

# Symptom Distress in Patients With Hepatocellular Carcinoma Toward the End of Life

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Hansen contributed to the conceptualization and design. Hansen and Kolbeck completed the data collection. Hansen, Dieckmann, Naugler, and Chang provided the analysis. Dieckmann provided statistical support. Hansen, Kolbeck, and Naugler contributed to the manuscript preparation.

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**Purpose/Objectives:** To describe the presence, frequency, severity, and distress of symptoms in outpatients with advanced hepatocellular carcinoma toward the end of life, and the variability in psychological and physical symptom distress between and within patients over time.

**Design:** A prospective, longitudinal, descriptive design.

**Setting:** Outpatient clinics at two healthcare institutions.

**Sample:** 18 patients (15 men and 3 women) with hepatocellular carcinoma and a mean age of 63.3 years (range = 54–81 years).

**Methods:** Data were collected monthly for six months. Patients completed the Memorial Symptom Assessment Scale, which reports a total score, and three subscales that provide global distress, psychological distress, and physical distress scores.

**Main Research Variables:** Global, psychological, and physical distress.

**Findings:** Patients reported lack of energy and pain as the most frequent and distressing symptoms. Problems with sexual interest or activity was the fourth most present symptom after drowsiness. Global Distress Index mean scores had notable variability between and within patients over time. During data collection, six patients died. None were referred to palliative care.

**Conclusions:** Gaining knowledge about symptom distress and prevalent symptoms experienced by patients with advanced hepatocellular carcinoma is critical for designing symptom management strategies that are comprehensive and tailored to patients to optimize their quality of life as they approach death.

**Implications for Nursing:** Nurses play a vital role in advocating for, initiating, and providing comprehensive holistic care based on individual patient needs by facilitating discussions about apparent and less apparent distressing symptoms, including those related to sexuality.

About 75% of all liver cancers are hepatocellular carcinomas (HCCs) (American Cancer Society [ACS], 2017b; International Agency for Research on Cancer, 2012), and the mortality rate for HCC is increasing in the United States (ACS, 2016). In 2017, an estimated 28,920 people will die from liver and intrahepatic bile duct cancers (ACS, 2017a). HCC is the fifth estimated cause of death in men and the eighth in women (ACS, 2017a). Its primary etiologies are chronic hepatitis from hepatitis C and B viruses and alcoholic cirrhosis. Despite the new antiviral agents available to treat hepatitis C, the incidence of HCC will continue to be a challenge because of the increase in obesity, type 2 diabetes, and nonalcoholic fatty liver disease (Mittal & El-Serag, 2013). Many patients are diagnosed with HCC at an advanced stage, and the five-year relative survival rate is 17% (ACS, 2016).

HCC is a symptom-free disease at the early stage and is, therefore, difficult to diagnose and treat. At this stage, treatment options include liver transplantation and locoregional therapies (e.g., transarterial chemoembolization [TACE], radioem-

bolization). At the advanced stage, locoregional therapies are often used, followed by systemic treatment, commonly sorafenib, a multiple kinase inhibitor (U.S. National Library of Medicine and National Institute of Diabetes and Digestive and Kidney Diseases, 2017). At an advanced and moderately advanced stage, patients may present with symptoms of pain, fatigue, loss of appetite, constipation, diarrhea, anger, and depressed mood (Fan & Eiser, 2012; Ryu et al., 2010).

Distress related to the combined symptom burden patients with HCC experience toward the end of life and their individual symptom variability over time have received little attention. Findings on symptom distress and symptom experiences of patients with HCC are limited and have been published primarily in studies conducted in Asian countries (Fan & Eiser, 2012; Lin et al., 2004). Other studies have included mostly patients with mildly or moderately impaired liver function during or after treatment and those who do not have evidence of metastatic disease or recurrent HCC (Mikoshiba, Miyashita, Sakai, Tateishi, & Koike, 2013; Ryu et al., 2010). Ryu et al. (2010) identified four symptom clusters in 180 Korean patients who were receiving active treatment for HCC. Most patients (83%) had mildly impaired liver function. The identified clusters were pain/appetite, fatigue-related, gastrointestinal, and itching/constipation. The five most common symptoms were fatigue, lack of energy, stomach pain/discomfort, loss of appetite, and pain. Based on the symptom severity experience, patients were categorized into two groups. One group scored significantly higher on all symptoms. More patients in the high-symptom group had poor functional status, and more had metastatic disease. The five main symptoms experienced by Taiwanese patients with HCC following TACE treatment were abdominal pain, fatigue, sleeplessness, fever, and abdominal distention (Li, Feng, & Chien, 2015). Their levels of fatigue and symptom distress diminished shortly after treatment.

The purpose of this study is to present findings from a U.S. pilot study on the presence, frequency, severity, and distress of symptoms in outpatients with advanced HCC toward the end of life and the variability in psychological and physical symptom distress between and within patients over time.

## Methods

In this prospective, longitudinal, descriptive study, data were collected from patients once a month for six months. The study was approved by institutional review boards at Oregon Health and Science University and VA Portland Health Care System.

**TABLE 1. Sample Characteristics by Group**

| Characteristic                                | Patients<br>(N = 18) |       | Family<br>Members<br>(N = 18) |       |
|---|----------------------|-------|-------------------------------|-------|
|   | $\bar{X}$            | Range | $\bar{X}$                     | Range |
| Age (years)                                   | 63.3                 | 54–81 | 54.1                          | 22–68 |
| Characteristic                                | n                    |       | n                             |       |
| <b>Gender</b>                                 |                      |       |                               |       |
| Male  | 15                   |       | 4                             |       |
| Female  | 3                    |       | 14                            |       |
| <b>Education</b>                              |                      |       |                               |       |
| Some college                                  | 9                    |       | 13                            |       |
| College degree or higher                      | 8                    |       | 4                             |       |
| Unknown                                       | 1                    |       | 1                             |       |
| <b>Ethnicity</b>                              |                      |       |                               |       |
| Not Hispanic or Latino                        | 16                   |       | 15                            |       |
| Hispanic or Latino                            | 2                    |       | 1                             |       |
| Unknown                                       | –                    |       | 2                             |       |
| <b>Etiology of liver disease</b>              |                      |       |                               |       |
| Hepatitis C and alcohol<br>and/or drug abuse  | 7                    |       | –                             |       |
| Nonalcoholic steatohepatitis                  | 5                    |       | –                             |       |
| Hepatitis C                                   | 4                    |       | –                             |       |
| Hepatitis B                                   | 1                    |       | –                             |       |
| Primary biliary cirrhosis                     | 1                    |       | –                             |       |
| <b>Occupational status</b>                    |                      |       |                               |       |
| Retired                                       | 8                    |       | 6                             |       |
| Disabled                                      | 5                    |       | 1                             |       |
| Employed outside home<br>(full- or part-time) | 3                    |       | 7                             |       |
| Medical leave                                 | 2                    |       | –                             |       |
| Unemployed                                    | –                    |       | 3                             |       |
| Unknown                                       | –                    |       | 1                             |       |
| <b>Race</b>                                   |                      |       |                               |       |
| White   | 16                   |       | 15                            |       |
| Black or African American                     | –                    |       | 1                             |       |
| Native Hawaiian or other<br>Pacific Islander  | –                    |       | 1                             |       |
| More than one race                            | 2                    |       | 1                             |       |
| <b>Relationship to patient</b>                |                      |       |                               |       |
| Spouse  | –                    |       | 15                            |       |
| Other <sup>a</sup>                            | –                    |       | 3                             |       |
| <b>Treatment therapy<sup>b</sup></b>          |                      |       |                               |       |
| Sorafenib                                     | 6                    |       | –                             |       |
| TACE  | 6                    |       | –                             |       |
| TACE and sorafenib                            | 3                    |       | –                             |       |
| Clinical trial                                | 1                    |       | –                             |       |
| Radiation                                     | 1                    |       | –                             |       |
| TACE and radiation                            | 1                    |       | –                             |       |
| None  | 1                    |       | –                             |       |

<sup>a</sup> Includes parents, adult siblings, and adult children

<sup>b</sup> Some patients received more than one treatment therapy. TACE—transarterial chemoembolization

## Sample

The sample consisted of 18 outpatients with HCC who could read and write English. The sample size was based on funding, the number of data collection points during the six-month study period, and a qualitative component to the study (Hansen, Rosenkranz, Vaccaro, & Chang, 2014). Inclusion criteria were an age of 21 years or older and a diagnosis of HCC beyond Milan criteria for transplantation. Milan criteria are a set of standards to assess liver transplantation suitability based on the number and size of liver lesions (Mazzaferro et al., 1996). Patients were excluded if they had another type of cancer or a previous liver transplantation.

Potential participants were chosen using a purposeful sampling strategy. A member of the participant's clinical team (a nurse, nurse practitioner, or physician) briefly explained and provided written information about the study during a scheduled clinic visit. Interested participants were then referred to the principal investigator (PI). The PI or a member of the research team approached the participant and further explained the study during the same clinic visit or later by telephone. Participants who agreed to participate provided written informed consent.

## Data Collection

Data were collected in person by the PI once a month for six months primarily in patients' homes because of disease severity and to minimize missing data. Patients completed a symptom questionnaire, and family members observed and rated patients' performance status. Family members also provided written informed consent. Data were collected from July 2010 to June 2013. Data collection procedures are described in more detail elsewhere (Hansen et al., 2014).

## Measures

The Memorial Symptom Assessment Scale (MSAS), a Likert-type scale, was used to measure 32 psychological and physical symptom characteristics (Portenoy et al., 1994). Patients were asked to rate (a) how often the symptom occurred on a scale from 1 (rarely) to 4 (almost constantly), (b) the severity of symptoms on a scale from 1 (slight) to 4 (very severe), and (c) how much the symptom distressed him or her on a scale from 1 (not at all) to 5 (very much) during the preceding week. The MSAS consists of a total score and three subscale scores: the Global Symptom Index (GDI) score, Psychological Symptom Subscale (PSYCH) score, and Physical Symptom Subscale (PHYS) score. The total MSAS score is the mean of all the frequency, severity, and distress ratings. The GDI score includes the

mean of 10 symptom ratings: frequency ratings for feeling sad, worrying, feeling irritable, and feeling nervous, and distress ratings for lack of appetite, lack of energy, pain, feeling drowsy, constipation, and dry mouth. The PSYCH score includes the mean of the frequency, severity, and distress ratings for six symptoms (feeling sad, feeling irritable, feeling nervous, worrying, difficulty sleeping, difficulty concentrating). The PHYS score includes the mean of the frequency, severity, and distress ratings for 12 symptoms (lack of appetite, lack of energy, pain, feeling drowsy, feeling bloated, constipation, dry mouth, nausea, vomiting, change in taste, weight loss, dizziness). If a symptom score was not present, it was coded as 0.

The MSAS takes 10–15 minutes to complete. Convergent, discriminant, and construct validity of the MSAS was demonstrated by Portenoy et al. (1994). Internal consistency of the MSAS and subscales has

**TABLE 2. Frequency of Symptoms Reported by Patients With Hepatocellular Carcinoma (N = 18)**

| Symptom                                   | n  |
|---|----|
| Lack of energy                            | 63 |
| Pain                                      | 55 |
| Feeling drowsy                            | 53 |
| Problems with sexual interest or activity | 52 |
| Difficulty sleeping                       | 51 |
| Itching                                   | 48 |
| Worrying                                  | 44 |
| Difficulty concentrating                  | 43 |
| Feeling sad                               | 42 |
| Feeling irritable                         | 39 |
| Lack of appetite                          | 39 |
| Swelling of arms or legs                  | 32 |
| Nausea                                    | 31 |
| Diarrhea                                  | 31 |
| Dry mouth                                 | 30 |
| Cough                                     | 30 |
| Dizziness                                 | 28 |
| Numbness/tingling in hands and feet       | 27 |
| Feeling bloated                           | 26 |
| Changes in skin                           | 23 |
| Change in the way food tastes             | 22 |
| Constipation                              | 21 |
| Weight loss                               | 21 |
| Shortness of breath                       | 21 |
| Do not look like myself                   | 18 |
| Sweats                                    | 18 |
| Feeling nervous                           | 15 |
| Problems with urination                   | 15 |
| Difficulty swallowing                     | 11 |
| Vomiting                                  | 10 |
| Mouth sores                               | 7  |
| Hair loss                                 | 4  |

*Note.* Variables are sorted in descending relative frequency as indicated by patients. N values reflect the total number of times patients indicated a symptom was present during the study.

been determined for patients with and without cancer near the end of life (Tranmer et al., 2003). The Cronbach alpha coefficient for the PSYCH was 0.85 for the cancer group and 0.77 for the without-cancer group. The Cronbach alpha coefficient for the three subgroups of physical symptoms ranged from 0.78–0.87 (Tranmer et al., 2003). The Cronbach alphas at baseline for the GDI, PSYCH, PHYS, and MSAS total score in the current study were 0.76, 0.77, 0.76, and 0.88, respectively.

The Eastern Cooperative Oncology Group (ECOG) Scale of Performance measures the performance status of individuals (ECOG-ACRIN Cancer Research Group, 2016; Oken et al, 1982). Performance status is defined as the level of function and capability of self-care. It is commonly used with patients with cancer and has been helpful in determining a prognosis for various malignant conditions. The patient is scored by an observer on a scale from 0–4, indicating the following:

- 0 = normal activity
- 1 = symptoms present but nearly fully ambulatory
- 2 = some bed time but needs to be in bed less than 50% of normal daytime
- 3 = needs to be in bed for more than 50% of normal daytime
- 4 = unable to get out of bed

This served as the measure of disease severity in the current study.

The ECOG has demonstrated reliability and convergent validity in patients with inoperable lung cancer and in patients with and without cancer who received palliative care (Myers et al., 2010; Suh, LeBlanc, Shelby, Samsa, & Abernethy, 2011). Using weighted kappa values, Myers et al. (2010) found good inter-rater reliabil-

ity for the ECOG among three healthcare professional dyads: 0.65 between a palliative care research assistant and a specialist palliative care physician, 0.68 between a research assistant and a primary oncology/palliative care nurse, and 0.61 between an RN and a physician.

Data Analysis

Data were analyzed using the R statistical software package, version 3.1.1. Given the small sample size and descriptive study aims, the current authors primarily used descriptive statistics to summarize data. Interindividual variability in symptom distress was quantified as the mean between-person standard deviation averaged across time, and intraindividual variability as the mean within-person standard deviation averaged (Nesselroade & Ram, 2011). The current authors also examined the relation between symptom distress and Model for End-Stage Liver Disease (MELD) and ECOG scores across time. The MELD score is a reliable measure of short-term survival over a range of liver disease severity levels and etiologies (Desai et al., 2004). The score is calculated using laboratory tests and ranges from 6 (less ill) to 40 (gravely ill). Using a linear mixed-effects approach (R package nlme), the authors modeled each symptom distress subscale as a continuous outcome and added the MELD and ECOG scores as time-varying covariates. Model testing revealed that intercepts were best modeled as random and slopes best modeled as fixed.

Findings

Six patients died during the data collection time period. Some questionnaire data were not obtained

TABLE 3. Ten Most Frequent, Severe, and Distressing Symptoms Reported by Patients Across Time (N = 18)

| Symptom  | Frequency |      | Severity  |      | Distress  |      |
|--|-----------|------|-----------|------|-----------|------|
|  | $\bar{X}$ | SD   | $\bar{X}$ | SD   | $\bar{X}$ | SD   |
| Lack of energy   | 2.74      | 1.08 | 2.1       | 0.78 | 2.9       | 1.21 |
| Pain <sup>a</sup>                                      | 2.5       | 1.41 | 1.82      | 1.1  | 2.68      | 1.64 |
| Feeling drowsy   | 2.02      | 1.09 | 1.49      | 0.85 | 1.88      | 1.19 |
| Difficulty sleeping                                    | 1.87      | 1.38 | 1.4       | 1.09 | 2.19      | 1.57 |
| Problems with sexual interest or activity <sup>b</sup> | 1.81      | 1.45 | 1.26      | 1.28 | 1.83      | 1.83 |
| Itching  | 1.57      | 0.9  | 1.33      | 0.77 | 1.93      | 1.25 |
| Lack of appetite                                       | 1.53      | 1.36 | 1.08      | 0.94 | 1.6       | 1.51 |
| Difficulty concentrating                               | 1.46      | 1.17 | 1.16      | 0.94 | 1.78      | 1.41 |
| Worrying   | 1.27      | 0.95 | 1.08      | 0.8  | 1.71      | 1.24 |
| Feeling irritable                                      | 1.25      | 1.09 | 0.97      | 0.88 | 1.72      | 1.44 |

<sup>a</sup> Severity n = 17, distress n = 17

<sup>b</sup> Frequency n = 16, severity n = 15, distress n = 16

Note. Participants who indicated they were not experiencing a symptom were scored as a 0. Frequency scores ranged from 1 (rarely) to 4 (almost constantly), severity scores ranged from 1 (slight) to 4 (very severe), and distress scores ranged from 1 (not at all) to 5 (very much). Average scores were computed across all patients who had at least one observation during the study. Variables are sorted in descending relative frequency.



because the patient died, did not feel well, or was lost to follow-up because of relocation. None of the patients were referred to palliative care, and two patients were referred to hospice.

### Symptom Distress Over Time: Presence, Frequency, and Severity

Sample demographics are listed in Table 1. Patients who reported experiencing any of the 32 symptoms included in the MSAS at any point during the study are presented in Table 2. The variables in the table are reported in descending order from most commonly to least commonly reported. Mean ratings over time for the 10 most frequent symptoms with accompanying severity and distress ratings are presented in Table 3. Average scores were computed across all patients who had at least one observation during the study. With the exception of feeling irritable, the symptoms reported in Tables 2 and 3 are the same but are represented in different order. The descriptive statistics for the total MSAS score and subscale (GDI, PSYCH, and PHYS) scores over the study are presented in Table 4. Table 5 shows the between and within patient variability on the MSAS summary scores. The first column of Table 5 shows the average results across time. The MSAS variability was notable between individual patients, and the results suggest relatively little average variability across time within each patient.

### Relation Among Symptom Distress and Other Scores Over Time

The average ECOG and MELD scores stayed relatively constant through the study (ECOG range = 2.06–2.38, MELD range = 11.52–14). ECOG (coefficient =  $-0.05$ ,  $p = 0.69$ ) and MELD (coefficient =  $0.05$ ,  $p = 0.21$ ) scores were nonsignificant predictors of psychological symptom distress over time. The authors found the same general pattern of effects for physical distress and global symptom distress, with nonsignificant effects of ECOG (PHYS coefficient =  $0.02$ ,  $p = 0.83$ ; GDI coefficient =  $-0.06$ ,  $p = 0.57$ ) and MELD (PHYS coefficient =  $0.04$ ,  $p = 0.12$ ; GDI coefficient =  $0.05$ ,  $p = 0.1$ ). Notably, most of the effects were in the expected direction given the limited statistical power in this sample.

## Discussion

This is the first study to longitudinally describe the psychological, physical, and global symptom distress in outpatients with advanced HCC toward the end of life. In contrast to findings by Shun et al. (2012), who examined symptom distress in Taiwanese patients at three time points after one course of TACE treatment, distress did not decrease in the

current sample but remained fairly stable over time. Similar to Shun's sample, the current study participants experienced little to somewhat distressing symptoms, although variability in the GDI, PSYCH, and PHYS scores between and within patients across time existed.

The exploration of symptom distress over time has focused primarily on patients receiving cancer treatment (Akin, Can, Aydinler, Ozdilli, & Durna, 2010; Cheng & Yeung, 2013; Knapp et al., 2012). Akin et al.

**TABLE 4. Patient Scores on the Memorial Symptom Assessment Scale (MSAS) at Each Time Point (N = 18)**

| Time Point                                    | n  | $\bar{X}$ | SD   |
|---|----|-----------|------|
| <b>Global Distress Index (GDI)</b>            |    |           |      |
| Time 1  | 18 | 1.17      | 0.74 |
| Time 2  | 16 | 1.31      | 0.65 |
| Time 3  | 15 | 1.23      | 0.7  |
| Time 4  | 9  | 1.17      | 0.74 |
| Time 5  | 9  | 1.07      | 0.57 |
| Time 6  | 5  | 1.26      | 0.57 |
| <b>Psychological Symptom Subscale (PSYCH)</b> |    |           |      |
| Time 1  | 18 | 1.14      | 0.82 |
| Time 2  | 16 | 1.13      | 0.8  |
| Time 3  | 14 | 1.2       | 0.72 |
| Time 4  | 9  | 1.24      | 1.02 |
| Time 5  | 9  | 1.14      | 0.62 |
| Time 6  | 5  | 1.32      | 0.53 |
| <b>Physical Symptom Subscale (PHYS)</b>       |    |           |      |
| Time 1  | 18 | 1.13      | 0.65 |
| Time 2  | 16 | 1.11      | 0.59 |
| Time 3  | 15 | 1.09      | 0.5  |
| Time 4  | 9  | 1         | 0.47 |
| Time 5  | 9  | 0.87      | 0.44 |
| Time 6  | 5  | 1.07      | 0.4  |
| <b>Total MSAS score</b>                       |    |           |      |
| Time 1  | 18 | 0.94      | 0.51 |
| Time 2  | 16 | 0.89      | 0.47 |
| Time 3  | 15 | 1.01      | 0.44 |
| Time 4  | 9  | 0.94      | 0.5  |
| Time 5  | 9  | 0.79      | 0.39 |
| Time 6  | 5  | 1.04      | 0.49 |

**Note.** The MSAS PSYCH sample size for patients at Time 3 differs from the sample size of other MSAS summary scores because a participant did not answer certain items that make up the PSYCH at this time point.

**Note.** Patients were asked to rate the frequency of symptoms on a scale from 1 (rarely) to 4 (almost constantly), the severity of symptoms on a scale from 1 (slight) to 4 (very severe), and how distressing each symptom was on a scale from 1 (not at all) to 5 (very much) during the preceding week. The GDI scores include the mean of 10 symptom ratings, including frequency and distress ratings. The PSYCH score includes the mean of the frequency, severity, and distress ratings for six symptoms. The PHYS score includes the mean of the frequency, severity, and distress ratings for 12 symptoms. The total MSAS score is the mean of all the frequency, severity, and distress ratings.

**TABLE 5. Average Between and Within Patient Variability on Memorial Symptom Assessment Scale (MSAS) Summary Scores (N = 18)**

| Variable                       | Between Patients |      |           | Within Patients |      |           |
|--------------------------------|------------------|------|-----------|-----------------|------|-----------|
|                                | $\bar{X}$        | SD   | Range     | $\bar{X}$       | SD   | Range     |
| Global Distress Index          | 1.25             | 0.53 | 0.12–2.06 | 0.45            | 0.28 | 0.13–1.4  |
| Psychological Symptom Subscale | 1.16             | 0.69 | 0.12–2.12 | 0.4             | 0.2  | 0.13–0.85 |
| Physical Symptom Subscale      | 1.15             | 0.55 | 0.28–2.73 | 0.36            | 0.28 | 0.06–1.24 |
| <b>Total MSAS score</b>        | 0.93             | 0.35 | 0.24–1.55 | 0.3             | 0.29 | 0.03–0.72 |

(2010) explored symptom distress in patients with lung cancer undergoing chemotherapy. Akin et al. (2010) reported that these patients suffer many limitations because of symptoms and disruptions to their quality of life arising from the disease process and treatment. Spichiger, Müller-Fröhlich, Stoll, Hantikainen, and Dodd (2011) explored symptom prevalence in outpatients with lymphoma, lung, breast, or colorectal cancer receiving chemotherapy, and found that patients' fatigue increased over time and that individual trajectories of fatigue varied greatly among and within patients. Fatigue, loss of appetite, diarrhea, and skin toxicities were spontaneously reported symptoms in Kaiser et al. (2014). Fatigue is commonly reported among patients with cancer (Bennett et al., 2016; Leak Bryant, Walton, & Phillips, 2015) and is considered as more distressing than other symptoms (Weis, 2011). The current authors did not measure fatigue, but lack of energy and feeling drowsy may have been synonymous. Patients with chronic liver disease also commonly experience it (Newton & Jones, 2012).

In the current study, pain was rated by patients with advanced HCC as the second most frequent and distressing symptom. It is one of the most common and feared symptoms in patients with advanced cancer (LeMay et al., 2011; Romem et al., 2015), is associated with limitation in function, and interferes with quality of life (Black et al., 2011; LeMay et al., 2011). In patients with HCC, abdominal pain has been associated with poorer outcomes of survival and poorer quality of life (Carr & Pujol, 2010). Carr and Pujol (2010) found that patients with unresectable HCC and a higher incidence of abdominal pain had poorer survival compared to patients with a lower incidence of pain and longer survival.

Problems with sexual interest or activity was the fourth most common symptom among patients in the current study. In a study by Deshields, Potter, Olsen, and Liu (2014), this symptom was rated as the most burdensome among patients with various cancer types. Cancer can interfere with sexuality and sexual identity in many ways, leading to poor body image, difficulties with sexual functioning, frustration, anger,

and relationship strain (Katz & Dizon, 2016; Male, Fergus, & Cullen, 2016; Ussher, Perz, & Gilbert, 2015). Maintaining physical sexual relations are highly variable and, for some patients, include physical touch of any kind and experiences of tenderness and affection. The specific ways in which HCC interferes with sexual desire and activity have received little attention. In their study of symptom clusters in Chinese patients with primary liver cancer, Wang, O'Connor, Xu, and Liu (2012) removed the sexuality item "I am satisfied with my sex life" from the Functional Assessment of Cancer Therapy–Hepatobiliary questionnaire. Their rationale was low response rates reported by Chinese patients in other studies. Culture influences sexuality and how patients perceive and respond to this integral and complex part of human experiences. Therefore, research sensitive to cultural context and differences is warranted to assess how HCC interferes with sexuality and intimacy as the disease progresses and at the end of life.

The average MELD and ECOG scores stayed relatively constant over time, and the ECOG score indicated that participants needed some time in bed during the daytime. A significant relationship exists between performance status and rate of transition to death (Sutradhar & Barbera, 2014), which was not captured in the current study. The ECOG scores of the six participants who died may not have reflected their disease severity. This could be because some patients may have transitioned to the end-of-life state between consecutive data collection points or family members may have observed and rated patients' performance status incorrectly.

## Implications for Nursing

Findings from this study suggest that assessment and management of symptom distress and individual symptoms must be specifically tailored to each patient, not just adjusted by cancer type. Unlike patients with other cancers, patients with HCC suffer from cancer and liver cirrhosis, which may complicate their symptom presentation and experience. For instance,

psychological distress can come from knowing that one has a terminal cancer. This distress may be complicated by physical distress caused by cirrhosis symptoms, such as ascites and potential hepatic encephalopathy. As stated by Brown (2014), nurses are in a perfect position to conduct and implement thorough distress assessment. They should regularly assess the frequency and severity of and how distressing each symptom is for patients, as well as their inter-relatedness as the disease progresses. Pain can interfere with other physical (e.g., fatigue) and psychological (e.g., worry) symptoms that are common in patients with cancer, many of which remain untreated (van den Beuken-van Everdingen et al., 2009). A patient with HCC may experience pain because of abdominal distension from ascites, which differs from carcinoma pain and needs different interventions.

Because of the coexistence of HCC and liver cirrhosis, nurses should be knowledgeable about pharmacologic and nonpharmacologic interventions. They need to advocate for appropriate pain and symptom management for patients. Patients with HCC, like patients with advanced liver disease without cancer, may receive ineffective pain and symptom management for several reasons (Poonja et al., 2014). Altered or decreased drug metabolism may be perceived by healthcare professionals as a barrier to effective pain control. Professionals may be concerned about poor medication metabolism and the development of hepatic encephalopathy. In addition, many patients with HCC have a history of substance abuse, raising the concern about potential abuse of pain medications.

Participants in the current study experienced problems with sexual interest or activity. The focus of the literature has been on the significant impact a cancer diagnosis or treatment has on sexuality but not so much at the end of life (Dow & Kennedy Sheldon, 2015; Katz, 2005b; McGrath, 2012). Patients' sexuality problems may seem less imperative than distress from other complex psychological and physical symptoms as they approach death; however, nurses should not make any assumptions about patients' sexual interest, activity, and intimacy-related needs. In a Turkish study, the most common reason nurses did not address sexuality was the belief that patients would feel ashamed (Oskay, Can, & Basgol, 2014). Nurses should be comfortable and take initiative in discussing these interests (Katz, 2005a), activities, and needs to improve patients' quality of life by providing comprehensive holistic care.

Six of 18 patients with HCC died during the study, only two participants were referred to hospice, and none were referred to palliative care. This speaks to the importance of nurses facilitating discussions about advanced care planning, goals of care, and pos-

## Knowledge Translation

- Hepatocellular carcinoma (HCC) and liver cirrhosis cause multiple symptoms requiring specifically tailored interventions.
- Advanced HCC causes patients to experience mild to moderate symptom distress, and global, psychological, and physical distress varies over time.
- Identification of symptoms that are not noticeably distressing, such as a patient's problem with sexual interest or activity, is critical in designing symptom management strategies that will decrease the combined symptom burden experience in patients with HCC.

sible referral to specialized palliative care early in the disease trajectory. Early discussions would allow for sooner integration of the interprofessional skills palliative care specialists can bring to the complex care of patients with HCC. "Palliative care is an approach that improves the quality of life of patients and their families facing life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual" (World Health Organization, 2017, para. 1). Referrals to specialized palliative care can occur any time during a patient's life-threatening illness but should be made at the time of diagnosis (Kazanowski & Kennedy Sheldon, 2014). In advanced cancer, palliative care has shown to improve symptoms (Tai et al., 2016), symptom management, quality of life (Catania et al., 2015; Greer, Jackson, Meier, & Temel, 2013), and survival (Higginson & Evans, 2010; Temel et al., 2010).

## Limitations

The sample size was small; studies consisting of larger and ethnically diverse samples are needed. Studies should include comparisons between patients who are receiving tumor-directed therapies with those who are not receiving treatments, as well as comparisons between treatment-related and disease-related symptoms. To compare symptoms and explore their relationships, larger studies should use more symptom-specific instruments. Preliminary trends of symptom subgroups were detected in the small sample; larger samples are needed to build on the work of Ryu et al. (2010), who identified two subgroups of patients.

## Conclusion

Findings suggest areas of improvement in symptom management for patients with advanced HCC toward the end of life. Healthcare professionals should



systematically assess all physical and psychological symptoms, including the presence, frequency, severity, and distress of each symptom, at each clinic appointment. Comprehensive symptom management strategies should be developed and implemented based on individualized care to address the variability of symptom distress experienced between and within patients and ultimately optimize their quality of life as they approach death.

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## References

Akin, S., Can, G., Aydinler, A., Ozdilli, K., & Durna, Z. (2010). Quality of life, symptom experience and distress of lung cancer patients undergoing chemotherapy. *European Journal of Oncology Nursing*, 14, 400–409. <https://doi.org/10.1016/j.ejon.2010.01.003>

American Cancer Society. (2016). *Cancer facts and figures, 2016*. Retrieved from <http://bit.ly/2svdlFX>

American Cancer Society. (2017a). *Cancer facts and figures, 2017*. Retrieved from <http://bit.ly/2y26oj2>

American Cancer Society. (2017b). Key statistics about liver cancer. Retrieved from <http://www.cancer.org/cancer/livercancer/detailedguide/liver-cancer-what-is-key-statistics>

Bennett, S., Pigott, A., Beller, E.M., Haines, T., Meredith, P., & Delaney, C. (2016). Educational interventions for the management of cancer-related fatigue in adults. *Cochrane Database of Systematic Reviews*, 11, CD008144. <https://doi.org/10.1002/14651858.CD008144.pub2>

Black, B., Herr, K., Fine, P., Sanders, S., Tang, X., Bergen-Jackson, K., . . . Forcucci, C. (2011). The relationships among pain, nonpain symptoms, and quality of life measures in older adults with cancer receiving hospice care. *Pain Medicine*, 12, 880–889. <https://doi.org/10.1111/j.1526-4637.2011.01113.x>

Brown, C.G. (2014). Screening and evidence-based interventions for distress in patients with cancer: Nurses must lead the way. *Clinical Journal of Oncology Nursing*, 18(Suppl. 1), S23–S25. <https://doi.org/10.1188/14.CJON.S1.23-25>

Carr, B.I., & Pujol, L. (2010). Pain at presentation and survival in hepatocellular carcinoma. *Journal of Pain*, 11, 988–993. <https://doi.org/10.1016/j.jpain.2010.01.265>

Catania, G., Beccaro, M., Costantini, M., Ugolini, D., De Silvestri, A., Bagnasco, A., & Sasso, L. (2015). Effectiveness of complex interventions focused on quality-of-life assessment to improve palliative care patients' outcomes: A systematic review. *Palliative Medicine*, 29, 5–21. <https://doi.org/10.1177/0269216314539718>

Cheng, K.K.F., & Yeung, R.M.W. (2013). Symptom distress in older adults during cancer therapy: Impact on performance status and quality of life. *Journal of Geriatric Oncology*, 4, 71–77. <https://doi.org/10.1016/j.jgo.2012.08.006>

Desai, N.M., Mange, K.C., Crawford, M.D., Abt, P.L., Frank, A.M., Markmann, J.W., . . . Markmann, J.F. (2004). Predicting outcome after liver transplantation: Utility of the model for end-stage liver disease and a newly derived discrimination function. *Transplantation*, 77, 99–106. <https://doi.org/10.1097/01.TP.0000101009.91516.FC>

Deshields, T.L., Potter, P., Olsen, S., & Liu, J. (2014). The persistence of symptom burden: Symptom experience and quality of life of cancer patients across one year. *Supportive Care in Cancer*, 22, 1089–1096. <https://doi.org/10.1007/s00520-013-2049-3>

Dow, J., & Kennedy Sheldon, L. (2015). Breast cancer survivors and sexuality: A review of the literature concerning sexual functioning, assessment tools, and evidence-based interventions.

*Clinical Journal of Oncology Nursing*, 19, 456–461. <https://doi.org/10.1188/15.CJON.456-461>

ECOG-ACRIN Cancer Research Group. (2016). ECOG performance status. Retrieved from <http://ecog-acrin.org/resources/ecog-performance-status>

Fan, S.-Y., & Eiser, C. (2012). Illness experience in patients with hepatocellular carcinoma: An interpretative phenomenological analysis study. *European Journal of Gastroenterology and Hepatology*, 24, 203–208. <https://doi.org/10.1097/MEG.0b013e32834ec184>

Greer, J.A., Jackson, V.A., Meier, D.E., & Temel, J.S. (2013). Early integration of palliative care services with standard oncology care for patients with advanced cancer. *CA: A Cancer Journal for Clinicians*, 63, 349–363. <https://doi.org/10.3322/caac.21192>

Hansen, L., Rosenkranz, S.J., Vaccaro, G.M., & Chang, M.F. (2014). Patients with hepatocellular carcinoma near the end of life: A longitudinal qualitative study of their illness experiences. *Cancer Nursing*, 38(4), E19–E27. <https://doi.org/10.1097/NCC.0000000000000188>

Higginson, I.J., & Evans, C.J. (2010). What is the evidence that palliative care teams improve outcomes for cancer patients and their families? *Cancer Journal*, 16, 423–435. <https://doi.org/10.1097/PPO.0b013e3281f684e5>

International Agency for Research on Cancer. (2012). All cancers (excluding non-melanoma skin cancer): Estimated incidence, mortality and prevalences worldwide in 2012. Retrieved from [http://globocan.iarc.fr/Pages/fact\\_sheets\\_cancer.aspx](http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx)

Kaiser, K., Mallick, R., Butt, Z., Mulcahy, M.F., Benson, A.B., & Cella, D. (2014). Important and relevant symptoms including pain concerns in hepatocellular carcinoma (HCC): A patient interview study. *Supportive Care in Cancer*, 22, 919–926. <https://doi.org/10.1007/s00520-013-2039-5>

Katz, A. (2005a). Do ask, do tell: Why do so many nurses avoid the topic of sexuality? *American Journal of Nursing*, 105(7), 66–68.

Katz, A. (2005b). The sounds of silence: Sexuality information for cancer patients. *Journal of Clinical Oncology*, 23, 238–241. <https://doi.org/10.1200/JCO.2005.05.101>

Katz, A., & Dizon, D.S. (2016). Sexuality after cancer: A model for male survivors. *Journal of Sexual Medicine*, 13, 70–78. <http://doi.org/10.1016/j.jsxm.2015.11.006>

Kazanowski, M., & Kennedy Sheldon, L. (2014). Working together. *Clinical Journal of Oncology Nursing*, 18(Suppl. 1), 45–48. <https://doi.org/10.1188/14.CJON.S1.45-48>

Knapp, K., Cooper, B., Koettters, T., Cataldo, J., Dhruva, A., Paul, S.M., . . . Miaskowski, C. (2012). Trajectories and predictors of symptom occurrence, severity, and distress in prostate cancer patients undergoing radiation therapy. *Journal of Pain and Symptom Management*, 44, 486–507.

Leak Bryant, A., Walton, A.L., & Phillips, B. (2015). Cancer related fatigue: Scientific progress has been made in 40 years. *Clinical Journal of Oncology Nursing*, 19, 137–139. <https://doi.org/10.1188/15.CJON.137-139>

LeMay, K., Wilson, K.G., Buenger, U., Jarvis, V., Fitzgibbon, E., Bhimji, K., & Dobkin, P.L. (2011). Fear of pain in patients with advanced cancer or in patients with chronic noncancer pain. *Clinical Journal of Pain*, 27, 116–124. <https://doi.org/10.1097/AJP.0b013e3281f3f667>

Li, C.-F., Feng, S.-H., & Chien, L.-Y. (2015). Relationship between symptom distress and fatigue in hepatocellular carcinoma patients who received transcatheter arterial embolization [Article in Chinese]. *Journal of Nursing*, 62, 57–65. <https://doi.org/10.6224/JN.62.3.57>

Lin, M.-H., Wu, P.-Y., Tsai, S.-T., Lin, C.-L., Chen, T.-W., & Hwang, S.J. (2004). Hospice palliative care for patients with hepatocellular carcinoma in Taiwan. *Palliative Medicine*, 18, 93–99. <https://doi.org/10.1191/0269216304pm851oa>

Male, D.A., Fergus, K.D., & Cullen, K. (2016). Sexual identity after breast cancer: Sexuality, body image, and relationship



- repercussions. *Current Opinion in Supportive and Palliative Care*, 10, 66–74. <https://doi.org/10.1097/SPC.0000000000000184>
- Mazzaferro, V., Regalia, E., Doci, R., Andreola, S., Pulverenti, A., Bozzetti, F., . . . Gennari, L. (1996). Liver transplantation for the treatment of small hepatocellular carcinomas in patients with liver cirrhosis. *New England Journal of Medicine*, 334, 693–699. <https://doi.org/10.1056/NEJM199603143341104>
- McGrath, P.D. (2012). The impact on sexuality after diagnosis and treatment for a hematologic malignancy: Findings from Australia. *Oncology Nursing Forum*, 39, 595–600. <https://doi.org/10.1188/12.ONF.595-600>
- Mikoshiba, N., Miyashita, M., Sakai, T., Tateishi, R., & Koike, K. (2013). Depressive symptoms after treatment in hepatocellular carcinoma survivors: Prevalence, determinants, and impact on health-related quality of life. *Psycho-Oncology*, 22, 2347–2353. <https://doi.org/10.1002/pon.3300>
- Mittal, S., & El-Serag, H.B. (2013). Epidemiology of hepatocellular carcinoma: Consider the population. *Journal of Clinical Gastroenterology*, 47(Suppl.), S2–S6. <https://doi.org/10.1097/MCG.0b013e3182872f29>
- Myers, J., Gardiner, K., Harris, K., Lilien, T., Bennett, M., Chow, E., . . . Zhang, L. (2010). Evaluating correlation and interrater reliability for four performance scales in the palliative care setting. *Journal of Pain and Symptom Management*, 39, 250–258. <https://doi.org/10.1016/j.jpainsymman.2009.06.013>
- Nesselroade, J.R., & Ram, N. (2011). Studying intraindividual variability: What we have learned that will help us understand lives in context. *Research in Human Development*, 1, 9–29. <http://doi.org/10.1080/15427609.2004.9683328>
- Newton, J.L., & Jones, D.E.J. (2012). Managing systemic symptoms in chronic liver disease. *Journal of Hepatology*, 56(Suppl. 1), S46–S55. [http://doi.org/10.1016/S0168-8278\(12\)60006-3](http://doi.org/10.1016/S0168-8278(12)60006-3)
- Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., & Carbone, P.P. (1982). Toxicity and response criteria of the Eastern Cooperative Oncology Group. *American Journal of Clinical Oncology*, 5, 649–655.
- Oskay, U., Can, G., & Basgol, S. (2014). Discussing sexuality with cancer patients: Oncology nurses attitudes and views. *Asian Pacific Journal of Cancer Prevention*, 15, 7321–7326. <https://doi.org/10.7314/APJCP.2014.15.17.7321>
- Poonja, Z., Brisebois, A., van Zanten, S.V., Tandon, P., Meeberg, G., & Karvellas, C.J. (2014). Patients with cirrhosis and denied liver transplants rarely receive adequate palliative care or appropriate management. *Clinical Gastroenterology and Hepatology*, 12, 692–698. <https://doi.org/10.1016/j.cgh.2013.08.027>
- Portenoy, R.K., Thaler, H.T., Kornblith, A.B., Lepore, J.M., Friedlander-Klar, H., Kiyasu, E., . . . Norton, L. (1994). The Memorial Symptom Assessment Scale: An instrument for the evaluation of symptom prevalence, characteristics and distress. *European Journal of Cancer*, 30A, 1326–1336.
- Romem, A., Tom, S.E., Beauchene, M., Babington, L., Scharf, S.M., & Romem, A. (2015). Pain management at the end of life: A comparative study of cancer, dementia, and chronic obstructive pulmonary disease patients. *Palliative Medicine*, 29, 464–469. <https://doi.org/10.1177/0269216315570411>
- 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.
- Shun, S.-C., Chen, C.-H., Sheu, J.-C., Liang, J.-D., Yang, J.-C., & Lai, Y.-H. (2012). Quality of life and its associated factors in patients with hepatocellular carcinoma receiving one course of transarterial chemoembolization treatment: A longitudinal study. *Oncologist*, 17, 732–739. <https://doi.org/10.1634/theoncologist.2011-0368>
- Spichiger, E., Müller-Fröhlich, C., Stoll, H., Hantikainen, V., & Dodd, M. (2011). Prevalence of symptoms, with a focus on fatigue, and changes of symptoms over three months in outpatients receiving cancer chemotherapy. *Swiss Medical Weekly*, 141, W133303. <https://doi.org/10.4414/smww.2011.13303>
- Suh, S.-Y., LeBlanc, T.W., Shelby, R.A., Samsa, G.P., & Abernethy, A.P. (2011). Longitudinal patient-reported performance status assessment in the cancer clinic is feasible and prognostic. *Journal of Oncology Practice*, 7, 374–381. <https://doi.org/10.1200/JOP.2011.000434>
- Sutradhar, R., & Barbera, L. (2014). A Markov multistate analysis of the relationship between performance status and death among an ambulatory population of cancer patients. *Palliative Medicine*, 28, 184–190. <https://doi.org/10.1177/0269216313499059>
- Tai, S.-Y., Lee, C.-Y., Wu, C.-Y., Hsieh, H.-Y., Huang, J.-J., Huang, C.-T., & Chien, C.-Y. (2016). Symptom severity of patients with advanced cancer in palliative care unit: Longitudinal assessments of symptoms improvement. *BMC Palliative Care*, 15, 32. <https://doi.org/10.1186/s12904-016-0105-8>
- Temel, J.S., Greer, J.A., Muzikansky, A., Gallagher, E.R., Admane, S., Jackson, V.A., . . . Lynch, T.J. (2010). Early palliative care for patients with metastatic non-small cell lung cancer. *New England Journal of Medicine*, 363, 733–742. <https://doi.org/10.1056/NEJMoa1000678>
- Tranmer, J.E., Heyland, D., Dudgeon, D., Groll, D., Squires-Graham, M., & Coulson, K. (2003). Measuring the symptom experience of seriously ill cancer and noncancer hospitalized patients near the end of life with the memorial symptom assessment scale. *Journal of Pain and Symptom Management*, 25, 420–429.
- U.S. National Library of Medicine and National Institute of Diabetes and Digestive and Kidney Diseases. (2017). About LIVER TOX®. Retrieved from <https://livertox.nih.gov/aboutus.html>
- Ussher, J.M., Perz, J., & Gilbert, E. (2015). Perceived causes and consequences of sexual changes after cancer for women and men: A mixed method study. *BMC Cancer*, 15, 268. <https://doi.org/10.1186/s12885-015-1243-8>
- van den Beuken-van Everdingen, M.H.J., de Rijke, J.M., Kessels, A.G., Schouten, H.C., van Kleef, M., & Patijn, J. (2009). Quality of life and non-pain symptoms in patients with cancer. *Journal of Pain and Symptom Management*, 38, 216–233. <http://doi.org/10.1016/j.jpainsymman.2008.08.014>
- Wang, Y., O'Connor, M., Xu, Y., & Liu, X. (2012). Symptom clusters in Chinese patients with primary liver cancer [Online exclusive]. *Oncology Nursing Forum*, 39, E468–E479. <https://doi.org/10.1188/12.ONF.E468-E479>
- Weis, J. (2011). Cancer-related fatigue: Prevalence, assessment and treatment strategies. *Expert Review of Pharmacoeconomics and Outcomes Research*, 11, 441–446. <https://doi.org/10.1586/erp.11.44>
- World Health Organization. (2017). WHO definition of palliative care. Retrieved from <http://www.who.int/cancer/palliative/definition/en>