ORIGINAL ARTICLE

Annals of Gastroenterology (2015) **28,** 124-129

Quality of life and factors predictive of burden among primary caregivers of chronic liver disease patients

Douglas L. Nguyen[a,b], Daniel Chao[a,b], Grace Ma[b], Timothy Morgan[a,b]

University of California, California, USA; VA Long Beach Health Care System, California, USA

Abstract

Background Chronic liver disease increases the socioeconomic and emotional burden on the patient's caregiver. This is important because a patient's adherence to therapy and transplant eligibility is dependent on the caregiver's ability to handle these challenges.

Methods This was a prospective, cross-sectional study of 50 primary caregivers of patients with advanced liver disease. Caregivers completed the RAND 36-item (Short Form [SF-36]) Health Survey and the Zarit Burden Scale survey. Caregiver quality of life, based on the SF-36, was compared using *t*-tests with the scores of the National reference population as controls.

Results In our cohort, the mean age of caregivers was 56.9±11.4 years, 40 (83.3%) were female, and 34 (70.8%) were spouses/significant others of the patient. Compared with the adjusted National norm data, caregivers scored substantially lower in categories of role limitations due to emotional problems (P<0.001), vitality (P=0.025), mental health (P=0.005), and social functioning (P=0.002). While the adjusted physical component score of the caregivers was comparable to the National mean, the mental component score (MCS) was lower than the National average (42.4±13.3 vs. 50.0±10, P<0.001). Though only 8 of 50 (16.0%) subjects reported a formal diagnosis of depression or anxiety, 23 (46.0%) had MCS <42, a strong predictor of clinical depression, based on previous studies.

Conclusions Primary caregivers of patients with advanced liver disease have significantly lower SF-36 mental health scores compared with the general population. Comparison of SF-36 scores to caregiver history suggests under recognition of mental health problems in this population.

Keywords Chronic liver disease, caregiver burden, depression

Ann Gastroenterol 2015; 28 (1): 124-129

Introduction

Chronic liver disease (CLD) and cirrhosis are leading causes of morbidity and mortality in the United States. The impact of liver disease and cirrhosis on the health care system has been previously studied [1-4]. However, the burden of cirrhosis on the family unit, consisting of patients and their caregivers, is relatively unknown. Bajaj *et al* reported that variables predictive of increased caregiver burden included model for end-stage liver disease (MELD) score, previous hepatic encephalopathy, alcoholic etiology, depression, anxiety, and years of relationship [5]. However, the study did not evaluate caregiver characteristics and other patient characteristics that may be predictive of increased provider burden. In addition, the study by Bajaj *et al* did not clearly define the quality of life of caregivers of patients with CLD. Further investigation is necessary to understand the burden of CLD on the family unit because patient's adherence to medical therapy and transplant eligibility is dependent on the ability of the family to absorb these challenges.

By determining the most common physical and mental manifestations of caregiver burden, it may be possible to develop screening protocols and have ancillary resources available for caregivers to help relieve stressors and potentially improve patient outcomes. The liver disease-related factors that contribute the most to caregiver burden, such as those explored by previous studies, may help providers identify caregivers at high risk for burden-related problems. The diagnoses and specific complications that result from caregiver burden,

[a]Division of Gastroenterology and Hepatology, University of California-Irvine (Douglas L. Nguyen, Daniel Chao, Timothy Morgan); [b]Division of Gastroenterology and Hepatology, VA Long Beach Health Care System, (Douglas L. Nguyen, Daniel Chao, Grace Ma, Timothy Morgan), California, USA

Conflict of Interest: None

Correspondence to: Douglas L. Nguyen MD, Assistant Clinical Professor of Medicine, Department of Medicine, UC Irvine School of Medicine, 333 City Blvd. West, Suite 400, Orange, CA 92868, USA, Tel.: +714 456 6745, Fax: 714 456 7753, e-mail: douglaln@uci.edu

Received 28 July 2014; accepted 17 August 2014

including depression, anxiety, other mental illness, financial loss, and difficulties with personal relationships, also requires further study.

This study's objective is to evaluate the quality of life of primary caregivers of patients with advanced liver disease using the Medical Outcomes Study Short Form 36 (SF-36) and caregiver burden using the revised Zarit Burden Interview (ZBI). A review of the patients' medical records was then conducted to determine the characteristics of advanced liver disease that are predictors of increased caregiver burden.

Patients and methods

Subject recruitment

Starting in March 2013, we recruited 50 consecutive caregivers who accompanied patients to their visit in the Liver Clinic the VA Long Beach Healthcare System. Inclusion criteria included: 1) caregiver age >18 years; 2) the patient must have clinical or laboratory evidence of advanced liver disease; and 3) the patient must have identified the caregiver as his primary caregiver at the time of recruitment. Advanced liver disease was defined as having an etiology of liver disease (i.e., chronic hepatitis C, a history of alcohol abuse) and meeting one or more of the following clinical or laboratory parameters: 1) platelet count <150 × 10^9/L; 2) albumin <3.5 g/dL; 3) bilirubin >2.0 mg/dL; and 4) a liver biopsy showing Ishak fibrosis score of 4 or greater out of 6. The study protocol was approved by the VA Long Beach Healthcare System Institutional Review Board.

Surveys included

Caregivers were asked to complete the data on demographic variables, relationship to patient, geographic location to patient, Medical Outcomes Study SF-36 and the ZBI. The SF-36 Health Survey consists of 36 questions measuring 8 different domains of physical functioning, bodily pain, role limitations due to physical condition, role limitations due to emotional health, social functioning, energy/fatigue, emotional well-being, and general health perceptions [6-10]. The Zarit Burden Scale consists of 22 questions, rating 0-9 (9 - highest level of burden) and measures physical, emotional, and financial toll of providing care [11-13].

Statistical analysis

The caregiver characteristics and demographics were summarized using descriptive statistics. The SF-36 Health Survey was scored using the previously established National norms across all domains [14-16]. The ZBI scores were recorded for each caregiver. A total ZBI score <21 was defined as no to little level of burden [17,18]. A multivariate logistic regression analysis was performed to identify patient and caregiver characteristics predictive of increased caregiver burden.

Results

Baseline caregiver characteristics

The baseline characteristics of primary caregivers of patients with CLD are summarized in Table 1. In our cohort, there was predominance in female caregivers (82.0%) and the majority of the caregivers (66.4%) identified as either spouse or unmarried significant other to the liver patient. The mean age of the caregivers was 56.9±11.6 years, and the mean age of the patients was 62.2±7.6 years. Of the 50 caregivers, only 14 (28.0%) were older in age than the patients. The median MELD score of patients at the time of study recruitment was 12. The median length serving as the patient's primary caregiver was 6 years. The reported median length of time spent caregiving per week was 40 hours.

As many as 48.0% of the caregivers were actively working either part-time or full-time. Only 11 of the 50 caregivers (22.0%) reported having to stop working because of caregiving for the patients. In addition, 22.0% of the caregivers also reported having a dependent <18 years of age within their household.

A total of 40.0% of caregivers reported having at least one chronic medical condition such as diabetes, osteoarthritis, CLD, chronic kidney disease, or heart disease. In contrast, only 8 of the 50 caregivers (16.0%) reported being formally diagnosed with a psychiatric condition such as schizoaffective disorder, depression, bipolar disorder, adjustment disorder, dysthymia, and anxiety disorder.

Quality of life of caregivers

Fig. 1 summarizes the component scores to the SF-36 for the caregivers. Compared with the established National norms, primary caregivers of liver patients scored lower on quality-of-life domains of limitation in role functioning due to emotional health (43.3±13.5 vs. 50.0±10.0, P<0.001), vitality (46.8±11.1 vs. 50.0±10, P=0.025); mental health (44.5±12.8 vs. 50.0±10.0, P=0.005); and social functioning (44.2±12.8 vs. 50.0±10.00, P=0.002). There were no statistical differences in the mean component scores of physical functioning (P=0.34), role limitation due to physical health (P=0.12), bodily pain (P=0.37), and general health (P=0.11) in the caregiver group compared with the established National norms.

Overall, caregivers of patients with CLD have a significantly lower mental component score (MCS) compared to the national norms (42.4±13.3 vs. 50.0±10.0, P<0.001), while the physical component score (PCS) was similar between the two groups (51.9±9.1 vs. 50.0±10.0, P=0.16). Though only 8 of 48 (16.7%) subjects reported a formal clinical diagnosis for depression or anxiety, 23 subjects (47.9%) had MCS <42, a strong predictor of clinical depression [7,8].

Factors predictive of increased caregiver burden

Among the surveyed respondents, 23 of the 50 caregivers (46%) reported little to no level of burden based on the Zarit Burden Scale [19,20]. The mean ZBI score among our caregivers was 22.4±12.6. Caregiver with a ZBI score >21 was defined as having an increased level of burden. Factors predictive of increased care provider burden on the multivariate analysis were: more than 1 dependent in the household (odds ratio [OR]: 3.83, 95% confidence interval [CI]: 1.91 - 15.98); more than 2 hospitalizations as a complication of liver disease in the last 12 months (OR: 7.67, 95% CI: 2.05 - 10.07); a history of hepatic encephalopathy (OR: 4.25, 95% CI: 2.04 - 15.53); active alcohol use at home (OR: 2.98, 95% CI: 1.58 - 8.82); and household income $30,000 or less (OR: 1.98, 95% CI: 1.67 - 12.82). Caregiver's age, relationship or proximity to the patient, and total time spent caregiving were not predictive of increased caregiver burden (Table 2).

Table 1 Baseline characteristics of primary caregivers of patients with chronic liver disease

Characteristics	No. (%)
Gender	
Male	9 (18.0)
Female	41 (82.0)
Mean age (years)	56.9±11.6
Relationship with patient	
Spouse or significant other	33 (66.0)
Child	7 (14.0)
Friend	5 (10.0)
Other	5 (10.0)
Total household income level	
$10,000- $30,000	27 (52.0)
$40,000- $60,000	14 (28.0)
$70,000 -$90,000	7 (14)
$100,000 or more	2 (4.0)
Current employment status	
Full time	14 (28.0)
Part time	10 (20.0)
Retired	13 (26.0)
Quit working because of caregiving	11 (22.0)
Unemployed	2 (4.0)
Median duration as caregiver (years, range)	6 (1-32)
Median time serving as caregiver weekly (h, range)	40 (2-160)
Proximity to patient	
Lives in the same house	37 (74.0)
Lives within close proximity (within 1 h drive)	7 (14.0)
Lives>1 h away	6 (12.0)
Personal history of mental health illness	8 (16.0)
Personal history of at least one chronic illness	20 (40)
More than 1 dependent (other than patient) at home	11 (22.0)
Patient's median MELD score	18 (6, 34)
Patient's mean age (years)	62.2±7.6
Etiology for patient's liver disease	
Viral hepatitis	32 (64.0)
Alcoholic hepatitis	7 (14.0)
Non-alcoholic fatty liver disease	5 (10.0)
Other	6 (12.0)

MELD, model for end-stage liver disease

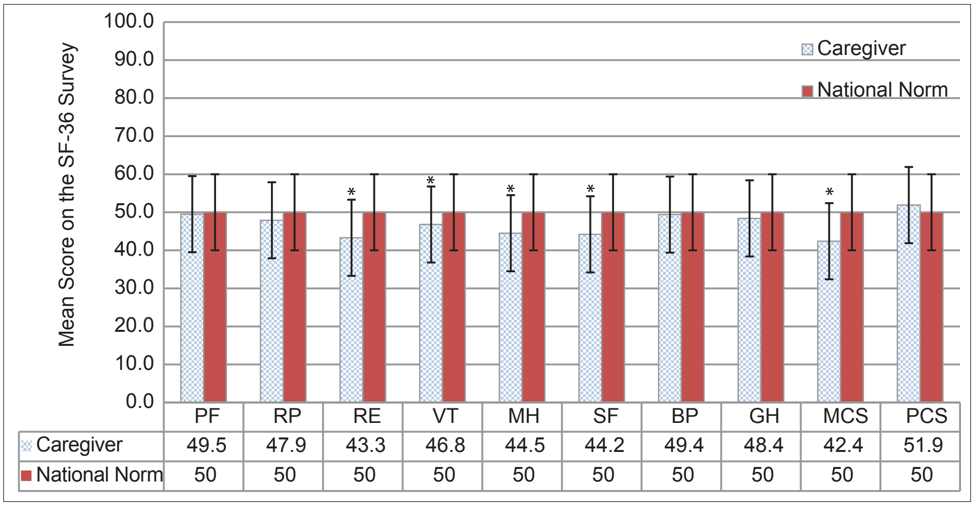
Discussion

CLD and cirrhosis are currently the 12th leading cause of death in the United States [20]. The leading cause of CLD and need for liver transplantation is chronic hepatitis C virus infection, with an affected population between 3 and 5 million [21]. Due to ongoing cost-containment efforts, there is an increased need for family-based care of chronically ill individuals. Debilitating symptoms of fatigue, pruritus, ascites, malnutrition, and encephalopathy are common manifestations of patients with CLD. The presence of CLD at home has a

Table 2 Multivariate of factors predictive of increased caregiver burden of patients with chronic liver disease

Factors	OR	95% CI
Caregiver's age>50	1.01	0.72-3.58
Caregiver older than patient	1.12	0.60-3.69
Relationship to patient		
Spouse/significant other	0.89	0.49-2.47
Non-spouse	1.00	
Caregiver with history of psychiatric illness or chronic illness	1.49	0.76-2.90
More than 1 dependent (other than patient) at home	3.83	1.91-15.98
Proximity to patient		
Within 1 h away	0.93	0.76-3.14
More than 1 h away	1.00	
Greater than 40 h/week	1.62	0.91-3.69
MELD score>15	1.48	0.58-6.81
More than 2 patient hospitalizations in the last 12 months	7.67	2.05-10.07
Patient with history of hepatic encephalopathy	4.25	2.04-15.53
Patient with active alcohol use	2.98	1.58-8.82
Household income ≤$30,000	1.98	1.67-12.82

OR, odds ratio; CI, confidence interval; MELD, model for end-stage liver disease



	PF	RP	RE	VT	MH	SF	BP	GH	MCS	PCS
▨ Caregiver	49.5	47.9	43.3	46.8	44.5	44.2	49.4	48.4	42.4	51.9
■ National Norm	50	50	50	50	50	50	50	50	50	50

Figure 1 Quality of life of caregivers with chronic liver disease compared to the National norm
PF, physical functioning; RP, role limitation due to physical health; RE, role limitation due to emotional health; VT, vitality; MH, mental health; SF, social functioning; BP, bodily pain; GH, general health; MCS, mental component score; PCS, physical component score
*Denotes P <0.05

significant impact on the primary caregivers and affects their overall quality of life. Similar to previous studies [22,23], we have demonstrated that caregivers in our cohort experienced a significantly lower mental health score with nearly one standard deviation below the reported National norm (MCS 42.4 vs. 50.0, P<0.05). Furthermore, though only a minority (16.7%) of caregivers reported a formal clinical diagnosis for depression or anxiety, nearly half of the caregivers had an MCS <42, a strong predictor of underlying depression based on previous studies [7-10]. This discrepancy underscores the fact that nearly 30% of caregivers in our study may have undiagnosed clinical depression. Chronic depression and stress in the presence of inadequate resources and increasing patient dependency has been linked to decline in both physical and mental health status of patients and caregivers of other chronic disease conditions [24-33].

Despite the fact that nearly half of our caregivers reported having a personal history of chronic medical condition, our study is the first to highlight that caregivers of CLD patients are less likely to experience limited quality-of-life from a physical health standpoint. In this cohort, PCS was similar between the caregiver group and the established US norm (51.9±9.1 vs. 50.0±10.0, P=0.16). This is in contrast to other studies among caregivers of patients with advanced disease such as cancer and dementia [34-36]. The difference between caregivers of CLD patients and other chronic illnesses could be due to the fact that CLD patients are more likely to have an indolent course of illness compared to patients with advanced cancer who are more likely to have a more progressive disease course. Therefore, caring for liver patients may be less physically demanding than caring for patients with more rapid deterioration in physical health such as cancer and dementia.

Increased caregiver burden has also been linked to increased mortality among the caregivers [37]. Over half of the caregivers in this study reported experiencing an increased level of burden (mean ZBI of 22.4±12.6). Though difficult to compare across studies, the caregivers in our cohort demonstrated a similar or perhaps even greater level of burden reported among caregivers of patients with acute brain injury (ZBI 21.7±10.1), Alzheimer's disease (ZBI 15.0±10.0), and advanced cancer (12.0±8.5) [38]. However, less than a fourth of our caregivers required quitting their current job because of caregiving. Interestingly, our cohort showed that factors that were independent of the caregiver burden was the caregiver's age, patient's MELD score, total time caring for the patient, caregiver's personal relationship to the patient, and proximity to the patient.

Previous studies have also used ZBI to look for factors predictive of caregiver burden; two of the studies coincided with the results from this study showing that– history of hepatic encephalopathy in the patient, lower household income, and having one or more dependents at home other than the patient are important predictive factors [4,5]. While previous studies have demonstrated that alcoholic cirrhosis led to increased caregiver burden compared to other causes of cirrhosis, we found that, in fact, active alcohol use in the patient was strongly associated with an increased burden. Interestingly, MELD score, previously found to have a direct relationship with caregiver burden, was not a significant predictor in this study, although our study used a threshold of 18, which may not have been high enough to detect a difference [5,22]. Our study did demonstrate that frequent hospitalizations for any cause were the strongest predictor of caregiver burden. Increased rates of hospitalization due to severely decompensated liver disease and comorbidities can increase the challenge of caregiving. It may suggest that there may be a MELD threshold past which caregiver burden increases, but further studies will need to elucidate this relationship. This also underscores the need to optimize management in patients with advanced liver disease to prevent complications for both the patient and caregiver's well-being. Previous studies have demonstrated that in other chronic diseases, social support groups for caregivers may also reduce caregiver burden and burnout [39,40]. Furthermore, a specialized multidisciplinary care management to manage complications related to CLD such as depression, ascites, malnutrition, and variceal bleeding in the outpatient setting may reduce caregiver burden and reduction in hospitalization. Morando *et al* [41] demonstrated that an outpatient, multidisciplinary approach for outpatient management of cirrhotics can reduce 12-month mortality and potentially caregiver burden.

There are several limitations in this study. Firstly, the present study has a cross-sectional design which only allows for the assessment of quality of life and burden at a single point in time. To fully study caregiver burden as a process, a longitudinal study is required as patterns of quality of life and burden likely fluctuate with the patient's disease activity. Secondly, given that this is a survey-based study, a recall bias is possible, thereby selecting a subset of caregivers with higher level burden and lower quality of life. Thirdly, the definitions utilized in our study, such as mental health, may not be specific enough, leaving room for personal interpretation.

In conclusion, this study demonstrated that primary caregivers of patients with advanced liver disease have significantly lower scores measuring mental well-being, compared with the general population. Depression among primary caregivers is also a significant problem with high prevalence and is most likely underdiagnosed. Health care providers need to be diligent in assessing caregivers regularly for signs and symptoms of depression, anxiety, and mental stress. Predictors of increased caregiver burden seem to include multiple factors that affect a patient's ability to comply with treatment and function mentally, and complications that require hospitalization are a significant, previously undiscovered factor that increased caregiver burden. Larger studies may help clarify predictors more accurately.

Unanswered questions include whether increased caregiver burden leads to decreased quality in the care provided to the patient by the caregiver, and whether this leads to an increase in patient non-compliance, hospitalization, complications of liver disease, and poorer outcomes. Conversely, the question of whether reducing caregiver burden can lead to improved care and subsequent positive outcomes for the patient is important. Finally, an effective protocol for screening caregivers for depression and an effective treatment protocol need to be established. Should all caregivers be screened at baseline, and what interval should follow-up visits be conducted? Will effective treatment of caregiver depression lead to a rebound in the quality of care provided, reduce caregiver burden and have a positive impact on caregiver and patient outcomes? While physicians are coached to "treat the whole patient", the future of longitudinal care for chronic diseases, including advanced liver disease, may require treating the person seated next to the patient as well.

Summary Box

What is already known:

- Chronic liver disease increases the socioeconomic and emotional burden on the patient's caregiver
- Patient's adherence to therapy and transplant eligibility is dependent on the caregiver's ability to handle these challenges

What the new findings are:

- We have demonstrated that caregivers in our cohort experienced a significantly lower mental health score with nearly one standard deviation below the reported National norm while the physical component score was similar to the National norm
- Factors predictive of increased care provider burden on the multivariate analysis were: more than 1 dependent in the household; more than 2 hospitalizations as a complication of liver disease in the last 12 months; history of hepatic encephalopathy; active alcohol use at home; and household income ≤$30,000
- The future of longitudinal care for chronic diseases, including advanced liver disease, may require treating the person seated next to the patient as well

References

1. US Burden of Disease Collaborators. The state of US health, 1990-2010: burden of diseases, injuries, and risk factors. *JAMA* 2013;**310**:591-608.
2. Tsochatzis EA, Bosch J, Burroughs AK. Liver cirrhosis. *Lancet* 2014;**383**:1749-1761.
3. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;**380**:2095-2128.
4. Blachier M, Leleu H, Peck-Radosavljevic M, Valla DC, Roudot-Thoraval F. The burden of liver disease in Europe: a review of available epidemiological data. *J Hepatol* 2013;**58**:593-608.
5. Bajaj JS, Wade JB, Gibson DP, et al. The multi-dimensional burden of cirrhosis and hepatic encephalopathy on patients and caregivers. *Am J Gastroenterol* 2011;**106**:1646-1653.
6. Machnicki G, Allegri RF, Ranalli CG, et al. Validity and reliability of the SF-36 administered to caregivers of patients with Alzheimer's disease: evidence from a south american sample. *Dement Geriatr Cogn Disord* 2009;**28**:206-212.
7. Silveira E, Taft C, Sundh V, Waern M, Palsson S, Steen B. Performance of the SF-36 health survey in screening for depressive and anxiety disorders in an elderly female Swedish population. *Qual Life Res* 2005;**14**:1263-1274.
8. Elliott TE, Renier CM, Palcher JA. Chronic pain, depression, and quality of life: correlations and predictive value of the SF-36. *Pain Med* 2003;**4**:331-339.
9. Ware JE, Snow KK, Kosinski M, et al. SF-36 Health Survey Manual and Interpretation Guide. Boston, MA: New England Medical Center, The Health Institute; 1993.

10. Ware JE, Kosinski M, Keller SF. SF-36 Physical and Mental Health Summary Scales: a User's Manual. Boston, MA: The Health Institute; 1994.
11. Gort AM, Mingot M, Gomez X, et al. Use of the Zarit scale for assessing caregiver burden and collapse in caregiving at home in dementias. *Int J Geriatr Psychiatry* 2007;**22**:957-962.
12. Ballesteros J, Santos B, González-Fraile E, Muñoz-Hermoso P, Domínguez-Panchón AI, Martín-Carrasco M. Unidimensional 12-item Zarit Caregiver Burden Interview for the assessment of dementia caregivers' burden obtained by item response theory. *Value Health* 2012;**15**:1141-1147.
13. Seng BK, Luo N, Ng WY, et al. Validity and reliability of the Zarit Burden Interview in assessing caregiving burden. *Ann Acad Med Singapore* 2010;**39**:758-763.
14. Keller SD, Majkut TC, Kosinski M, Ware JE Jr. Monitoring health outcomes among patients with arthritis using the SF-36 Health Survey: overview. *Med Care* 1999;**37**:MS1-MS9.
15. Kosinski M, Keller SD, Hatoum HT, Kong SX, Ware JE Jr. The SF-36 Health Survey as a generic outcome measure in clinical trials of patients with osteoarthritis and rheumatoid arthritis: tests of data quality, scaling assumptions and score reliability. *Med Care* 1999;**37** 5 Suppl: MS10-MS22.
16. Kosinski M, Keller SD, Ware JE Jr, Hatoum HT, Kong SX. The SF-36 Health Survey as a generic outcome measure in clinical trials of patients with osteoarthritis and rheumatoid arthritis: relative validity of scales in relation to clinical measures of arthritis severity. *Med Care* 1999;**37** 5 Suppl: MS23-MS39.
17. Zarit SH, Reever KE, Bach-Peterson J. Relatives of the impaired elderly: correlates of feelings of burden. *Gerontologist* 1980;**20**:649-655.
18. Brown LJ, Potter JF, Foster BG. Caregiver burden should be evaluated during geriatric assessment. *J Am Geriatr Soc* 1990;**38**:455-460.
19. Herbert R, Bravo G, Preville M. Reliability, validity, and reference values of the zarit burden interview for assessing informal caregivers of community-dwelling older persons with dementia. *Can J Aging* 2000;**19**:494-507.
20. Murphy SL, Xu J, Kochanek KD. Deaths: final data for 2010. *Natl Vital Stat Rep* 2013;**61**:1-117.
21. Centers for Disease Control and Prevention. Hepatitis C information for health professionals. Available from: http://www.cdc.gov/hepatitis/hcv/hcvfaq.htm. [Last updated on 2014 Feb 10; Last accessed on 2014 Jun 30].
22. Bolden L, Wicks MN. Predictors of mental health, subjective burden, and rewards in family caregivers of patients with chronic liver disease. *Arch Psychiatr Nurs* 2010;**24**:89-103.
23. Kaneda Y, Fujii A. The relation between anxiety and depressive symptoms in normal subjects and patients with anxiety and/or mood disorders. *J Med Invest* 2000;**47**:14-18.
24. Pearlin LI, Mullan JT, Semple SJ, Skaff MM. Caregiving and the stress process: an overview of concepts and their measures. *Gerontologist* 1990;**30**:583-594.
25. Miyazaki ET, Dos Santos R Jr, Miyazaki MC, et al. Patients on the waiting list for liver transplantation: caregiver burden and stress. *Liver Transpl* 2010;**16**:1164-1168.
26. Bolkhir A, Loiselle MM, Evon DM, Hayashi PH. Depression in primary caregivers of patients listed for liver or kidney transplantation. *Prog Transplant* 2007;**17**:193-198.
27. Goetzinger AM, Blumenthal JA, O'Hayer CV, et al. Stress and coping in caregivers of patients awaiting solid organ transplantation. *Clin Transplant* 2012;**26**:97-104.
28. Yikilkan H, Aypak C, Görpelioglu S. Depression, anxiety and quality of life in caregivers of long-term home care patients. *Arch Psychiatr Nurs* 2014;**28**:193-196.
29. Grunfeld E, Coyle D, Whelan T, et al. Family caregiver burden: results of a longitudinal study of breast cancer patients and their principal caregivers. *CMAJ* 2004;**170**:1795-1801.
30. Andrews SC. Caregiver burden and symptom distress in people with cancer receiving hospice care. *Oncol Nurs Forum* 2001;**28**:1469-1474.
31. Kozachik SL, Given CW, Given BA, et al. Improving depressive symptoms among caregivers of patients with cancer: results of a randomized clinical trial. *Oncol Nurs Forum* 2001;**28:**1149-1157.
32. Haley WE, LaMonde LA, Han B, Burton AM, Schonwetter R. Predictors of depression and life satisfaction among spousal caregivers in hospice: application of a stress process model. *J Palliat Med* 2003;**6**:215-224.
33. Grov EK, Dahl AA, Moum T, Fosså SD. Anxiety, depression, and quality of life in caregivers of patients with cancer in late palliative phase. *Ann Oncol* 2005;**16**:1185-1191.
34. Butow PN, Price MA, Bell ML, et al. Caring for women with ovarian cancer in the last year of life: a longitudinal study of caregiver quality of life, distress and unmet needs. *Gynecol Oncol* 2014;**132:**690-697.
35. Li TC, Lee YD, Lin CC, Amidon RL. Quality of life of primary caregivers of elderly with cerebrovascular disease or diabetes hospitalized for acute care: assessment of well-being and functioning using the SF-36 health questionnaire. *Qual Life Res* 2004;**13**:1081-1088.
36. Tan SB, Williams AF, Morris ME, Tan EK. Health-related quality of life of caregivers of people with Parkinson's disease in Singapore. *Proc Singapore Healthc* 2010;**19**:297-302.
37. Schulz R, Beach SR. Caregiving as a risk factor for mortality: the Caregiver Health Effects Study. *JAMA* 1999;**282**:2215-2219.
38. Higginson IJ, Gao W, Jackson D, Murray J, Harding R. Short-form Zarit Caregiver Burden Interviews were valid in advanced conditions. *J Clin Epidemiol* 2010;**63**:535-42.
39. Han JW, Jeong H, Park JY, et al. Effects of social supports on burden in caregivers of people with dementia. *Int Psychogeriatr* 2014:1-10.
40. Lopez-Hartmann M, Wens J, Verhoeven V, Remmen R. The effect of caregiver support interventions for informal caregivers of community-dwelling frail elderly: a systematic review. *Int J Integr Care* 2012;**12**:e133.
41. Morando F, Maresio G, Piano S, et al. How to improve care in outpatients with cirrhosis and ascites: a new model of care coordination by consultant hepatologists. *J Hepatol* 2013;**59**:257-264.