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Background and Design of the Symptom Burden in End-Stage Liver Disease Patient-Caregiver Dyad Study

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Abstract

Over half a million Americans are affected by cirrhosis, the cause of end-stage liver disease (ESLD). Little is known about how symptom burden changes over time in adults with ESLD and their informal caregivers, which limits our ability to develop palliative care interventions that can optimize symptom management and quality of life in different patient-caregiver dyads. The purpose of this article is to describe the background and design of a prospective, longitudinal descriptive study, “Symptom Burden in End-Stage Liver Disease Patient-Caregiver Dyads,” which is currently in progress. The study is designed to (1) identify trajectories of change in physical and psychological symptom burden in adults with ESLD; (2) identify trajectories of change in physical and psychological symptom burden in caregivers of adults with ESLD; and (3) determine predictors of types of patient-caregiver dyads that would benefit from tailored palliative care interventions. We aim for a final sample of 200 patients and 200 caregivers who will be followed over 12 months. Integrated multilevel and latent growth mixture modeling will be used to identify trajectories of change in symptom burden, linking those changes to clinical events and quality of life outcomes and characterizing types of patient-caregiver dyads based on patient-, caregiver-, and

Conflict of Interest:

All authors declare no conflicts of interest.

dyad-level factors. Challenges we have encountered include unexpected attrition of study participants, participants not returning their baseline questionnaires, and hiring and training of research staff. The study will lay the foundation for future research and innovation in ESLD, end-of-life and palliative care, and caregiving.

Keywords

Liver Cirrhosis; Caregivers; Palliative Care; Quality of Life; research protocol

End-stage liver disease (ESLD) caused by cirrhosis is associated with profound physical and psychological suffering, and without liver transplantation leads to death. Of the estimated 633,300 Americans affected by liver cirrhosis (Scaglione et al., 2015), only about 7,130 receive transplants each year (US Department of Health and Human Services, 2016), and more than 38,000 die annually (Centers for Disease Control and Prevention, 2016; Kochanek, Murphy, Xu, & Tejada-Vera, 2014). Patients with ESLD facing death typically continue to receive aggressive therapies and rarely receive appropriate symptom management and palliative care (Hansen et al., 2012; Poonja et al., 2014).

The burden of complex ESLD care is left to informal caregivers, who in other contexts have poor quality of life (QOL; Dahlrup, Ekstrom, Nordell, & Elmstahl, 2015), poor mental health (Haley, Roth, Hovater, & Clay, 2015), poor physical health (Anderson et al., 2013), and increased mortality (Schulz & Beach, 1999). Consequences for caregivers may be intensified in ESLD, given that liver disease is more frequently linked to substance abuse and related long-standing family conflicts.

Although patients dying from ESLD may have experiences similar to those dying from other end-stage diseases, we know very little about how ESLD influences the physical and psychological health of patients with ESLD or their caregivers, or how changes in health occur at the level of the patient-caregiver dyad. The purpose of this article is to describe the background and design of a prospective, longitudinal descriptive study currently in progress, "Symptom Burden in End-Stage Liver Disease Patient-Caregiver Dyads." This study was developed to identify patient and caregiver subgroups with distinct trajectories of change in physical and psychological symptoms, examine how these trajectories relate to changes in QOL, and identify subgroups of patient-caregiver dyads who would benefit most from early tailored palliative care interventions.

Background

Chronic Liver Disease: A Significant Societal and Clinical Problem

Chronic liver disease is a progressive destruction of the liver parenchyma leading to cirrhosis. The final stage of chronic liver disease is ESLD; at that stage there is irreversible damage to the cells, tissues, structures, and functions of the liver, leading to complete liver failure. Chronic liver disease is a significant cause of morbidity, mortality and health-care utilization in the United States (Scaglione et al., 2015). Affecting more than 5.5 million Americans, chronic liver disease is the twelfth leading cause of death (Kochanek, et al.,

2014), accounts for more than 240,000 hospitalizations and 290,000 emergency room visits annually, and is the most expensive gastrointestinal condition (Peery et al., 2015).

Causes of ESLD include viral hepatitis, alcoholic cirrhosis, and diabetes; many persons with cirrhosis are unaware of having liver disease (Holmberg, Spradling, Moorman, & Denniston, 2013; Scaglione et al., 2015). A shift in cause of mortality from viral hepatitis to non-alcoholic fatty liver disease is anticipated over the next two decades (Younossi et al., 2016).

Physical and Psychological Symptoms in Patients with ESLD

Research on ESLD has focused primarily on patients who are liver transplant candidates (Santos et al., 2010; Stewart, Hart, Gibson, & Fisher, 2014) and pre- and post-transplantation (Garcia-Rodriguez et al., 2015; Kalaitzakis et al., 2012). Patients awaiting transplantation experience marked worsening of overall health (Lai et al., 2015), physical symptoms like fatigue, affective symptoms like depression and anxiety (Stewart et al., 2014), uncertainty (Kimbell, Boyd, Kendall, Iredale, & Murray, 2015), poor QOL, fear of dying (Bjork & Naden, 2008; Derck et al. 2015), and worsening ascites and confusion due to hepatic encephalopathy (Onyekwere, Ogbera, & Hameed, 2011). Adults with ESLD toward the end of life experience pain (Hansen, Leo, Chang, Zucker, & Sasaki, 2014), symptom distress (Hansen et al., 2015), dyspnea, and depression (Poonja et al., 2014). QOL in ESLD is significantly worse compared to QOL in patients with other advanced conditions such as chronic obstructive pulmonary disease and heart failure (Verma & Navarro, 2015; Younossi et al., 2000).

Some evidence suggests that patients with ESLD find care, information, and symptom management offered by providers to be inadequate (Baker & McWilliam, 2003; Valery et al., 2015). In the absence of support from providers, patients learn to manage their symptoms through trial and error (Baker & McWilliam, 2003) and with the support of their informal caregivers. There is considerable room for the improvement of care for patients living with ESLD and their caregivers.

Physical and Psychological Symptoms in Caregivers of Patients with ESLD

In the limited research available, informal caregivers of patients with ESLD are depressed (Malik et al., 2014) and feel overwhelmed (Kunzler-Heule, Beckmann, Mahrer-Imhof, Semela, & Handler-Schuster, 2016). They experience uncertainty, fears (Meltzer & Rodrigue, 2001), and significant caregiver strain (Bajaj et al., 2011; Miyazaki et al., 2010). Rodrigue and colleagues (2011) provided evidence that caregivers have poor mental QOL and mood disturbances. Miyazaki and colleagues (2010) found that caregivers of patients with a Model for End-Stage Liver Disease (MELD) score of ≥ 15 (a reliable measure of short-term survival; higher score indicates shorter survival) experienced greater caregiver burden, general strain, and social isolation than did caregivers of patients with a MELD score of <15 .

Early Referral to Palliative Care is Important in ESLD

Early palliative care referral of outpatients is associated with better end-of-life care compared with late referral (Barton, 2014; Hui et al., 2014). In one of the few studies of

palliative care in patients with ESLD, an early palliative care intervention decreased patients' depression and other symptoms (Baumann et al., 2015). Despite documented benefits, referral to palliative care or hospice tends to occur late in the progression of ESLD (Hansen et al., 2014; Potosek, Curry, Buss & Chittenden, 2014). Patients with ESLD receive most of their care in outpatient settings (Meier & Beresford, 2008; Rabow et al., 2013); hence, early referral could mean early symptom amelioration and resolution of other problems before they evolve into crises (Lee, Lo, Ko, Huang, & Lee, 2014).

Most evidence on the value of palliative care has been for other conditions like cancer (Bakitas et al., 2009; Temel et al., 2010), cardiovascular, and pulmonary diseases (Rabow, Dibble, Pantilat, & McPhee, 2004; Rabow et al., 2013). There is evidence from oncology that palliative care increases patient and caregiver QOL and decreases caregiver distress and burden (Groh, Vyhnaelek, Feddersen, Fuhrer, & Borasio, 2013). Better symptom control and QOL (Bakitas et al., 2009; Follwell et al., 2009), as well as lower healthcare resource utilization and longer life have been associated with palliative care for patients with other conditions (Greer et al., 2012; Temel et al., 2010).

Caregivers of patients who receive palliative care have reported fewer unmet needs (Abernethy et al., 2008). Research focusing on the palliative care needs and symptom burden of caregivers or on the patient-caregiver dyad as a unit of care, however, is quite limited (Hudson & Payne, 2011).

It is recommended that palliative care interventions be guided by the specific disease trajectory (Mahtani-Chugani, Gonzalez-Castro, de Ormijana-Hernandez, Martin-Fernandez, & de la Vega, 2010), be implemented as patients approach the end of life, before new symptoms arise with the increasing severity of disease (Poonja et al., 2014), focus on both patients and their caregivers (Gaertner, Wolf, Hallek, Glossmann, & Voltz, 2011), and address them as a unit of care (Hudson & Payne, 2011). Non-disease specific models of palliative care may not present patients with ESLD and their caregivers with support systems that are aligned with their unique experiences and needs (Gaertner et al., 2011). The current study will provide key knowledge about distinct trajectories of change in symptom burden in ESLD patients and their caregivers. Importantly, this study is also in line with the movement towards a dyadic perspective on the illness experience (Revenson, Kayser, & Bodenmann, 2005) and may also reduce barriers in integrating palliative care interventions into routine liver clinical care.

Research Design and Methods

Biobehavioral Research Framework

The study design was influenced significantly by Lenz's Theory of Unpleasant Symptoms (Lenz, Pugh, Milligan, Gift, & Suppe, 1997; Lenz, Suppe, Gift, Pugh, & Milligan, 1995) with respect to associations among symptoms (physical and psychological), pathophysiological factors (ESLD), situational factors (patient & caregiver predictor factors), and performance (QOL), for patients with ESLD and their caregivers individually and within patient-caregiver dyads. The relationship among symptoms is a major omission

from many symptom models. Our framework (Figure 1; based on C. S. Lee, Mudd et al. (2015) overcomes this limitation.

A second important element of our study design is our intention to identify distinct subgroups or typologies in patients and their caregivers. Previous researchers have focused on quantifying the frequency of certain symptoms (Bolkhir, Loiselle, Evon, & Hayashi, 2007; Santos et al., 2010) and correlations among symptoms (Bajaj et al., 2011), but these analyses do not reflect the complex interacting symptoms experienced by patients with ESLD and their caregivers. Hypothetically, we may find a group of patients with a steep decline in physical and psychological wellbeing and a group with relative stability in symptoms over time. Minimally, we expect to identify at least one subgroup of patients who have worse pain, symptom distress, and QOL than others and who would particularly benefit from different evaluation and treatment strategies and early palliative care referral. Similarly, we expect to identify at least one group of caregivers who are particularly burdened with worse symptoms and poor QOL and who would benefit most from early supportive palliative care interventions. Cumulatively we expect to identify at least two types of patient-caregiver dyads that would benefit from different palliative care interventions.

Study Design

A prospective, longitudinal descriptive design is being used to identify multiple trajectories of change in physical and psychological symptoms in patients with ESLD and their caregivers. Data collection occurs at patients' routine appointments at baseline, 3, 6, 9, and 12 months. Baseline for this study is defined as the time a patient with ESLD has an appointment in a liver clinic and enrolls in the study. In addition to methodological reasons to collect data every 3 months to detect change in symptoms and outcomes, most patients have routine scheduled appointments at least every 3 months. A large number of patients live >50 miles from the study sites, and timing the study visits with clinic appointments is feasible and convenient. Conducting the study in context of current clinical practice will also allow us to identify patients and caregivers in need of early care escalation. The one-year timeframe enables us to obtain data at 5 data points. We also considered the sample size, attrition, and survival rate, as well as the feasibility of the study design over a 5-year study period.

Data collection methods involve (a) collecting medical history, liver cirrhosis etiology, liver transplant status, medications and clinical events from the electronic medical records; (b) administering questionnaires; (c) assessment and documentation of disease severity by hepatologists and nurse practitioners; and (d) collection of blood samples during scheduled phlebotomy for assessment of liver disease severity and function. The joint Institutional Review Board (IRB) at the two study sites approved all study procedures.

Specific Aims and Hypotheses

The overarching goals of the study are (1) to characterize distinct trajectories of change in symptoms of patients and caregivers and to link those changes over 12 months to clinical events, QOL, and disease severity for patients and QOL for caregivers and (2) to characterize types of patient-CG dyads based on patient-, caregiver-, and dyad-level factors.

Specific aim 1: Identify trajectories of change in physical and psychological symptom burden in adults with ESLD

Subjective data on physical (pain and symptom distress) and psychological (uncertainty, depression) symptoms will be collected from patients. We will collect data on QOL, liver disease severity, and function at the same time points, and clinical event (e.g., hospitalization) data throughout 12 months.

Hypothesis 1.1: At least two distinct trajectories of change in physical and psychological symptoms can be identified, and will be associated with significant differences in clinical events and patient QOL.

Hypothesis 1.2: there will be significant congruence between changes in symptoms and indices of liver disease severity and function over time.

Hypothesis 1.3: Socio-demographic and clinical (e.g., liver transplant status) determinants of worsening patient symptom trajectories can be identified.

Specific aim 2: Identify trajectories of change in physical and psychological symptom burden in caregivers of adults with ESLD

Subjective data on physical (sleep, burden) and psychological (uncertainty, depression) symptoms will be collected from caregivers along with corresponding data on QOL.

Hypothesis 2.1: At least two distinct trajectories of change in physical and psychological symptoms can be identified, and will be associated with significant differences in caregiver QOL.

Hypothesis 2.2: Socio-demographic determinants of worsening caregiver symptom trajectories can be identified.

Specific aim 3: Determine patterns and predictors of types of patient-caregiver dyads that would benefit from early tailored palliative care interventions

Hypothesis 3.1: At least two types of patient-caregiver dyads can be identified and differentiated based on patient-, caregiver-, and dyad-level factors.

Setting

The sample is being recruited and enrolled from seven outpatient liver clinics, six outpatient paracentesis clinics, and two pre-transplant liver clinics in two health care systems. The outpatient liver clinics are staffed by 11 health care providers, the paracentesis clinics by three providers, and the pre-transplant clinics by nine. The recruitment of study participants at the first study site started in May 2016 (3 months after study approval and funding was received) and in June 2016 at the second site.

Sample

The target population for the study is adult men and women with ESLD and their informal caregivers. A caregiver is any adult identified by the patient (e.g., a spouse or partner, parent, adult child or grandchild, sibling, identified significant other, or close friend). To account for

attrition we plan to enroll an estimated 240 patients and 240 caregivers to reach a final evaluable sample of 200 patients and 200 caregivers.

The inclusion and exclusion criteria are presented in Table 1. There are over 2,650 patients diagnosed with cirrhosis at the participating clinics. Of these patients, more than 335 are estimated to have a MELD score of ≥ 15 (M. Chang & W. Naugler, personal communication, October 12, 2015). Patients with a MELD score of <15 will be excluded because they are likely to be asymptomatic, have no progressive symptoms, or have few disease complications in the study's timeframe. MELD of 15 was determined to be the point at which 1-year survival after liver transplant was better than 3-month survival on the liver transplant waiting list (Meriona et al., 2005). A MELD score of ≥ 15 indicates a 3-month 12% mortality rate and an estimated 15% 1 year mortality. Because the study sample of patients is expected to include mostly men and the study sample of caregivers is expected to be mostly women, the sample is expected to include 50% women and 50% men. Ethnic groups other than European-American will be poorly represented due to limited presence in the geographical regions of the study, but we are assigning recruitment preference to minority patients.

Sample Size Justification and Power

We will enroll approximately 8 patients and 8 caregivers per month over 30 months of recruitment (to reach a final evaluable sample of 200 patients and 200 caregivers who complete the study). A sample size of 240 is adequate to detect moderate associations of predictors and patterns of symptoms with alpha adjustment for multiple tests (Benjamini & Hochberg, 1995). Recruiting 240 participants is feasible and will allow for attrition.

Latent growth mixture modeling (GMM) will be used to address key study aims. No single approach is widely accepted for sample size calculation in GMM, but with four primary indices of physical and psychological symptoms and four indices of liver severity for ESLD patients in our most complex model, our *n*-to-item ratio of 20:1 matches sample size recommendations for the closest related analyses (Harrell, Lee, Califf, Pryor, & Rosati, 1984; MacCallum, Widaman, Zhang, & Hong, 1999). Although simulation methods are available to help estimate sample size more precisely for GMM, these methods require known values for all model parameters, which are not available for our research questions. Using a formula provided by Raudenbush and Bryk (2002), a sample size of 240 dyads measured five times over 12 months has power of .80 to detect change over time with up to 20% case loss to missing data/attrition. We will use parsimonious models after extensive preliminary analyses to identify predictors of favorable trajectory membership. Cox proportional modeling, and by extension survival modeling in GMM, is resilient to small sample sizes when there are strong, independent relationships.

Measurements

Instruments were selected that have been used successfully with chronic illness samples and family members of chronically ill, in dyadic research, and in our preliminary studies. The measures and their characteristics are presented in Table 2.

Patients' physical and psychological symptoms—The patient symptoms being measured in the study are pain, symptom distress, uncertainty, and depression. Pain is measured using the modified Wisconsin Brief Pain Inventory (BPI). The BPI is a multidimensional instrument measuring pain history, etiology, location, intensity and interference (Daut, Cleeland, & Flanery, 1983). Four severity items and seven interference with activities items are used as measures of pain severity and pain interference, respectively. The BPI has established reliability and construct validity for clinical (Tan, Jensen, Thornby, & Shanti, 2004) and research purposes (Daut et al., 1983; Zelman, Gore, Dukes, Tai, & Brandenburg, 2005). In our preliminary study, Cronbach's alphas were .88 and .92 for the pain severity and interference scales (Hansen et al., 2014).

Symptom distress is measured using the Condensed Memorial Symptom Assessment Scale (CMSAS; V. T. Chang, Hwang, Kasimis, & Thaler, 2004). The CMSAS includes 14 prevalent physical and psychological symptoms measured by presence and distress, and has three subscales (CMSAS SUM, CMSAS PHYS, and CMSAS PSYCH). Individuals are asked to rate symptoms on a 5-point Likert-type scale. The CMSAS subscales have demonstrated reliability (Cronbach's alphas ranged from 0.79 to 0.87) and validity with cancer patients (Lam et al., 2008). In our preliminary study, the Cronbach's alphas at baseline for the global symptom distress index (GDI), the psychological symptom distress (PSYCH), the physical symptom distress (PHYS), and MSAS total score were .83, .94, .87, and .93, respectively (Hansen et al., 2015).

Uncertainty is measured using the Uncertainty in Illness Scales for Adults (MUIS-A; Mishel, 1981, 1983). The MUIS-A has 33 items, and its total score ranges from 33–165. The scale can be totaled with one score or scored in four subscales (item 15 not included): Ambiguity (13 items), Complexity (7 items), Inconsistency (7 items), and Unpredictability (5 items). Reliability and validity have been established for the MUIS-A (Mishel, 1983, 1997). The MUIS-A has been widely used with chronic illness samples and samples with hepatitis C (Bailey et al., 2009; Mishel, 1997).

Depression is measured using the Patient Health Questionnaire (PHQ-9; Pfizer Inc., 1999; Kroenke, Spitzer, & Williams, 2001). The PHQ-9 assesses presence and severity of depressive symptoms, producing a score for each of the 9 DSM-IV criteria. The response scores on the 10 items are summed to give a total score. The PHQ-9 was chosen because it is a brief, reliable and valid measure (American Psychological Association, 2017; Kroenke et al., 2001).

Patients' clinical characteristics—The etiology and duration of patients' liver cirrhosis, co-morbidities, and medication use (e.g. analgesics and antidepressants) are collected from their medical records. Comorbidities are collected using the Charlson Comorbidity Index, a simple and valid method of estimating risk of death from comorbid diseases (Charlson, Pompei, Ales, & MacKenzie, 1987).

Current and past substance abuse is measured using the Severity of Dependence Scale (SDS; Gossop et al., 1995; Lawrinson, Copeland, Gerber, & Gilmour, 2007). The SDS is a 5-item

scale that can be adapted to measure use of alcohol and different drugs over various timespans.

Practical support is measured by caregiver observation using the Barthel Index (BI). The BI is a 10-item measure of activities of daily living (ADL) grouped into self-care and mobility (Mahoney & Barthel, 1965). Scoring ranges from 0 to 100 in intervals of 5 points. The BI has been judged a reliable, valid, and responsive measure of basic ADL (Duffy, Gajree, Langhorne, Stott, & Quinn, 2013; Hsueh, Lin, Jeng, & Hsieh, 2002).

Patients' liver disease—Disease severity and function are determined by assessment by hepatologists and nurse practitioners and by laboratory values at routine 3-month appointments. The assessment includes West Haven Criteria, ascites assessment, Child's-Turcotte-Pugh (CTP) scores and Model for End-Stage Liver Disease (MELD).

West Haven Criteria grades the severity of hepatic encephalopathy based on the patient's state of consciousness and intellectual function, personality, behavior, and neuromuscular abnormalities on a scale of 1 (*least severe - trivial lack of awareness*) to 4 (*most severe - coma: unresponsive to verbal or noxious stimuli*; Ferenci et al., 2002; Hassanein et al., 2009). Ascites assessment is classified as: 1=*mild*; 2=*detectable*; 3=*visible* (Moore et al., 2003). The CTP score includes 5 variables: Ascites, encephalopathy, bilirubin, albumin, and international normalized ratio (INR; Dolan & Arnold, 2008). Based on the sum of the scores for the 5 variables, patients are grouped into 3 classes. Patients scoring 5–6 have “Class A” liver failure. Patients scoring 7–9 have “Class B” liver failure. Patients scoring 10–15 have “Class C” and far greater mortality than the other two classes (1-year median survival is 45% and 2-year is 38%; Dolan & Arnold, 2008). The MELD score is an important physical indicator and is a reliable measure of short-term survival over a range of liver disease severity levels and diverse etiologies (Desai et al., 2004; Heuman et al., 2004). The score is calculated using levels of serum bilirubin, creatinine, and INR (Kamath et al., 2001) and ranges from 6 (less ill) to 40 (gravely ill).

Patient outcomes—Quality of life and clinical events experienced by patients were chosen as outcome measures. Clinical events are any health-related interactions with health care systems in addition to patients' routine 3 months appointments in the liver clinics, or change in health or transplant status. Every 30 days we complete a review of patients' clinical medical records, looking for clinical events: a) emergency department (ED) visits, b) hospitalizations, c) additional clinic visits, d) paracentesis, e) palliative/hospice referrals, f) liver transplant status or change in status, g) liver transplantations, h) and death. We calculate the number of days between baseline data collection and clinical events, the number of events and the reasons for the events.

Quality of life is measured using the SF-36 and Measuring Quality of Life at the End of Life (QUAL-E) questionnaire. The SF-36 is a multi-purpose health survey with 36 questions and has been used in surveys of general and specific populations including patients with ESLD (dos Santos et al., 2014; Garratt, Ruta, Abdalla, & Russell, 1994) The SF-36 yields an 8-scale profile of functional health and well-being scores as well as physical and mental health summary measures and a preference-based health utility index (Brazier et al., 1992). The

QUAL-E is a 25-item scale measuring QOL at the end of life. It consists of four subscales: Life completion (7 items), Symptom Impact (4 items), Relationship with Health Care Provider (5 items), and Preparation (4 items). Participants are asked how true statements are for them from 1 (*not at all*) to 5 (*completely*). Reliability and convergent and discriminant validity have been established (Steinhauser et al., 2002; Steinhauser et al., 2004).

Caregivers' physical and psychological symptoms—The caregiver symptoms being measured are sleep, burden, uncertainty, and depression. Sleep is measured using the Pittsburgh Sleep Quality Index (PSQI). The PSQI measures self-reported sleep quality and disturbance. Nineteen individual items generate seven component scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The sum of scores for components yields a global score between 0 and 21. A PSQI score of >5 is an indicator of relevant sleep disturbances (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). The PSQI is considered a reliable and valid measure that has been used in a variety of populations (Buysse et al., 1989; Carpenter & Andrykowski, 1989).

Burden is measured using the Multidimensional Caregiver Strain Index (MCSI). Strain is defined as a caregiver's response to a subjective burden. The MCSI is an 18-item questionnaire with six subscales: Physical (3 items), social (4 items), financial (2 items), interpersonal strain (5 items), time constraints (2 items), and care receiver demands (2 items; Stull, 1996). Reliability and validity have been established with different types of caregivers (Stull, 1996). The MCSI was chosen because it is multidimensional.

Uncertainty is measured using the Uncertainty in Illness Scale for Family Members (MUIS-FM; Mishel, 1981, 1983). The MUIS-FM has 31-items, each scored from 1 (*strongly disagree*) to 5 (*strongly agree*). The total score ranges from 31–155. Reliability and validity have been established for the MUIS-FM (Mishel, 1997). The MUIS-FM was chosen because it has been widely used with family members of chronically ill.

Depression is measured using the PHQ-9 (described above). The PHQ-9 has been used with adults with chronic liver diseases (K. Lee, Otgonsuren, Younoszai, Mir, & Younossi, 2013) and will enable comparison of scores with patients.

Caregivers' clinical characteristics—Co-morbidities and medication use (e.g. sleep medications and antidepressants) are collected with the Charlson Comorbidity Index (Charlson et al., 1987), the PSQI (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989), and the PHQ-9 (Pfizer Inc., 1999), described above for patients.

Caregiver outcomes—Quality of life is measured using the SF-36. It was chosen for both patients and caregivers in this study because of its wide use as a quality of life measure (RAND Corporation, 1994–2017).

Patient and caregiver socio-demographics and situational factors—Socio-demographic data are collected at baseline using a socio-economic sheet. The situational

factors measured are patient and caregiver optimism, pessimism, coping style, relationship quality, and perceived social support.

Optimism and Pessimism is measured by the Life Orientation Test-Revised (LOT-R; Scheier, Carver, & Bridges, 1994), a reliable and valid measure (Glaesmer et al., 2012; Herzberg, Glaesmer, & Hoyer, 2006). Participants are asked the extent to which they agree to six statements from 0 (*strongly disagree*) to 4 (*strongly agree*). Three statements measure optimism, and three measure pessimism. The LOT-R has been successfully used in patient and caregiver research (Benzing et al., 2015; Lyons, Stewart, Archbold, Carter, & Perrin, 2004).

Coping style is being measured using two subscales from the Revised Ways of Coping Checklist (RWCCCL; Aldwin, Folkman, Shaefer, Coyne, & Lazarus, 1980; Folkman & Lazarus, 1980), which includes a 15-item problem-focused coping scale and a 10-item avoidance scale. For each item, the respondents are asked to record the degree to which they used that strategy to deal with their problem. Options include *never used*, *rarely used*, *sometimes used*, and *regularly used*. Reliability and validity have been established (Vitaliano, Russo, Carr, Maiuro, & Becker, 1985).

Relationship quality is measured using the 15-item Mutuality Scale (Archbold, Stewart, Greenlick, & Harvath, 1990; Archbold et al., 1995). The Mutuality Scale was chosen because of its successful use in dyadic research (Lyons, Sayer, Archbold, Hornbrook, & Stewart, 2007)

Social support is measured using the 12-item Perceived Social Support Scale (PSSS; Blumenthal et al., 1987; Zimet, Dahlem, Zimet, & Farley, 1988). The scale measures support received from three different sources: significant others, family members, and friends. Reliability and validity have been established (Blumenthal et al., 1987; Zimet et al., 1988).

Statistical Analysis Plan

Standard descriptive statistics of frequency, central tendency, and dispersion will be used to describe the sample at applicable levels of measurement. Comparison of characteristics between/among observed trajectories will be made using Student's *t*, Mann-Whitney *U*, Fisher's exact or Kruskal-Wallis tests, or Pearson χ^2 analysis or ANOVA as appropriate. All analyses will be performed using StataMP v14 (College Station, TX), HLM v7 (Skokie, IL) and/or Mplus v7.2 (Los Angeles, CA).

As described in Table 3,

Full-information maximum likelihood estimation (FIMLE as implemented in Mplus) or principled methods of multiple imputation (Kenward & Carpenter, 2007) such as the method of incremental chained equations in Stata (Royston P, 2004, 2005; StataCorp, 2009), will be used to handle data that are missing at random (MAR). In the case of missingness not at random, pattern mixture modeling (Birmingham & Fitzmaurice, 2002; Maruotti, 2011; Wilkins & Fitzmaurice, 2007) will be used to allow the analysis of the proposed aims in the case of patient or caregiver withdrawal. Analytic procedures by aim and hypothesis are detailed in Table 3.

Discussion: Challenges and Lessons Learned

During the first year of this 5-year study, we have encountered several challenges and learned several lessons. The first challenge was to put in place a competent team for operationalizing the study. Hiring an experienced project director who had in-depth knowledge and expertise in study start-up and the conduct of complex longitudinal studies was a must. As principal investigator (PI, first author), I was more than fortunate when a co-investigator suggested that his project director should work with me get all processes in place before hiring others. This project director has extraordinary interpersonal qualities; exceptional organizational, management, and communication skills; and expertise in managing large studies while paying attention to critical details.

Just as important is creating an inter-professional research team of members who work well together and who have empathy and compassion toward the particularly vulnerable and often stigmatized population of patients with ESLD. Many of the patients feel rejected and unvalued and feel themselves to be a burden without much to contribute to their families and society. Their caregivers may feel overwhelmed and over-extended. The study team likely encounters them during the most stressful time of their lives. Sensitivity is needed toward potential and enrolled study participants by all members of the research team.

The project director and PI hired research staff with expertise and interpersonal qualities to work with these patients and their caregivers. However, the hiring of staff took several months. Although the study is conducted at two sites with a process for joint IRB approval, the requirements at each site differ for procedures, hiring, and training of research staff. The differences between the two sites added an additional layer of complexity and delayed the start date of the study. This was a concern for the PI, who needed systems, procedures, and databases in place to show progression and advancement during the first year to ensure funding for subsequent years. Start-up time can easily be underestimated, but we were able to begin participant recruitment within 3 months of funding despite all challenges.

Second, the recruited patients have been very ill. Based on our experience of high attrition in preliminary work with patients with MELD scores of 18, we proposed a MELD score of 15 to reduce attrition, but already have encountered more liver transplantations and sudden deaths than expected. To mitigate this challenge, we closely evaluate patients with MELD scores of >25 before enrollment. Overall attrition is about 20%. Some patients and caregivers who enrolled have not returned the baseline questionnaires despite follow-up telephone calls from research team members. These patients and caregivers may have the best intentions but find it difficult to follow through.

Third, about 10% of patients and caregivers have declined to participate in the study for various reasons, including that patients are too sick and are hospitalized and/or caregivers are too overwhelmed. To ensure success of recruitment and enrollment, we may need to increase our estimated sample size above 240 patients and 240 caregivers. This may bring more personnel and financial challenges. Careful and continuous evaluation of allocated resources is critical. Currently, recruitment is going as planned at an average of two patient-

caregiver dyads every week. We will be recruiting and enrolling study participants over a 30-month period.

Fourth, we needed to align our efforts with health care providers for recruitment of study participants. This requires working with multiple providers in busy out-patient clinics with different schedules and styles, while being flexible and accommodating. We have developed modalities (e.g., timing of e-mails) that fit each individual clinician and each system of operation, to minimize workload burden or disruption.

We learned early on that patients with ESLD are not asked about symptom experiences in great detail by health care providers, and their caregivers in particular are rarely asked. When patients and their caregivers learned about the gaps in science regarding their symptom experiences, they wanted to tell us more. To address this wish, we have added three open-ended questions to the surveys at all five data collection points. One question is the same across the five data points. The other questions are tailored to the time the surveys are to be completed. For example, at baseline, we ask patients, "In addition to the survey questions, is there anything else you would like us to know about you, your family member, and/or your liver disease?" At 3 months, a question is, "How has living with liver disease affected you and your family?" whereas at 6 months, a question is asked, "What would help you and your family member manage your liver disease better?"

An experienced and committed inter-professional research team and supportive and invested clinicians are essential to ensure the success of this large and complex study. Based on the strength and expertise of the team, we plan to navigate through these and other study challenges while maintaining its progression and integrity.

Conclusion

Based on the results of this study, we plan to develop palliative care interventions that can be tailored to different types of patient-caregiver dyads in need of early palliative care. Early and timely interventions will inform these dyads about what to expect, decrease their uncertainty, optimize their QOL, and likely prevent aggressive therapies and care that many do not want and may not improve their QOL (Garrido, Balboni, Maciejewski, Bao, & Prigerson, 2015; Institute of Medicine, 2014).

Because we are studying patients dealing with ESLD regardless of their trajectories and whether or not they are liver transplant candidates, it will give us a broad look at the challenges faced by families who may or may not have an option for recovery from the disease. The results of this study will give us great insight into the lives of a wide range of patients and families dealing with ESLD.

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EDITOR'S NOTE

This is the first example of a new article type for this journal, a research protocol. The aim of this type of article is to describe an innovative, substantial, externally funded work in progress and report on issues encountered in implementation that may be of interest to readers doing similar work.

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Figure 1. Research Framework

To effectively capture interactions among symptoms, we will quantify patterns of association among multiple patient (C_1) and caregiver (C_2) symptoms over time. These observed trajectories may have different intercepts (i), slopes (s), and non-linear patterns of change over time (q). Many approaches to understanding symptoms fail to demonstrate sufficient clinical relevance of the findings. Our approach is to link patterns with significant and clinically meaningful differences and QOL and clinical events (H1.1; H2.1). We will also help establish the clinical relevance of patient symptoms by quantifying the degree of agreement in change (a.k.a. concordance) between symptoms and indices of disease severity and function (H1.2). Because our long-term goal is to design and test early, specifically tailored palliative care interventions, we are interested in the socio-demographic and clinical characteristics that help determine which type of patient and caregiver is more likely to have worsening of symptoms over time (H1.3; H2.2). Finally, identifying a typology of ESLD dyads is integral to our research approach. We will be able to identify distinct patterns of patients with ESLD and their caregivers and differentiate them based on patient- (e.g., optimism), caregiver- (e.g., pessimism), and dyadic-level (i.e., relationship quality) factors (H3.1).

Table 1

Inclusion and Exclusion Criteria: Adults with End-Stage Liver Disease (ESLD) and their Adult Family Caregivers

Criteria	Adults with ESLD	Caregivers
Inclusion criteria	<ul style="list-style-type: none"> • Willing and able to provide informed consent • Age > 21 years^a • Able to read and comprehend 5th grade English • Reachable by telephone • Have an adult caregiver identified by patient • MELD score ≥ 15^b 	<ul style="list-style-type: none"> • Willing and able to provide informed consent • Age > 18 years • Able to read and comprehend 5th grade English • Reachable by telephone
Exclusion criteria	<ul style="list-style-type: none"> • Major and uncorrected hearing impairment • Not well controlled major psychiatric illness • Concomitant terminal illness that would impede participation in a longitudinal study • Prior liver transplantation • Undergoing antiviral treatments 	<ul style="list-style-type: none"> • Major and uncorrected hearing impairment • Not well controlled major psychiatric illness • Terminal illness that would impede participation in a longitudinal study

^aBecause liver disease is not common in childhood and the caregiving relationship differs, children were excluded as patients. Adult children from age 18 to 21 are included as caregivers.

^bPatients with a MELD score of <15 will be excluded because these would likely be asymptomatic, have no progressive symptoms, and have fewer disease complications in the study's timeframe.

Table 2

Measures and Schedule of Assessment for Patients and Caregivers

Participant	Category	Measurement	Reliability (α)	Minutes to Complete
Patient	Physical and psychological symptoms			
	Pain Severity/interference	Wisconsin Brief Pain Inventory ^c	.88 – .92	<7
	Symptom distress	Condensed Memorial Symptom Assessment Scale ^d	.79 – .87	<4
	Uncertainty	Adult Uncertainty in Illness Scale ^e	.60 – .90	<10
	Depression	Patient Health Questionnaire ^f	.89	<4
	Clinical characteristics			
	Cirrhosis etiology/duration ^a	Medical record abstraction	–	
	Comorbidities ^a	Charlson Comorbidity Index ^g	–	
	Medications used	Medical Record Abstraction	–	
	Substance abuse	Severity of Dependence Scale ^h	.80 – .90	<3
	Practical support	Barthel Index ⁱ	.84	<3
	Liver disease			
	Disease severity/function	Clinical assessment: West Haven Criteria & Ascites	–	
		Child's-Turcotte-Pugh score	–	
		Model for End-Stage Liver Disease score	–	
	Outcomes			
	Quality of life	SF-36 ^j	.68 – .96	<10
Caregiver		Quality of Life at the End of Life ^k	.68 – .87	<7
	Clinical events ^b	Clinical event assessment record	–	
	Physical and psychological symptoms			
	Sleep	Pittsburgh Sleep Quality Index ^l	.87	<7
	Burden	Multidimensional Caregiver Strain Index ^m	.90	<7
	Uncertainty	Family Member Uncertainty in Illness Scale ^e	.91	<10
	Depression	Patient Health Questionnaire ^f	.89	<7
	Clinical characteristics			
	Comorbidities ^a	Charlson Comorbidity Index ^g	–	<2
	Medications used	Medication questionnaire	–	<2
Patient and Caregiver	Outcomes			
	Quality of life	SF-36 ^j	.73 – .96	<10
Patient and Caregiver	Socio-demographics ^a	Socio-demographic questionnaire		<3
	Situational Factors			

Participant	Category	Measurement	Reliability (α)	Minutes to Complete
	Optimism and pessimism ^a	Life Orientation Test-Revised ⁿ	.70 – .74	<3
	Coping styles ^a	Revised Ways of Coping Checklist ^o	.76 – .92	<7
	Relationship quality ^a	Mutuality Scale ^p	.91	<5
	Social support ^a	Perceived Social Support Scale ^q	.85 – .91	<3

Note. Data collected at baseline and months 3, 6, 9, and 12, unless otherwise noted.

^aData collected at baseline only.

^bData collected at months 3, 6, 9, and 12 only.

^cDaut, Cleeland, & Flanery, 1983

^dV. T. Chang, Hwang, Kasimis, & Thaler, 2004

^eMishel, 1981, 1983

^fPfizer Inc., 1999

^gCharlson, Pompei, Ales, & MacKenzie, 1987

^hGossop et al., 1995

ⁱMahoney & Barthel, 1965

^jRAND Corporation, 1994–2017

^kSteinhauser et al., 2002; Steinhauser et al., 2004

^lBuyse, Reynolds, Monk, Berman, & Kupfer, 1989

^mStull, 1996

ⁿScheier, Carver, & Bridges, 1994

^oAldwin, Folkman, Shaefer, Coyne, & Lazarus, 1980; Folkman & Lazarus, 1980

^pArchbold, Stewart, Greenlick, & Harvath, 1990

^qBlumenthal et al., 1987; Zimet et al., 1988.

Table 3

Hypotheses and Analytic Procedures

Aim and Hypothesis	Analytic Procedure
Aim 1, Hypothesis 1.1: At least two distinct trajectories of change in symptoms can be identified, and will be associated with significant differences in clinical events and patient QOL.	1 Develop separate growth models for each symptom (BPI, CMSAS, MUIS-A, PHQ-9) to quantify mean change and examine fit between linear and non-linear models (Preacher, Wichman, MacCallum, & Briggs, 2008). All procedures for Aim 1 will be performed in Mplus v7.2.
	2 Generate parallel process models (i.e. 2 growth models with random effects among the intercepts and slopes; Cheong, Mackinnon, & Khoo, 2003; Roesch et al., 2009) between all two-way combinations of symptom measures to quantify concordance and identify complementary measures that will be incorporated into GMM (below). Common thresholds of fit (i.e., comparative fit indices and Tucker-Lewis indices > 0.95, root mean square errors of approximation < 0.08, and standardized root mean square residuals < 0.10; (Schnermelleh-Engel, Moosbrugger, & Muller, 2003), will be used to quantify concordance.
	3 Integrate non-redundant symptoms into GMM to identify distinct trajectories of change over time. Our approach to GMM is based on common procedures (Ram & Grimm, 2009); the Lo-Mendell-Rubin adjusted likelihood ratio test (Lo, Mendell, & Rubin, 2001), entropy, the proportion of sample in each class, and posterior probabilities will be used to compare alternative models (e.g., solutions with 3 vs. 2 distinct trajectories; Jung & Wickrama, 2008; Nylund, Asparouhov, & Muthen, 2007).
	4 Event-free survival will be modeled as a function of symptom trajectory membership derived from step 3. Using GMM, we will model both discrete-time (Muthen & Masyn, 2005) and continuous time survival (Asparouhov, Masyn, & Muthen, 2006). We also will follow recent guidance on competing risks (Southern et al., 2006; Varadhan et al., 2010; Wolbers, Koller, Witteman, & Steyerberg, 2009) and analyze event-free survival from all-cause a) emergency department (ED) visits, b) hospitalizations, c) additional clinic visits, d) paracentesis, e) palliative/hospice referrals, f) liver transplant status or change in status, g) liver transplantations, and h) death rather than cause-specific or cumulative incidence functions.
	5 Develop a growth model for QOL (SF-36 (primary), QUAL-E (secondary)), and test the influence of symptom trajectory membership derived from step 3 on the intercept, slope, and quadratic term of QOL over time; results will be reported in estimates, standard errors, z-tests, and statistical significance similar to our recent work (Lee et al., 2015a).
Aim 1, Hypothesis 1.2: There will be significant congruence between changes in symptoms and indices of liver disease severity and function over time.	Generate random effects parallel process models (Cheong et al., 2003; Roesch et al., 2009) to quantify concordance between symptoms (BPI, CMSAS, MUIS-A, PHQ-9) and indices of liver severity and function (West Haven, ascites, CTP, MELD). Common thresholds of fit (i.e., comparative fit indices and Tucker-Lewis indices > 0.95, root mean square errors of approximation < 0.08, and standardized root mean square residuals < 0.10; Schnermelleh-Engel et al., 2003), will be used to quantify significant concordance.
Aim 1, Hypothesis 1.3: Socio-demographic and clinical (e.g., liver transplant status) determinants of worsening patient symptom trajectories can be identified.	To identify candidate predictors of worsening trajectories, univariate associations between socio-demographic and clinical characteristics, and physical and psychological symptoms will be quantified. Univariate statistics will include Student's t, Mann-Whitney U, Fisher's exact or Kruskal-Wallis tests, Pearson χ^2 analysis, ANOVA, Pearson's r, or Spearman's rho where appropriate. Factors that are significantly associated with symptoms (P < 0.20) will be incorporated into multivariate GMM predicting trajectory membership. Results are comparable to logistic/multinomial regression with estimates (like odds ratios), standard errors, z-tests and statistical significance.
Aim 2, Hypothesis 2.1: At least two distinct trajectories of change in physical and psychological symptoms can be identified, and will be associated with significant differences in caregiver QOL.	GMM procedures for identifying distinct trajectories that are explicated under Specific Aim 1 will be replicated to address this aim, replacing ESLD patient-level symptom data with physical and psychological symptoms that are experienced by caregivers over time (i.e. PSQI, MCSI, MUIS-FM, PHQ-9). A growth model for caregiver QOL (SF-36) will be generated and caregiver symptom trajectory membership will be compared with the intercept, slope, and quadratic term of caregiver QOL over time; results will be reported in estimates, standard errors, z-tests, and statistical significance.
Aim 2, Hypothesis 2.2: Socio-demographic determinants of worsening caregiver symptom trajectories can be identified.	Univariate associations between socio-demographic and physical and psychological symptoms will be quantified to identify candidate predictors of worsening trajectories. Univariate statistics will include Student's t, Mann-Whitney U, Fisher's exact or Kruskal-Wallis tests, Pearson χ^2 analysis, ANOVA, Pearson's r, or Spearman's rho where appropriate. Factors that are significantly associated with symptoms (P < 0.20) will be incorporated into GMM predicting trajectory membership.
Aim 3, Hypothesis 3.1: At least two types of patient-caregiver dyads can be identified and differentiated based on patient-, caregiver-, and dyad-level factors.	1 Generate Empirical Bayes estimates of the patient-caregiver dyad's pattern of change in depression (PHQ-9) and QOL (SF-36) in two separate unconditional Level-2 longitudinal dyad models (Raudenbush, Brennan, & Barnett, 1995; performed in HLM v7). χ^2 tests will be performed to determine if there is significant variation around the average of these measures. Conditional Level-2 models (one for each measure) will be generated to include patient- (e.g., optimism), caregiver- (e.g., pessimism), and dyadic-

Aim and Hypothesis	Analytic Procedure
	<p>level (i.e., relationship quality) factors to explain the significant heterogeneity, including cross-partner effects. Results would be similar to dyadic approaches by this team to understand and predict changes in symptoms over time (Lyons et al., 2014; Lyons et al., 2007).</p> <p>2 Incorporate symptom measures that are not common between members of the dyad (e.g., patient pain and caregiver sleep quality) into random effects parallel process models in Mplus wherein independence between patients and caregivers is not assumed (Cheong et al., 2003; Roesch et al., 2009); concordance between changes in physical and psychological symptoms between patients and their caregivers will be quantified.</p> <p>3 Integrate non-redundant symptom measures identified in steps 1 and 2 into progressive GMM to determine if there are distinct and naturally-occurring patterns of change in symptoms over time with the dyad as the unit of analysis. If more than one trajectory is identified using GMM, patient-, caregiver- and dyad-level determinants of fitting one pattern of change over the other(s) will be modeled using logistic, multinomial or ordinal regression [formal test of Hypothesis 3.1]. This integrated multilevel and mixture modeling approach has been revolutionary in our recent dyadic work (C. S. Lee, Vellone et al., 2015), as it allows us to identify types of patient-caregiver dyads and differentiate them based on patient-, caregiver-, and dyadic-level factors.</p>

Note. References cited in the table are listed in the reference list.