen, H.H. (1993). Performance status assessment in cancer patients: An inter-observer variability study. *British Journal of Cancer, 67,* 773–775.

Steel, J.L., Geller, D.A., Gamblin, T.C., Olek, M.C., & Carr, B.I. (2007). Depression, immunity, and survival in patients with hepatobiliary carcinoma. *Journal of Clinical Oncology, 25,* 2397–2405.

Steel, J.L., Kim, K.H., Dew, M.A., Unruh, M.L., Antoni, M.H., Olek, M.C., . . . Gamblin, T.C. (2010). Cancer-related symptom clusters, eosinophils, and survival in hepatobiliary cancer: An exploratory study. *Journal of Pain and Symptom Management, 39,* 859–871.

Sun, V., Ferrell, B., Juarez, G., Wagman, L.D., Yen, Y., & Chung, V. (2008). Symptom concerns and quality of life in hepatobiliary cancers [Online exclusive]. *Oncology Nursing Forum, 35,* E45–E52. doi:10.1188/08.ONF.E45-E52

Talcott, J.A., Manola, J., Clark, J.A., Kaplan, I., Beard, C.J., Mitchell, S.P., . . . D'Amico, A.V. (2003). Time course and predictors of symptoms after primary prostate cancer therapy. *Journal of Clinical Oncology, 21,* 3979–3986. doi:10.1200/JCO.2003.01.199

Tsai, J.S., Wu, C.H., Chiu, T.Y., & Chen, C.Y. (2010). Significance of symptom clustering in palliative care of advanced cancer patients. *Journal of Pain and Symptom Management, 39,* 655–662. doi:10.1016/j.jpainsymman.2009.09.005

Tsay, S.L., Chen, H.L., Chen, S.C., Lin, H.R., & Lin, K.C. (2008). Effects of reflexotherapy on acute postoperative pain and anxiety among patients with digestive cancer. *Cancer Nursing, 31,* 109–115. doi:10.1097/01.NCC.0000305694.74754.7b

Wang, X.S., Wang, Y., Guo, H., Mendoza, T.R., Hao, X.S., & Cleeland, C.S. (2004). Chinese version of the M.D. Anderson Symptom Inventory: Validation and application of symptom measurement in cancer patients. *Cancer, 101,* 1890–1901.

Wang, Y., Shen, J., & Xu, Y. (2011). Symptoms and quality of life of advanced cancer patients at home: A cross-sectional study in Shanghai, China. *Supportive Care in Cancer, 19,* 789–797. doi:10.1007/s00520-010-0884-z

Wong, W.S., & Fielding, R. (2008). Eating ability predicts subsequent quality of life in Chinese patients with breast, liver, lung, or nasopharyngeal carcinoma: A longitudinal analysis. *Acta Oncologica, 47,* 71–80. doi:10.1080/02841860701441814

Xiao, C.H. (2010). The state of science in the study of cancer symptom clusters. *European Journal of Oncology Nursing, 14,* 417–434.

Yount, S., Cella, D., Webster, K., Heffernan, N., Chang, C., Odom, L., & van Gool, R. (2002). Assessment of patient-reported clinical outcome in pancreatic and other hepatobiliary cancers: The FACT–Hepatobiliary Symptom Index. *Journal of Pain and Symptom Management, 24,* 32–44. doi:10.1016/S0885-3924(02)00422-0

Zheng, Y., Wang, J.J., Zou, J.J., Wu, C.X., Bao, P.P., & Lu, W. (2007). Quality of life and its influential factors of cancer patients in Shanghai. *Chinese Journal of Cancer, 26,* 613–619.

Zhu, A.X. (2003). Hepatocellular carcinoma: Are we making progress? *Cancer Investigation, 21,* 418–428. doi:10.1081/CNV-120018233

Zhu, Z.C., Lang, Q.B., Chen, Z., Li, D.T., & Ling, C.Q. (2008). Evaluation of Chinese version of the Functional Assessment of Cancer Therapy–Hepatobiliary questionnaire. *Journal of Chinese Integrative Medicine, 6,* 341–345. doi:10.3736/jcim20080403