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Fatigue and its Associated factors in liver transplant recipients in Beijing: a cross-sectional study

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Fatigue and its influencing factors in liver transplant recipients: a cross-sectional study

Abstract:

Objectives: Fatigue is a highly prevalent symptom experienced by patients who underwent the liver transplantation. However, the influencing factors of fatigue are poorly understood by health care professionals. The purpose of this study was to examine the intensity, interference, duration, and prevalence of fatigue in patients after liver transplantation and to explore the influencing factors of post-transplantation fatigue.

Design: A cross-sectional design was used in this study.

Methods: A convenience sample of liver transplant recipients was recruited at an outpatient transplant clinic of a general hospital in Beijing, China. Self-report survey data were provided by liver transplant recipients using the Fatigue Symptom Inventory (FSI), the Hospital Anxiety and Depression Scale (HADS), the Perceived Social Support Scale (PSSS), and the Athens Insomnia Scale (AIS). Demographic, clinical, psycho-social parameters were evaluated as fatigue influencing factors.

Results: Participants (n=285) included 69 women and 216 men. Fatigue was found in 87.02% of liver transplant recipients. Mean scores of fatigue intensity items were 4.47±2.85, 1.93±1.97, 3.15±2.13, 2.73±2.42 (Most fatigue, Least fatigue, Average fatigue, Fatigue now). Mean score of fatigue interference were 2.27±2.09. Number of days fatigued in the previous week was 2.26±2.02 and the amount of time fatigued each day was 2.75±2.44. Spearman Correlation Analysis showed that fatigue intensity was associated with anxiety, depression, and insomnia ($P<0.001$ for all), while fatigue interference was associated with gender, anxiety, depression, and insomnia ($P<0.05$ for all). In the multiple linear regression analysis, anxiety and insomnia were associated with fatigue intensity ($P<0.001$), and insomnia, depression and anxiety were associated with fatigue interference ($P<0.001$).

Conclusions: Fatigue is common in liver transplant recipients, and it is strongly associated with insomnia, anxiety, and depression.

Strengths and limitations of this study

- This study examined the intensity, interference, duration, and prevalence of fatigue in patients after liver transplantation in China.
- This is the first study to explore the influencing factors of post-transplantation fatigue in liver transplantation recipients in China.
- Single-center cross-sectional survey may lead to problems about representativeness of the liver transplantation recipients in China.

Introduction

Fatigue is generally described and measured as a multidimensional phenomenon, including experienced fatigue and physiological fatigue: experienced fatigue is usually defined as an overwhelming sense of tiredness, lack of energy and feeling of exhaustion, while physiological fatigue has been defined as an exercise-induced reduction in maximal voluntary muscle force [1]. Fatigue is a common complaint among patients with chronic disease, such as cancer survivors, multiple sclerosis, neurologic illnesses, post-stroke patients and so on [2-5]. It reported that many end-stage liver diseases patients experienced severe fatigue and the fatigue reduce their level of physical activity and quality of life [6-7]. The pathogenesis of fatigue in cirrhosis is complex, with numerous associated peripheral and central nervous system (CNS) features [8]. Cholestasis causes degenerative CNS change affecting areas of the brain regulating autonomic dysfunction and sleep, and these changes lead directly to some manifestations of fatigue and the associated cognitive impairment. In addition to this, autonomic dysfunction contributes to the impact of this metabolic change by limiting the capacity of the muscle to respond through increased proton/lactate efflux from cells and outflow from tissues [8]. Many studies found that fatigue among end-stage liver diseases patients was associated with their depression, autonomic dysfunction, sleep disturbance [9-10].

Liver transplantation (LT) has emerged as the best liver replacement therapy of choice and an excellent, life-saving treatment option for patients with end-stage liver disease. However, the role of LT for the relief of fatigue in patients with end-stage liver disease is unclear. The literature comparing fatigue severity in patients with cirrhosis before and after liver transplantation determined that LT recipients had a significant improvement on fatigue scores after LT [11-12]. However, some scholars doubted the conclusion and pointed out that there may be some bias in these studies: the group of patients was small, and had a considerable drop-out rate (mainly due to death or to the withdrew from the study after LT), for whom died or withdrew after LT might have more fatigue than those stayed in the study [12-14]. In addition, compared with general population and community controls, LT recipients fatigue scores were significantly worse [11-12]. High rates of fatigue prevalence (66%) have been reported after successful LT [15], and fatigue is a still major problem in patients after LT.

The theory of unpleasant symptoms (TOUS) asserts that there are three categories of factors influencing patient's symptom experience: physiological factors, psychological factors, and situational factors [16]. Physiological factors include anatomical/structural, physiological, genetic, illness-related, and treatment-related variables; psychological factors include both affective and cognitive variables; situational factors include the individual's social environment and physical environment [17]. Fatigue, as a common symptom in patients after liver transplant, might be influenced by these diverse factors. This cross-sectional study examines the fatigue of liver transplant recipients in China and explores whether demographic variables, insomnia, social support and mood disorders were associated with fatigue, thereby providing a basis for health professionals to facilitate the development and implementation of specific interventions to relieve fatigue of liver transplant recipients.

Participants and methods

Participants

This investigation employed a cross-sectional design to assess the fatigue status in liver transplant

recipients and its influencing factors. Two hundred and eighty-five adult liver transplant recipients were recruited, using a convenience sampling strategy, when they visited transplant follow-up clinics in one general hospital in Beijing, China from April to November 2015. Recipients who met the following criteria were eligible to participate: (1) at least 18 years old, (2) 3 months or more post liver transplantation, (3) functional liver graft, (4) ability to speak and read Chinese, and (5) willingness to participate in this study. Patients who had multiple organ transplants or who had more than one liver transplants were excluded from this study.

Measurement

A structured questionnaire was used to assess fatigue, physical status, psychological variables and situational factors of liver transplant recipients. The questionnaire was composed of five sections examining: demographic information, fatigue, anxiety and depression, insomnia, and social support. Questionnaire was completed in the transplant follow-up clinics. Demographic information included current age, gender, BMI, employment status, education, marital status, whether the transplant was self-paid or national insurance paid and family financial income. Transplant specific information, such as the date of transplant and whether the liver was from a living or cadaveric donor, was also collected.

Fatigue

The Fatigue Symptom Inventory (FSI) was adopted to assess the transplant recipient's fatigue during the past week. The scale was developed by Hann in 1998 [18]. Yang Shoumei and Chen Zhendong [19] translated FSI into Chinese and used it in 121 Chinese cancer patients receiving chemotherapy. This 13-item self-report measurement was designed to measure the fatigue intensity (four items) and duration of fatigue (two items) as well as a subscale (seven items) which measures the extent to which fatigue interfered with quality of life. The intensity items require a respondent's rating of the most, least, and average fatigue in the past week, and current fatigue on an 11 point scale (0 = not at all fatigued and 10 = extreme fatigue). The average of four intensity items scores is intensity scale score, with higher score indicating more intense fatigue. Two duration item assess fatigue duration, including the number days in the past week (0-7 days) and the amount of time each day (0 = none of the day and 10 = the entire day) fatigue was present. The interference items assess the extent to which fatigue interfered with a respondent's general activity level, ability to bathe and dress, work activity, ability to concentrate, relations with others, enjoyment of life and mood during the previous week using an 11 point rating scale (0 = no interference and 10 = extreme interference). The average of seven interference items scores is interference scale score, with higher score indicating more influence of fatigue to quality of life. The interference scale was found to have good internal consistency (Cronbach′s α=0.93). In this study, the Cronbach α coefficient of FSI interference scale was 0.941.

Anxiety and depression

Anxiety and depression of liver transplant recipients were measured by the Hospital Anxiety and Depression Scale (HADS), formulated by Zigmond and Snaith (1983) [20] to identify possible or probable anxiety and depression among patients in non-psychiatric clinical settings. The HADS anxiety and depression sub-scales each consist of seven related items. Each item is rated on a four-point scale from 0 to 3, yielding a maximum score of 21 for each sub-scale. Score of 8 or

more with either sub-scale is considered to indicate a significant disorder. A score of 7or less is considered normal. The optimal balance between sensitivity and specificity for both sub-scales was suggested by the original authors, a score of 8 or more for anxiety has a specificity of 0.78 and a sensitivity of 0.90, and for depression a specificity of 0.79 and a sensitivity of 0.83. The HADS has been translated into Chinese version by Leung in 1993 [21]. The Cronbach α coefficient of HADS anxiety and depression sub-scales in this study were 0.821 and 0.783 respectively.

Insomnia

The Athens Insomnia Scale (AIS) was used to measure insomnia in liver transplant recipients. AIS was developed by Soldatos CR (2000) [22] and has been widely used in different population around the world. It includes eight items: the first five pertain to sleep induction, awakenings during the night, final awakening, total sleep duration, and sleep quality; while the last three refer to well-being, functioning capacity, and sleepiness during the day. Each item scores from 0 (no problem at all) to 3 (a very serious problem). This gives a total score ranging from 0 to 24. A total score of 6 or more indicates insomnia. The Cronbach′s α of AIS was 0.89, and the test-retest reliability correlation coefficient was found 0.89 at a 1-week interval, with individual item values ranging from 0.70 to 0.86. The Cronbach's α coefficient of AIS in this study was 0.874.

Social support

The Perceived Social Support Scale (PSSS) was adopted to assess the liver transplant recipient's social support. PSSS was developed by Zimet (1988) and demonstrated good internal reliability (Cronbach's α = 0.85~0.91) and good stability (test-retest value = 0.72~0.85) [23]. Huang Li [24] translated PSSS into Chinese version and examined its components with factor analysis. PSSS includes 12 items and the items were divided into three sub-scales relating to the source of the support (family, friends, and significant other). Each of these sub-scales consists of four items, and each item ranges from very strongly disagree (score=1) to very strongly agree (score=7). Average score of four items in each sub-scale was the sub-scale score (range=1~7), and average score of all 12 items was the total score (range=1~7), with higher scores indicating higher perceived social support from their social networks. In this study, the Cronbach α coefficient of PSSS sub-scales (family, friends, and significant other) and scale as a whole were 0.815, 0.918, 0.813, and 0.917 respectively.

Ethical considerations

Ethical approval had been obtained from the hospital and university ethics committee, which requires processes to ensure the confidentiality of all data. The purpose, risks and benefits of this study were explained to the patients before they were asked to participate. The patients were assured that participation was voluntary, and that choosing not to participate would not influence their clinical care.

Data collection procedures

Investigators were trained before the survey to make sure that they were familiar with the requirements and methods of data collection. The principal investigator prepared survey questionnaires. Survey packets and a cover letter with a description of the project, response

confidentiality, consent procedure, and investigator contact information were packaged in unsealed envelopes. Packets were distributed to liver transplant recipients when they attended at the liver transplant follow-up clinic. Written informed consent was obtained from all participants. The investigators were present at the clinic to answer patients' questions. Patients returned the survey packet after they completed at the clinic. Patients did not put their name or any other identifying information on the surveys.

Statistical analysis

Original data were input into Excel software and checked by two research assistants. Data was statistically analyzed using SPSS 21.0 software. Data were summarized as the mean and standard deviation or as frequency and percentages for all demographic, clinical and outcome measures. Spearman Correlation Analysis was conducted to find the correlation relationship between fatigue intensity and demographic, anxiety, depression, insomnia, and social support. To find the fatigue influencing factors among demographic, clinical, psycho-social parameters, multiple linear regression analysis was conducted. Statistical significance was set at $P < 0.05$, two tails.

Results

Participant characteristics

A total of 300 questionnaires were distributed and all were returned (the return rate is 100%); of which 15 were incomplete and therefore invalid. Data from the remaining 285 questionnaires was included in the analysis. The characteristics of the 285 recipients are shown in Table 1.

Table 1. Liver transplant recipients characteristics

Variables		n（%）	Mean/SD	Range
Age（years）			53.31/10.18	26~75
Gender	Male	216（75.8）		
	Female	69（24.2）		
BMI	<18.5	16 (5.6)		
	18.5~23.9	137 (48.1)		
	24.0~27.9	97 (34.0)		
	≥28.0	35 (12.3)		
Employed	Yes	107（37.5）		
	Not	178（62.5）		
Education	middle school or below	60（21.1）		
	high school or technical secondary school	71（24.9）		
	college degree or above	154（54.0）		
Marital status	Married	273（95.8）		
	Single/widowed/divorced	12（4.2）		
Medical payment	by self	58（20.4）		
	public service or medical insurance	227（79.6）		
Family income （CNY / month）	≤3000	64（22.5）		
	3000~6000	113（39.6）		

	>6000	108（37.9）		
Economic burden	no burden	28 (9.8)		
	mild	64 (22.5)		
	moderate	99 (34.7)		
	severe	94 (33.0)		
Donor	Deceased	281（98.6）		
	Living	4（1.4）		
Duration after LT（month）			59.80/46.93	3.02~314.17
Anxiety	≥8	36 (12.6)	3.83/3.27	0~13
	<8	249 (87.4)		
Depression	≥8	39 (13.7)	3.41/3.23	0~13
	<8	246 (86.3)		
Insomnia	≥6	138 (48.4)	5.75/4.09	0~19
	<6	147 (51.6)		
Social support	Family		6.08/1.03	1~7
	Friends		5.33/1.34	1~7
	Significant other		5.45/1.17	1~7

Intensity, interference, duration, and prevalence of fatigue

A total of 248 (87.0%) liver transplant recipients reported fatigue on the average in the last week. The intensity, interference, and duration of fatigue are shown in Table 2. Mean scores of fatigue intensity items were 4.47±2.85, 1.93±1.97, 3.15±2.13, 2.73±2.42 (Most fatigue, Least fatigue, Average fatigue, Fatigue now). Number of days fatigued in the previous week was 2.26±2.02 and the amount of time fatigued each day was 2.75±2.44 (0 = none of the day and 10 = the entire day) . Mean score of fatigue interference were 2.27±2.09. Ranking fatigue interference scores in descending order, the seven dimensions were fatigue interfered with general activity level, enjoyment of life, mood, relations with others, ability to concentrate, work activity, and ability to bathe and dress.

Table 2. Liver transplant recipients' scores on the FSI

	Range	Mean	SD
Intensity ratings (sub-scale score)		3.07	2.05
Most fatigue	0~10	4.47	2.85
Least fatigue	0~9	1.93	1.97
Average fatigue	0~9	3.15	2.13
Fatigue now	0~10	2.73	2.42
Duration ratings			
Number of days fatigued	0~7	2.26	2.02
Amount of time fatigued	0~10	2.75	2.44
Interference scale (sub-scale score)		2.27	2.09
General activity level	0~10	2.78	2.62

Ability to bathe and dress	0~10	1.39	2.13
Work activity	0~10	2.12	2.42
Ability to concentrate	0~10	2.21	2.22
Relations with others	0~9	2.26	2.34
Enjoyment of life	0~10	2.61	2.70
Mood	0~10	2.48	2.59

Association between fatigue and other variables

Neither the scores of fatigue intensity or fatigue interference obeyed the normal distribution, Spearman Correlation Analysis was adopted to find the association between fatigue and other variables. The correlations between fatigue intensity/interference and other variables are shown in Table 3. Fatigue intensity was significantly and positively correlated with anxiety (r_s = 0.454, P<0.001), depression(r_s = 0.429, P<0.001), and insomnia (r_s = 0.561, P<0.001), while fatigue interference was significantly and positively correlated with gender (r_s = 0.119, P = 0.044), anxiety (r_s = 0.534, P<0.001), depression (r_s = 0.489, P<0.001), and insomnia (r_s = 0.541, P<0.001). There were no significant correlation between fatigue with age, BMI, employment status, duration after LT, and social support from others (P>0.05).

Table 3. Correlations between fatigue scores and scores on other variables

	Fatigue intensity		Fatigue interference	
	r_s	P	r_s	P
Age	-0.002	0.978	-0.013	0.821
Gender	0.101	0.088	0.119	0.044*
BMI	-0.032	0.594	-0.106	0.073
Employment	0.043	0.469	0.056	0.342
Duration after LT	0.073	0.219	-0.037	0.529
Anxiety	0.454	0.000*	0.534	0.000*
Depression	0.429	0.000*	0.489	0.000*
Insomnia	0.561	0.000*	0.541	0.000*
Family support	-0.062	0.301	-0.055	0.355
Friends support	-0.038	0.520	-0.094	0.114
Significant other support	-0.088	0.138	-0.089	0.132

* P<0.05

Influencing factors of fatigue

A multiple linear regression analysis was conducted to determine the influencing factors of fatigue as assessed by FSI intensity score and interference score. Variables which were significant correlated with fatigue intensity and fatigue interference in the Spearman correlation analysis (Table 3, anxiety, depression, and insomnia were associated with fatigue intensity; gender, anxiety, depression, and insomnia were associated with fatigue interference) entered into the regression analysis as independent variables. Through the backward and forward methods, it found that anxiety and insomnia were included in the linear regression model of fatigue intensity, and insomnia, depression and anxiety were included in the linear regression model of fatigue

interference (Table 4 and Table 5). The variables explained 31.3% (fatigue intensity: R = 0.560, R^2 = 0.313) and 36.2% (fatigue interference: R = 0.602, R^2 = 0.362) of the total variance, and each made a significant contribution to the prediction of fatigue (P<0.001 for each variable). F value were 64.352 (fatigue intensity, P<0.05) and 53.103 (fatigue interference, P<0.05), indicating that the linear regression equations were statistically significant.

Table 4. Regression analysis of fatigue intensity in liver transplant recipients

	B	SE	β'	*t*	*P*
Constant	1.350	0.182	—	7.409	0.000*
Insomnia	0.209	0.029	0.418	7.278	0.000*
Anxiety	0.135	0.036	0.216	3.754	0.000*

* P<0.05

Table 5. Regression analysis of fatigue interference in liver transplant recipients

	B	SE	β'	*t*	*P*
Constant	0.397	0.181	—	2.196	0.029*
Insomnia	0.167	0.029	0.326	5.836	0.000*
Depression	0.134	0.047	0.207	2.885	0.004*
Anxiety	0.118	0.048	0.184	2.463	0.014*

* P<0.05

Discussion

Fatigue is common among liver transplant recipients

Fatigue is often experienced after liver transplantation. In our study, 87.0% liver transplant recipients reported fatigue on the average in the last week, indicating a high prevalence of fatigue in LT recipients. The result is in agreement with those from previously published studies (66%~76%) [15,25]. The average score of fatigue intensity during the previous week was 3.07 (10 = extreme fatigue) and there were 2.26 days last week recipients experienced fatigue, indicating a frequent and mild fatigue the LT recipients experienced. Even three years after LT, fatigue was still the third most frequent and distressing symptom [26]. Although compared to the pretransplant patients, LT recipients had more slight fatigue, but they still had a greater load of fatigue compared to normal individuals [11-12]. It's reported that apart from hepatic mechanism, extra-hepatic mechanism may lead to fatigue in patients with liver diseases, including autonomic nervous system dysfunction, progesterone metabolites, psychological elements, mitochondrial dysfunction, cytokines and adipokines as well as structural cerebral abnormalities [14]. Extra-hepatic mechanism and the persistent organic brain injury caused by liver diseases before LT may explain why patients' fatigue persisted after liver transplantation.

Interference of fatigue on recipients' quality of life and daily activities

Fatigue has a major impact on quality of life and daily activities [27]. Berbke's research found that patients with more severe complaints of fatigue had larger deficits in cardiorespiratory fitness than

patients with less severe complaints of fatigue, implying that cardiorespiratory fitness and body composition were impaired in liver transplant recipients and that fitness was related with severity of fatigue and quality of life [28]. It reported that liver transplant recipients experience physical fatigue and had reduced activity rather than mental fatigue and reduced motivation [15,29]. In our study, we found that fatigue among LT recipients had moderate interference on their quality of life, and general activity level was the most affected aspect. This was similar to previous studies results. Fatigue is a complex symptom and makes people feel malaise, exhaustion, lethargy, and loss of motivation and social interest [13], which had an impact on recipients' enjoyment of life, mood, relations with others, ability to concentrate and work activity.

Factors influencing fatigue intensity and interference in LT recipients

Several studies have found that sleep quality of LT recipients was associated with fatigue [30], patients with high fatigue severity were significantly more likely to have been taking sleep medication than do patients with low fatigue severity [25]. In our study, insomnia was moderate positively correlated with fatigue intensity and fatigue interference, and the result of linear regression showed that insomnia was the influencing factors of fatigue among LT recipients, indicating that poor sleep quality are at increased risk of fatigue intensity and interference post-transplantation. Having poor sleep quality at night, recipients often felt tired and found it hard to concentrate in the daytime; their exercise decreased, finally affecting their physiological function and complaining more weakness and fatigue.

Another influencing factor of fatigue among LT recipients was mood disturbance. It reported that high fatigue severity was associated with higher total mood disturbance [25,30]. We found that both anxiety and depression were positively correlated with fatigue intensity and fatigue interference, and the result of linear regression showed that anxiety was the influencing factor of fatigue intensity while anxiety and depression was the influencing factors of fatigue interference among LT recipients. Anxiety and depression in LT recipients may be due to recipients' experience of a major life event or because they have adopted the "sick role" and have difficulty readjusting to a healthy role [31]. These negative emotions make recipients lose interest and enthusiasm for life, and may lead to recipients' mental and emotional fatigue. In addition to this, mood disturbance and insomnia often interact and aggravate each other, which may lead to patients' physical fatigue. Insomnia, anxiety, and depression, these factors often co-exist with fatigue and should be targeted by health care providers' interventions designed to reduce fatigue in LT recipients.

In our study, gender was correlated to fatigue interference, indicating that female recipients obtained more fatigue interference on their quality of life than male recipients. This result met with van den Berg‐Emons and his colleagues' research [15], which found women were more severely fatigued than men. No relation were found between fatigue with age, employment status, and duration after LT in our study, however, there were different results in previous studies. It found that the older recipients were more severely fatigued than younger recipients [15]; working and having undergone LT 4 to 5 years previously were associated with less physical fatigue than not working and having undergone LT 1 to 3 years previously [29]. The difference in results may be due to differences in sampling groups. In our study, recipients who had a liver transplantation less than 3 months were excluded, considering their condition was not stable. These excluded recipients might have different fatigue sense comparing with those included in the study.

Berg-Emons included recipients who were discharged 3 weeks or more [15], and Aadahl excluded recipients who received their liver transplant less than 1 year because they are not long-time survivors [29].

Conclusion

The current study showed that fatigue is common among liver transplant recipient in China and fatigue negatively influences the recipient's quality of life and daily activities. Anxiety, depression, and insomnia were the influencing factors of fatigue intensity and fatigue interference. Health care providers should pay more attention on recipients' fatigue and other co-exist symptoms. Some intervention, such as rehabilitation program, antidepressant drugs treatment, and sleep medicine, may be helpful.

Limitations and Recommendations

This study had certain limitations such as being a single-center cross-sectional survey. Additional longitudinal studies of fatigue in liver transplant recipients are needed. More influencing factors, such as renal function, cardiorespiratoty fitness, anemia, and primary disease diagnosis, should be considered and explored in the future research.

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Competing interests

There is no conflict of interest. The results presented in this paper have not been published previously.

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Contributors

X-H. Lin participated in the data collection and data analysis and drafted the manuscript. H-X. Liu designed the study and revised the manuscript. Y-J. Zang, L. Wang and J. Zhang participated in the data collection. J. Zhang provided suggestions for the manuscript. S. Teng, and Y-B. Shang executed the scheme and collected data. All authors read and approved the final manuscript.

Data Sharing

No additional data available.

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Manuscript Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Yes, Page 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Yes, Page 2
Introduction			
Background /rationale	2	Explain the scientific background and rationale for the investigation being reported	Yes, Page 3
Objectives	3	State specific objectives, including any prespecified hypotheses	Yes, Page 3
Methods			
Study design	4	Present key elements of study design early in the paper	Yes, Page 3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Yes, Page 4-5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	Yes, Page 4
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Yes, Page 4-5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Yes, Page 4-5
Bias	9	Describe any efforts to address potential sources of bias	No
Study size	10	Explain how the study size was arrived at	No
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Yes, Page 6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Yes, Page 6
		(*b*) Describe any methods used to examine subgroups and interactions	Yes, Page 6
		(*c*) Explain how missing data were addressed	No
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	No
		(*e*) Describe any sensitivity analyses	

Continued on next page

Results			
Participants	13 *	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Yes, Page 6
		(b) Give reasons for non-participation at each stage	No
		(c) Consider use of a flow diagram	No
Descriptive data	14 *	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Yes, Page 6-7
		(b) Indicate number of participants with missing data for each variable of interest	No
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15 *	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	Yes, Page 7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Yes, Page 7-9
		(*b*) Report category boundaries when continuous variables were categorized	Not categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	No
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Yes, Page 9
Discussion			
Key results	18	Summarise key results with reference to study objectives	Yes, Page 9-10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Yes, Page 11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Yes, Page 11
Generalisability	21	Discuss the generalisability (external validity) of the study results	Yes, Page 11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Yes, Page 11

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Fatigue and its Associated factors in liver transplant recipients in Beijing: a cross-sectional study

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Fatigue and its Associated factors in liver transplant recipients in Beijing: a cross-sectional study

Abstract:

Objectives: Fatigue is a highly prevalent symptom experienced by patients who underwent the liver transplantation. However, the influencing factors of fatigue are poorly understood by health care professionals. This study was aim to examine the intensity, interference, duration, and prevalence of fatigue in liver transplantation recipients and to explore the influencing factors of post-transplantation fatigue.

Design: A cross-sectional design was used in this study.

Methods: A convenience sample of liver transplant recipients was recruited at an outpatient transplant clinic of a general hospital in Beijing, China. Self-report survey data were provided by liver transplant recipients using the Fatigue Symptom Inventory (FSI), the Hospital Anxiety and Depression Scale (HADS), the Perceived Social Support Scale (PSSS), and the Athens Insomnia Scale (AIS). Demographic, clinical, psycho-social parameters were evaluated as fatigue influencing factors.

Results: Participants (n=285) included 69 women and 216 men. Fatigue was found in 87.0% of liver transplant recipients. Mean scores of fatigue intensity items were 4.47±2.85, 1.93±1.97, 3.15±2.13, 2.73±2.42 (Most fatigue, Least fatigue, Average fatigue in the week prior to assesment, and Fatigue at the point of assesment). Mean score of fatigue interference were 2.27±2.09. Number of days fatigued in the week prior to assesment was 2.26±2.02 and the amount of time fatigued each day was 2.75±2.44. Spearman Correlation Analysis showed that fatigue intensity was positively associated with anxiety, depression, and insomnia ($P<0.001$ for all), while fatigue interference was positively associated with gender, anxiety, depression, and insomnia ($P<0.05$ for all). In the multiple linear regression analysis, anxiety and insomnia were positively associated with fatigue intensity ($P<0.001$), and insomnia, depression and anxiety were positively associated with fatigue interference ($P<0.001$).

Conclusions: Fatigue is common in liver transplant recipients, and it is strongly associated with insomnia, anxiety, and depression.

Strengths and limitations of this study

- This study examined the intensity, interference, duration, and prevalence of fatigue in patients after liver transplantation in China.
- This is the first study to explore the influencing factors of post-transplantation fatigue in liver transplantation recipients in China.
- Single-center cross-sectional survey may lead to problems about representativeness of the liver transplantation recipients in China.

Introduction

Fatigue is generally described and measured as a multidimensional phenomenon, including experienced fatigue and physiological fatigue: experienced fatigue is usually defined as an overwhelming sense of tiredness, lack of energy and feeling of exhaustion, while physiological fatigue has been defined as an exercise-induced reduction in maximal voluntary muscle force [1]. Fatigue is a common complaint among patients with chronic disease, such as cancer survivors, multiple sclerosis, neurologic illnesses, post-stroke patients and so on [2-5]. It reported that many end-stage liver diseases patients experienced severe fatigue and the fatigue reduce their level of physical activity and quality of life [6-7]. The pathogenesis of fatigue in cirrhosis is complex, with numerous associated peripheral and central nervous system (CNS) features [8]. Cholestasis causes degenerative CNS change affecting areas of the brain regulating autonomic dysfunction and sleep, and these changes lead directly to some manifestations of fatigue and the associated cognitive impairment. In addition to this, autonomic dysfunction contributes to the impact of this metabolic change by limiting the capacity of the muscle to respond through increased proton/lactate efflux from cells and outflow from tissues [8]. Sarcopenia, a frequent complication in cirrhosis, while the loss of skeletal muscle mass may lead to patients' fatigue, was reported to have adverse effect on patients' recovery and post liver transplantation survival [9]. Another complication in cirrhosis, hepatic encephalopathy, may be another reason for patients' fatigue, for it is related to anemia and fat-free mass depletion [10]. Many studies found that fatigue among end-stage liver diseases patients was associated with their depression, autonomic dysfunction, sleep disturbance [11-12].

Liver transplantation (LT) has emerged as the best liver replacement therapy of choice and an excellent, life-saving treatment option for patients with end-stage liver disease. However, the role of LT for the relief of fatigue in patients with end-stage liver disease is unclear. The literature comparing fatigue severity in patients with cirrhosis before and after liver transplantation determined that LT recipients had a significant improvement on fatigue scores after LT [13-14]. However, some scholars doubted the conclusion and pointed out that there may be some bias in these studies: the group of patients was small, and had a considerable drop-out rate (mainly due to death or to the withdrew from the study after LT), for whom died or withdrew after LT might have more fatigue than those stayed in the study [14-16]. In addition, compared with general population and community controls, LT recipients fatigue scores were significantly worse [13-14]. High rates of fatigue prevalence (66%) have been reported after successful LT [17], and fatigue is a still major problem in patients after LT.

The theory of unpleasant symptoms (TOUS) asserts that there are three categories of factors influencing patient's symptom experience: physiological factors, psychological factors, and situational factors [18]. Physiological factors include anatomical/structural, physiological, genetic, illness-related, and treatment-related variables; psychological factors include both affective and cognitive variables; situational factors include the individual's social environment and physical environment [19]. Fatigue, as a common symptom in patients after liver transplant, might be influenced by these diverse factors. Severe fatigue may reduce LT recipients' daily activites and hinder their recovery and return to work. For those recipients who had back to work, chronic fatigue may reduce their work efficiency and increase security risks. In addition, long-term fatigue may increase negative emotions. This cross-sectional study examines the fatigue of liver transplant recipients in China and explores whether demographic variables, insomnia, social support and mood disorders were associated with fatigue, thereby providing a basis for health

professionals to facilitate the development and implementation of specific interventions to relieve fatigue of liver transplant recipients.

Participants and methods

Participants

This investigation employed a cross-sectional design to assess the fatigue status in liver transplant recipients and its influencing factors. Two hundred and eighty-five adult liver transplant recipients were recruited, using a convenience sampling strategy, when they visited transplant follow-up clinics in one general hospital in Beijing, China from April to November 2015. Recipients who met the following criteria were eligible to participate: (1) at least 18 years old, (2) 3 months or more post liver transplantation, (3) functional liver graft, (4) ability to speak and read Chinese, and (5) willingness to participate in this study. Patients who had multiple organ transplants or who had more than one liver transplants were excluded from this study.

Measurement

A structured questionnaire was used to assess fatigue, physical status, psychological variables and situational factors of liver transplant recipients. The questionnaire was composed of five sections examining: demographic information, fatigue, anxiety and depression, insomnia, and social support. Questionnaire was completed in the transplant follow-up clinics. Demographic information included current age, gender, BMI, employment status, education, marital status, whether the transplant was self-paid or national insurance paid and family financial income. Transplant specific information, such as the date of transplant and whether the liver was from a living or deceased donor, was also collected. According to the theory of unpleasant symptoms, these above-mentioned variables which may influence LT recipients' fatigue symptom can be divided into three categories. Physiological factors included recipients' age, gender, BMI, duration after LT (calculated by the date of transplant and the date of assesment) and insomnia. Psychological factors included anxiety and depression, while situational factors included recipients' employment status and social support.

Fatigue

The Fatigue Symptom Inventory (FSI) was adopted to assess the transplant recipient's fatigue during the past week. The scale was developed by Hann in 1998 [20]. Yang Shoumei and Chen Zhendong [21] translated FSI into Chinese and used it in 121 Chinese cancer patients receiving chemotherapy. This 13-item self-report measurement was designed to measure the fatigue intensity (four items) and duration of fatigue (two items) as well as a subscale (seven items) which measures the extent to which fatigue interfered with quality of life. The intensity items require a respondent's rating of the most, least, and average fatigue in the week prior to assesment, and fatigue at the point of assesment on an 11 point scale (0 = not at all fatigued and 10 = extreme fatigue). The average of four intensity items scores is intensity scale score, with higher score indicating more intense fatigue. Two duration item assess fatigue duration, including the number days in the week prior to assesment (0-7 days) and the amount of time each day (0 = none of the day and 10 = the entire day) fatigue was present. The interference items assess the extent to which fatigue interfered with a respondent's general activity level, ability to bathe and dress, work activity, ability to concentrate, relations with others, enjoyment of life and mood during the

previous week prior to assesment using an 11 point rating scale (0 = no interference and 10 = extreme interference). The average of seven interference items scores is interference scale score, with higher score indicating more influence of fatigue to quality of life. The interference scale was found to have good internal consistency (Cronbach′s α=0.93). In this study, the Cronbach α coefficient of FSI interference scale was 0.941.

Anxiety and depression

Anxiety and depression of liver transplant recipients were measured by the Hospital Anxiety and Depression Scale (HADS), formulated by Zigmond and Snaith (1983) [22] to identify possible or probable anxiety and depression among patients in non-psychiatric clinical settings. The HADS anxiety and depression sub-scales each consist of seven related items. Each item is rated on a four-point scale from 0 to 3, yielding a maximum score of 21 for each sub-scale. Score of 8 or more with either sub-scale is considered to indicate a significant disorder. A score of 7or less is considered normal. The optimal balance between sensitivity and specificity for both sub-scales was suggested by the original authors, a score of 8 or more for anxiety has a specificity of 0.78 and a sensitivity of 0.90, and for depression a specificity of 0.79 and a sensitivity of 0.83. The HADS has been translated into Chinese version by Leung in 1993 [23]. The Cronbach α coefficient of HADS anxiety and depression sub-scales in this study were 0.821 and 0.783 respectively.

Insomnia

The Athens Insomnia Scale (AIS) was used to measure insomnia in liver transplant recipients. AIS was developed by Soldatos CR (2000) [24] and has been widely used in different population around the world. It includes eight items: the first five pertain to sleep induction, awakenings during the night, final awakening, total sleep duration, and sleep quality; while the last three refer to well-being, functioning capacity, and sleepiness during the day. Each item scores from 0 (no problem at all) to 3 (a very serious problem). This gives a total score ranging from 0 to 24. A total score of 6 or more indicates insomnia. The Cronbach′s α of AIS was 0.89, and the test-retest reliability correlation coefficient was found 0.89 at a 1-week interval, with individual item values ranging from 0.70 to 0.86. The Cronbach's α coefficient of AIS in this study was 0.874.

Social support

The Perceived Social Support Scale (PSSS) was adopted to assess the liver transplant recipient's social support. PSSS was developed by Zimet (1988) and demonstrated good internal reliability (Cronbach's α = 0.85~0.91) and good stability (test-retest value = 0.72~0.85) [25]. Huang Li [26] translated PSSS into Chinese version and examined its components with factor analysis. PSSS includes 12 items and the items were divided into three sub-scales relating to the source of the support (family, friends, and significant other). Each of these sub-scales consists of four items, and each item ranges from very strongly disagree (score=1) to very strongly agree (score=7). Average score of four items in each sub-scale was the sub-scale score (range=1~7), and average score of all 12 items was the total score (range=1~7), with higher scores indicating higher perceived social support from their social networks. In this study, the Cronbach α coefficient of PSSS sub-scales (family, friends, and significant other) and scale as a whole were 0.815, 0.918, 0.813, and 0.917 respectively.

Ethical considerations

Ethical approval had been obtained from the hospital and university ethics committee, which requires processes to ensure the confidentiality of all data. The purpose, risks and benefits of this study were explained to the patients before they were asked to participate. The patients were assured that participation was voluntary, and that choosing not to participate would not influence their clinical care.

Data collection procedures

Investigators were trained before the survey to make sure that they were familiar with the requirements and methods of data collection. The principal investigator prepared survey questionnaires. Survey packets and a cover letter with a description of the project, response confidentiality, consent procedure, and investigator contact information were packaged in unsealed envelopes. Packets were distributed to liver transplant recipients when they attended at the liver transplant follow-up clinic. Written informed consent was obtained from all participants. The investigators were present at the clinic to answer patients' questions. Patients returned the survey packet after they completed at the clinic. Patients did not put their name or any other identifying information on the surveys.

Statistical analysis

Original data were input into Excel software and checked by two research assistants. Data was statistically analyzed using SPSS 21.0 software. Data were summarized as the mean and standard deviation or as frequency and percentages for all demographic, clinical and outcome measures. Spearman Correlation Analysis was conducted to find the correlation relationship between fatigue intensity and demographic, anxiety, depression, insomnia, and social support. To find the fatigue influencing factors among demographic, clinical, psycho-social parameters, multiple linear regression analysis was conducted. Statistical significance was set at $P < 0.05$, two tails.

Results

Participant characteristics

A total of 300 questionnaires were distributed and all were returned (the return rate is 100%); of which 15 were incomplete and therefore invalid. Data from the remaining 285 questionnaires was included in the analysis. The characteristics of the 285 recipients are shown in Table 1.

Table 1. Liver transplant recipients characteristics

Variables		n（%）	Mean/SD	Range
Age（years）			53.31/10.18	26~75
Gender	Male	216（75.8）		
	Female	69（24.2）		
BMI	<18.5	16 (5.6)		
	18.5~23.9	137 (48.1)		
	24.0~27.9	97 (34.0)		
	≥28.0	35 (12.3)		
Employed	Yes	107（37.5）		

	Not	178（62.5）		
Education	middle school or below	60（21.1）		
	high school or technical secondary school	71（24.9）		
	college degree or above	154（54.0）		
Marital status	Married	273（95.8）		
	Single/widowed/divorced	12（4.2）		
Medical payment	by self	58（20.4）		
	public service or medical insurance	227（79.6）		
Family income （CNY / month）	≤3000	64（22.5）		
	3000~6000	113（39.6）		
	>6000	108（37.9）		
Economic burden	no burden	28 (9.8)		
	mild	64 (22.5)		
	moderate	99 (34.7)		
	severe	94 (33.0)		
Donor	Deceased	281（98.6）		
	Living	4（1.4）		
Duration after LT（month）			59.80/46.93	3.02~314.17
Anxiety	≥8	36 (12.6)	3.83/3.27	0~13
	<8	249 (87.4)		
Depression	≥8	39 (13.7)	3.41/3.23	0~13
	<8	246 (86.3)		
Insomnia	≥6	138 (48.4)	5.75/4.09	0~19
	<6	147 (51.6)		
Social support	Family		6.08/1.03	1~7
	Friends		5.33/1.34	1~7
	Significant other		5.45/1.17	1~7

Intensity, interference, duration, and prevalence of fatigue

A total of 248 (87.0%) LT recipients reported fatigue on the average in the week prior to assesment (their average fatigue score > 0). The intensity, interference, and duration of fatigue are shown in Table 2. Mean scores of fatigue intensity items were 4.47±2.85, 1.93±1.97, 3.15±2.13, 2.73±2.42 (Most fatigue, Least fatigue, Average fatigue in the week prior to assesment, Fatigue at the point of assesment). Number of days fatigued in the previous week prior to assesment was 2.26±2.02 and the amount of time fatigued each day was 2.75±2.44 (0 = none of the day and 10 = the entire day) . Mean score of fatigue interference were 2.27±2.09. Ranking fatigue interference scores in descending order, the seven dimensions were fatigue interfered with general activity level, enjoyment of life, mood, relations with others, ability to concentrate, work activity, and ability to bathe and dress.

Table 2. Liver transplant recipients' scores on the FSI

	Range	Mean	SD
Intensity ratings (sub-scale score)		3.07	2.05
Most fatigue	0~10	4.47	2.85
Least fatigue	0~9	1.93	1.97
Average fatigue	0~9	3.15	2.13
Fatigue at the point of assesment	0~10	2.73	2.42
Duration ratings			
Number of days fatigued	0~7	2.26	2.02
Amount of time fatigued	0~10	2.75	2.44
Interference scale (sub-scale score)		2.27	2.09
General activity level	0~10	2.78	2.62
Ability to bathe and dress	0~10	1.39	2.13
Work activity	0~10	2.12	2.42
Ability to concentrate	0~10	2.21	2.22
Relations with others	0~9	2.26	2.34
Enjoyment of life	0~10	2.61	2.70
Mood	0~10	2.48	2.59

Considering that LT recipients who had longer time after liver transplantation may have better functional recovery and less fatigue than those who had liver transplantation in the short time, we divided 285 LT recipients into early post transplant recipient group (time after LT $\leqslant$ 5 years) and late post transplant recipient group (time after LT > 5 years). We compared the FSI 13-item scores between the two groups with Nonparametric Test (none of the scores obeyed the normal distribution), and it found that there were no significant differences between the two groups scores (Table 3).

Table 3. FSI scores in early and late post transplant recipient groups

	Mean Rank (early post group, *n* =157)	Mean Rank (late post group, *n* =128)	*Z*	*P*
Intensity ratings				
Most fatigue	140.51	146.05	-0.569	0.569
Least fatigue	139.66	147.09	-0.775	0.438
Average fatigue	139.25	147.61	-0.860	0.390
Fatigue at the point of assesment	137.83	149.34	-1.187	0.235
Duration ratings				
Number of days fatigued	143.32	142.61	-0.073	0.942
Amount of time fatigued	143.92	141.88	-0.226	0.822
Interference scale				
General activity level	149.65	134.84	-1.551	0.121
Ability to bathe and dress	143.78	142.05	-0.180	0.857

Work activity	141.29	145.10	-0.397	0.692
Ability to concentrate	143.21	142.74	-0.049	0.961
Relations with others	143.93	141.86	-0.215	0.830
Enjoyment of life	144.66	140.97	-0.383	0.702
Mood	146.38	138.86	-0.776	0.437

Association between fatigue and other variables

Neither the scores of fatigue intensity or fatigue interference obeyed the normal distribution, Spearman Correlation Analysis was adopted to find the association between fatigue and other variables. The correlations between fatigue intensity/interference and other variables are shown in Table 4. Fatigue intensity was significantly and positively correlated with anxiety (r_s = 0.454, P<0.001), depression(r_s = 0.429, P<0.001), and insomnia (r_s = 0.561, P<0.001), while fatigue interference was significantly and positively correlated with gender (r_s = 0.119, P = 0.044), anxiety (r_s = 0.534, P<0.001), depression (r_s = 0.489, P<0.001), and insomnia (r_s = 0.541, P<0.001). There were no significant correlation between fatigue with age, BMI, employment status, duration after LT, and social support from others (P>0.05).

Table 4. Correlations between fatigue scores and scores on other variables

	Fatigue intensity		Fatigue interference	
	r_s	P	r_s	P
Age	-0.002	0.978	-0.013	0.821
Gender(1=male, 2=female)	0.101	0.088	0.119	0.044*
BMI	-0.032	0.594	-0.106	0.073
Employment	0.043	0.469	0.056	0.342
Duration after LT	0.073	0.219	-0.037	0.529
Anxiety	0.454	0.000*	0.534	0.000*
Depression	0.429	0.000*	0.489	0.000*
Insomnia	0.561	0.000*	0.541	0.000*
Family support	-0.062	0.301	-0.055	0.355
Friends support	-0.038	0.520	-0.094	0.114
Significant other support	-0.088	0.138	-0.089	0.132

* P<0.05

Influencing factors of fatigue

A multiple linear regression analysis was conducted to determine the influencing factors of fatigue as assessed by FSI intensity score and interference score. Variables which were significant correlated with fatigue intensity and fatigue interference in the Spearman correlation analysis (Table 4, anxiety, depression, and insomnia were associated with fatigue intensity; gender, anxiety, depression, and insomnia were associated with fatigue interference) entered into the regression analysis as independent variables. Through the backward and forward methods, it found that anxiety and insomnia were included in the linear regression model of fatigue intensity, and insomnia, depression and anxiety were included in the linear regression model of fatigue

interference (Table 5 and Table 6). The variables explained 31.3% (fatigue intensity: R = 0.560, R^2 = 0.313) and 36.2% (fatigue interference: R = 0.602, R^2 = 0.362) of the total variance, and each made a significant contribution to the prediction of fatigue (P<0.001 for each variable). F value were 64.352 (fatigue intensity, P<0.05) and 53.103 (fatigue interference, P<0.05), indicating that the linear regression equations were statistically significant.

Table 5. Regression analysis of fatigue intensity in liver transplant recipients

	B	SE	β'	*t*	*P*
Constant	1.350	0.182	—	7.409	0.000*
Insomnia	0.209	0.029	0.418	7.278	0.000*
Anxiety	0.135	0.036	0.216	3.754	0.000*

* P<0.05

Table 6. Regression analysis of fatigue interference in liver transplant recipients

	B	SE	β'	*t*	*P*
Constant	0.397	0.181	—	2.196	0.029*
Insomnia	0.167	0.029	0.326	5.836	0.000*
Depression	0.134	0.047	0.207	2.885	0.004*
Anxiety	0.118	0.048	0.184	2.463	0.014*

* P<0.05

Discussion

Fatigue is common among liver transplant recipients

Fatigue is often experienced after liver transplantation. In our study, 87.0% liver transplant recipients reported fatigue on the average in the week prior to assesment, indicating a high prevalence of fatigue in LT recipients. The result is in agreement with those from previously published studies (66%~76%) [17,27]. The average score of fatigue intensity during the previous week before assesment was 3.07 (10 = extreme fatigue) and there were 2.26 days in the week prior to assesment recipients experienced fatigue, indicating a frequent and mild fatigue the LT recipients experienced. Even three years after LT, fatigue was still the third most frequent and distressing symptom [28]. In our study, there were no significant differences between early and late post transplant recipient groups in FSI 13-item scores, indicating that recipients' fatigue symptom persisted for a long time after LT. Although compared to the pretransplant patients, LT recipients had more slight fatigue, but they still had a greater load of fatigue compared to normal individuals [13-14]. It's reported that apart from hepatic mechanism, extra-hepatic mechanism may lead to fatigue in patients with liver diseases, including autonomic nervous system dysfunction, progesterone metabolites, psychological elements, mitochondrial dysfunction, cytokines and adipokines as well as structural cerebral abnormalities [16]. Extra-hepatic mechanism and the persistent organic brain injury caused by liver diseases before LT may explain why patients' fatigue persisted after liver transplantation.

Interference of fatigue on recipients' quality of life and daily activities

Fatigue has a major impact on quality of life and daily activities [29]. Berbke's research found that patients with more severe complaints of fatigue had larger deficits in cardiorespiratory fitness than patients with less severe complaints of fatigue, implying that cardiorespiratory fitness and body composition were impaired in liver transplant recipients and that fitness was related with severity of fatigue and quality of life [30]. It reported that liver transplant recipients experience physical fatigue and had reduced activity rather than mental fatigue and reduced motivation [17,31]. In our study, we found that fatigue among LT recipients had moderate interference on their quality of life, and general activity level was the most affected aspect. This was similar to previous studies results. Fatigue is a complex symptom and makes people feel malaise, exhaustion, lethargy, and loss of motivation and social interest [15], which had an impact on recipients' enjoyment of life, mood, relations with others, ability to concentrate and work activity.

Factors influencing fatigue intensity and interference in LT recipients

Several studies have found that sleep quality of LT recipients was associated with fatigue [32], patients with high fatigue severity were significantly more likely to have been taking sleep medication than do patients with low fatigue severity [27]. In our study, insomnia was moderate positively correlated with fatigue intensity and fatigue interference, and the result of linear regression showed that insomnia was the influencing factors of fatigue among LT recipients, indicating that poor sleep quality are at increased risk of fatigue intensity and interference post-transplantation. Having poor sleep quality at night, recipients often felt tired and found it hard to concentrate in the daytime; their exercise decreased, finally affecting their physiological function and complaining more weakness and fatigue.

Another influencing factor of fatigue among LT recipients was mood disturbance. It reported that high fatigue severity was associated with higher total mood disturbance [27,32]. We found that both anxiety and depression were positively correlated with fatigue intensity and fatigue interference, and the result of linear regression showed that anxiety was the influencing factor of fatigue intensity while anxiety and depression was the influencing factors of fatigue interference among LT recipients. Anxiety and depression in LT recipients may be due to recipients' experience of a major life event or because they have adopted the "sick role" and have difficulty readjusting to a healthy role [33]. These negative emotions make recipients lose interest and enthusiasm for life, and may lead to recipients' mental and emotional fatigue. In addition to this, mood disturbance and insomnia often interact and aggravate each other, which may lead to patients' physical fatigue. Insomnia, anxiety, and depression, these factors often co-exist with fatigue and should be targeted by health care providers' interventions designed to reduce fatigue in LT recipients.

In our study, gender was correlated to fatigue interference, indicating that female recipients obtained more fatigue interference on their quality of life than male recipients. This result met with van den Berg‐Emons and his colleagues' research [17], which found women were more severely fatigued than men. No relation were found between fatigue with age, employment status, and duration after LT in our study, however, there were different results in previous studies. It found that the older recipients were more severely fatigued than younger recipients [17]; working and having undergone LT 4 to 5 years previously were associated with less physical fatigue than not working and having undergone LT 1 to 3 years previously [31]. The difference in results may

be due to differences in sampling groups. In our study, recipients who had a liver transplantation less than 3 months were excluded, considering their condition was not stable. These excluded recipients might have different fatigue sense comparing with those included in the study. Berg-Emons included recipients who were discharged 3 weeks or more [17], and Aadahl excluded recipients who received their liver transplant less than 1 year because they are not long-time survivors [31].

Conclusion

The current study showed that fatigue is common among liver transplant recipient in China and fatigue negatively influences the recipient's quality of life and daily activities. Anxiety, depression, and insomnia were the influencing factors of fatigue intensity and fatigue interference. The recipients who had severe insomnia and mood disorders, felt severer fatigue and greater influence caused by fatigue. It suggests that health care providers should not only pay more attention on recipients' fatigue but also on other co-exist symptoms. Some intervention, such as rehabilitation program, antidepressant drugs treatment, and sleep medicine, may be necessary and helpful.

Limitations and Recommendations

This study had certain limitations such as being a single-center cross-sectional survey. Additional longitudinal studies of fatigue in liver transplant recipients are needed. We only measured LT recipients' BMI, and other indices of their nutritional and sarcopenic status were not assessed and measured. Also, we did not report LT recipients' indications, MELD scores and post-transplant status which might be associated with their fatigue. More influencing factors, such as recipients' nutritional status, sarcopenic status, renal function, cardiorespiratoty fitness, anemia, primary disease diagnosis, and pre-transplant and post-transplant status should be considered and explored in the future research.

Acknowledgments

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Competing interests

There is no conflict of interest. The results presented in this paper have not been published previously.

Data sharing statement

No additional data available.

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Contributors

X-H. Lin participated in the data collection and data analysis and drafted the manuscript. H-X. Liu designed the study and revised the manuscript. Y-J. Zang, L. Wang and J. Zhang participated in the data collection. J. Zhang provided suggestions for the manuscript. S. Teng, and Y-B. Shang

executed the scheme and collected data. All authors read and approved the final manuscript.

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Manuscript Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Yes, Page 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Yes, Page 2
Introduction			
Background /rationale	2	Explain the scientific background and rationale for the investigation being reported	Yes, Page 3
Objectives	3	State specific objectives, including any prespecified hypotheses	Yes, Page 3
Methods			
Study design	4	Present key elements of study design early in the paper	Yes, Page 3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Yes, Page 4-5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	Yes, Page 4
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Yes, Page 4-5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Yes, Page 4-5
Bias	9	Describe any efforts to address potential sources of bias	No
Study size	10	Explain how the study size was arrived at	No
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Yes, Page 6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Yes, Page 6
		(*b*) Describe any methods used to examine subgroups and interactions	Yes, Page 6
		(*c*) Explain how missing data were addressed	No
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	No
		(*e*) Describe any sensitivity analyses	

Continued on next page

Results			
Participants	13 *	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Yes, Page 6
		(b) Give reasons for non-participation at each stage	No
		(c) Consider use of a flow diagram	No
Descriptive data	14 *	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Yes, Page 6-7
		(b) Indicate number of participants with missing data for each variable of interest	No
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15 *	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	Yes, Page 7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Yes, Page 7-9
		(*b*) Report category boundaries when continuous variables were categorized	Not categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	No
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Yes, Page 9
Discussion			
Key results	18	Summarise key results with reference to study objectives	Yes, Page 9-10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Yes, Page 11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Yes, Page 11
Generalisability	21	Discuss the generalisability (external validity) of the study results	Yes, Page 11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Yes, Page 11

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Fatigue and its associated factors in liver transplant recipients in Beijing: a cross-sectional study

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Fatigue and its Associated factors in liver transplant recipients in Beijing: a cross-sectional study

Abstract:

Objectives: Fatigue is a highly prevalent symptom experienced by patients who underwent the liver transplantation. However, the influencing factors of fatigue are poorly understood by health care professionals. This study was aim to examine the intensity, interference, duration, and prevalence of fatigue in liver transplantation recipients and to explore the influencing factors of post-transplantation fatigue.

Design: A cross-sectional design was used in this study.

Methods: A convenience sample of liver transplant recipients was recruited at an outpatient transplant clinic of a general hospital in Beijing, China. Self-report survey data were provided by liver transplant recipients using the Fatigue Symptom Inventory (FSI), the Hospital Anxiety and Depression Scale (HADS), the Perceived Social Support Scale (PSSS), and the Athens Insomnia Scale (AIS). Demographic, clinical, psycho-social parameters were evaluated as fatigue influencing factors.

Results: Participants (n=285) included 69 women and 216 men. Fatigue was found in 87.0% of liver transplant recipients. Mean scores of fatigue intensity items were 4.47±2.85, 1.93±1.97, 3.15±2.13, 2.73±2.42 (Most fatigue, Least fatigue, Average fatigue in the week prior to assesment, and Fatigue at the point of assesment). Mean score of fatigue interference were 2.27±2.09. Number of days fatigued in the week prior to assesment was 2.26±2.02 and the amount of time fatigued each day was 2.75±2.44. Spearman Correlation Analysis showed that fatigue intensity was positively associated with anxiety, depression, and insomnia ($P<0.001$ for all), while fatigue interference was positively associated with gender, anxiety, depression, and insomnia ($P<0.05$ for all). In the multiple linear regression analysis, anxiety and insomnia were positively associated with fatigue intensity ($P<0.001$), and insomnia, depression and anxiety were positively associated with fatigue interference ($P<0.001$).

Conclusions: Fatigue is common in liver transplant recipients, and it is strongly associated with insomnia, anxiety, and depression.

Strengths and limitations of this study

- This study examined the intensity, interference, duration, and prevalence of fatigue in patients after liver transplantation in China.
- This is the first study to explore the influencing factors of post-transplantation fatigue in liver transplantation recipients in China.
- Single-center cross-sectional survey may lead to problems about representativeness of the liver transplantation recipients in China.

Introduction

Fatigue is generally described and measured as a multidimensional phenomenon, including experienced fatigue and physiological fatigue: experienced fatigue is usually defined as an overwhelming sense of tiredness, lack of energy and feeling of exhaustion, while physiological fatigue has been defined as an exercise-induced reduction in maximal voluntary muscle force [1]. Fatigue is a common complaint among patients with chronic disease, such as cancer survivors, multiple sclerosis, neurologic illnesses, post-stroke patients and so on [2-5]. It reported that many end-stage liver diseases patients experienced severe fatigue and the fatigue reduce their level of physical activity and quality of life [6-7]. The pathogenesis of fatigue in cirrhosis is complex, with numerous associated peripheral and central nervous system (CNS) features [8]. Cholestasis causes degenerative CNS change affecting areas of the brain regulating autonomic dysfunction and sleep, and these changes lead directly to some manifestations of fatigue and the associated cognitive impairment. In addition to this, autonomic dysfunction contributes to the impact of this metabolic change by limiting the capacity of the muscle to respond through increased proton/lactate efflux from cells and outflow from tissues [8]. Sarcopenia, a frequent complication in cirrhosis, while the loss of skeletal muscle mass may lead to patients' fatigue, was reported to have adverse effect on patients' recovery and post liver transplantation survival [9]. Another complication in cirrhosis, hepatic encephalopathy, may be another reason for patients' fatigue, for it is related to anemia and fat-free mass depletion [10]. Many studies found that fatigue among end-stage liver diseases patients was associated with their depression, autonomic dysfunction, sleep disturbance [11-12].

Liver transplantation (LT) has emerged as the best liver replacement therapy of choice and an excellent, life-saving treatment option for patients with end-stage liver disease. However, the role of LT for the relief of fatigue in patients with end-stage liver disease is unclear. The literature comparing fatigue severity in patients with cirrhosis before and after liver transplantation determined that LT recipients had a significant improvement on fatigue scores after LT [13-14]. However, some scholars doubted the conclusion and pointed out that there may be some bias in these studies: the group of patients was small, and had a considerable drop-out rate (mainly due to death or to the withdrew from the study after LT), for whom died or withdrew after LT might have more fatigue than those stayed in the study [14-16]. In addition, compared with general population and community controls, LT recipients fatigue scores were significantly worse [13-14]. High rates of fatigue prevalence (66%) have been reported after successful LT [17], and fatigue is a still major problem in patients after LT.

The theory of unpleasant symptoms (TOUS) asserts that there are three categories of factors influencing patient's symptom experience: physiological factors, psychological factors, and situational factors [18]. Physiological factors include anatomical/structural, physiological, genetic, illness-related, and treatment-related variables; psychological factors include both affective and cognitive variables; situational factors include the individual's social environment and physical environment [19]. Fatigue, as a common symptom in patients after liver transplant, might be influenced by these diverse factors. Severe fatigue may reduce LT recipients' daily activites and hinder their recovery and return to work. For those recipients who had back to work, chronic fatigue may reduce their work efficiency and increase security risks. In addition, long-term fatigue may increase negative emotions. This cross-sectional study examines the fatigue of liver transplant recipients in China and explores whether demographic variables, insomnia, social support and mood disorders were associated with fatigue, thereby providing a basis for health

professionals to facilitate the development and implementation of specific interventions to relieve fatigue of liver transplant recipients.

Participants and methods

Participants

This investigation employed a cross-sectional design to assess the fatigue status in liver transplant recipients and its influencing factors. Two hundred and eighty-five adult liver transplant recipients were recruited, using a convenience sampling strategy, when they visited transplant follow-up clinics in one general hospital in Beijing, China from April to November 2015. Recipients who met the following criteria were eligible to participate: (1) at least 18 years old, (2) 3 months or more post liver transplantation, (3) functional liver graft, (4) ability to speak and read Chinese, and (5) willingness to participate in this study. Patients who had multiple organ transplants or who had more than one liver transplants were excluded from this study.

Measurement

A structured questionnaire was used to assess fatigue, physical status, psychological variables and situational factors of liver transplant recipients. The questionnaire was composed of five sections examining: demographic information, fatigue, anxiety and depression, insomnia, and social support. Questionnaire was completed in the transplant follow-up clinics. Demographic information included current age, gender, BMI, employment status, education, marital status, whether the transplant was self-paid or national insurance paid and family financial income. Transplant specific information, such as the date of transplant and whether the liver was from a living or deceased donor, was also collected. According to the theory of unpleasant symptoms, these above-mentioned variables which may influence LT recipients' fatigue symptom can be divided into three categories. Physiological factors included recipients' age, gender, BMI, and duration after LT (calculated by the date of transplant and the date of assesment). Psychological factors included anxiety, depression, and insomnia, while situational factors included recipients' employment status and social support.

Fatigue

The Fatigue Symptom Inventory (FSI) was adopted to assess the transplant recipient's fatigue during the past week. The scale was developed by Hann in 1998 [20]. Yang Shoumei and Chen Zhendong [21] translated FSI into Chinese and used it in 121 Chinese cancer patients receiving chemotherapy. This 13-item self-report measurement was designed to measure the fatigue intensity (four items) and duration of fatigue (two items) as well as a subscale (seven items) which measures the extent to which fatigue interfered with quality of life. The intensity items require a respondent's rating of the most, least, and average fatigue in the week prior to assesment, and fatigue at the point of assesment on an 11 point scale (0 = not at all fatigued and 10 = extreme fatigue). The average of four intensity items scores is intensity scale score, with higher score indicating more intense fatigue. Two duration item assess fatigue duration, including the number days in the week prior to assesment (0-7 days) and the amount of time each day (0 = none of the day and 10 = the entire day) fatigue was present. The interference items assess the extent to which fatigue interfered with a respondent's general activity level, ability to bathe and dress, work activity, ability to concentrate, relations with others, enjoyment of life and mood during the

previous week prior to assesment using an 11 point rating scale (0 = no interference and 10 = extreme interference). The average of seven interference items scores is interference scale score, with higher score indicating more influence of fatigue to quality of life. The interference scale was found to have good internal consistency (Cronbach′s α=0.93). In this study, the Cronbach α coefficient of FSI interference scale was 0.941.

Anxiety and depression

Anxiety and depression of liver transplant recipients were measured by the Hospital Anxiety and Depression Scale (HADS), formulated by Zigmond and Snaith (1983) [22] to identify possible or probable anxiety and depression among patients in non-psychiatric clinical settings. The HADS anxiety and depression sub-scales each consist of seven related items. Each item is rated on a four-point scale from 0 to 3, yielding a maximum score of 21 for each sub-scale. Score of 8 or more with either sub-scale is considered to indicate a significant disorder. A score of 7or less is considered normal. The optimal balance between sensitivity and specificity for both sub-scales was suggested by the original authors, a score of 8 or more for anxiety has a specificity of 0.78 and a sensitivity of 0.90, and for depression a specificity of 0.79 and a sensitivity of 0.83. The HADS has been translated into Chinese version by Leung in 1993 [23]. The Cronbach α coefficient of HADS anxiety and depression sub-scales in this study were 0.821 and 0.783 respectively.

Insomnia

The Athens Insomnia Scale (AIS) was used to measure insomnia in liver transplant recipients. AIS was developed by Soldatos CR (2000) [24] and has been widely used in different population around the world. It includes eight items: the first five pertain to sleep induction, awakenings during the night, final awakening, total sleep duration, and sleep quality; while the last three refer to well-being, functioning capacity, and sleepiness during the day. Each item scores from 0 (no problem at all) to 3 (a very serious problem). This gives a total score ranging from 0 to 24. A total score of 6 or more indicates insomnia. The Cronbach′s α of AIS was 0.89, and the test-retest reliability correlation coefficient was found 0.89 at a 1-week interval, with individual item values ranging from 0.70 to 0.86. The Cronbach's α coefficient of AIS in this study was 0.874.

Social support

The Perceived Social Support Scale (PSSS) was adopted to assess the liver transplant recipient's social support. PSSS was developed by Zimet (1988) and demonstrated good internal reliability (Cronbach's α = 0.85~0.91) and good stability (test-retest value = 0.72~0.85) [25]. Huang Li [26] translated PSSS into Chinese version and examined its components with factor analysis. PSSS includes 12 items and the items were divided into three sub-scales relating to the source of the support (family, friends, and significant other). Each of these sub-scales consists of four items, and each item ranges from very strongly disagree (score=1) to very strongly agree (score=7). Average score of four items in each sub-scale was the sub-scale score (range=1~7), and average score of all 12 items was the total score (range=1~7), with higher scores indicating higher perceived social support from their social networks. In this study, the Cronbach α coefficient of PSSS sub-scales (family, friends, and significant other) and scale as a whole were 0.815, 0.918, 0.813, and 0.917 respectively.

Ethical considerations

Ethical approval had been obtained from the hospital and university ethics committee, which requires processes to ensure the confidentiality of all data. The purpose, risks and benefits of this study were explained to the patients before they were asked to participate. The patients were assured that participation was voluntary, and that choosing not to participate would not influence their clinical care. Organ transplant donors involved in our study were not from a vulnerable population and they were informed and voluntary to donate their organ.

Data collection procedures

Investigators were trained before the survey to make sure that they were familiar with the requirements and methods of data collection. The principal investigator prepared survey questionnaires. Survey packets and a cover letter with a description of the project, response confidentiality, consent procedure, and investigator contact information were packaged in unsealed envelopes. Packets were distributed to liver transplant recipients when they attended at the liver transplant follow-up clinic. Written informed consent was obtained from all participants. The investigators were present at the clinic to answer patients' questions. Patients returned the survey packet after they completed at the clinic. Patients did not put their name or any other identifying information on the surveys.

Statistical analysis

Original data were input into Excel software and checked by two research assistants. Data was statistically analyzed using SPSS 21.0 software. Data were summarized as the mean and standard deviation or as frequency and percentages for all demographic, clinical and outcome measures. Spearman Correlation Analysis was conducted to find the correlation relationship between fatigue intensity and demographic, anxiety, depression, insomnia, and social support. To find the fatigue influencing factors among demographic, clinical, psycho-social parameters, multiple linear regression analysis was conducted. Statistical significance was set at $P < 0.05$, two tails.

Results

Participant characteristics

A total of 300 questionnaires were distributed and all were returned (the return rate is 100%); of which 15 were incomplete and therefore invalid. Data from the remaining 285 questionnaires was included in the analysis. The characteristics of the 285 recipients are shown in Table 1.

Table 1. Liver transplant recipients characteristics

Variables		n（%）	Mean/SD	Range
Age（years）			53.31/10.18	26~75
Gender	Male	216（75.8）		
	Female	69（24.2）		
BMI	<18.5	16 (5.6)		
	18.5~23.9	137 (48.1)		
	24.0~27.9	97 (34.0)		
	≥28.0	35 (12.3)		

Employed	Yes	107（37.5）		
	Not	178（62.5）		
Education	middle school or below	60（21.1）		
	high school or technical secondary school	71（24.9）		
	college degree or above	154（54.0）		
Marital status	Married	273（95.8）		
	Single/widowed/divorced	12（4.2）		
Medical payment	by self	58（20.4）		
	public service or medical insurance	227（79.6）		
Family income （CNY / month）	≤3000	64（22.5）		
	3000~6000	113（39.6）		
	>6000	108（37.9）		
Economic burden	no burden	28 (9.8)		
	mild	64 (22.5)		
	moderate	99 (34.7)		
	severe	94 (33.0)		
Donor	Deceased	281（98.6）		
	Living	4（1.4）		
Duration after LT（month）			59.80/46.93	3.02~314.17
Anxiety	≥8	36 (12.6)	3.83/3.27	0~13
	<8	249 (87.4)		
Depression	≥8	39 (13.7)	3.41/3.23	0~13
	<8	246 (86.3)		
Insomnia	≥6	138 (48.4)	5.75/4.09	0~19
	<6	147 (51.6)		
Social support	Family		6.08/1.03	1~7
	Friends		5.33/1.34	1~7
	Significant other		5.45/1.17	1~7

Intensity, interference, duration, and prevalence of fatigue

A total of 248 (87.0%) LT recipients reported fatigue on the average in the week prior to assesment (their average fatigue score > 0). The intensity, interference, and duration of fatigue are shown in Table 2. Mean scores of fatigue intensity items were 4.47±2.85, 1.93±1.97, 3.15±2.13, 2.73±2.42 (Most fatigue, Least fatigue, Average fatigue in the week prior to assesment, Fatigue at the point of assesment). Number of days fatigued in the previous week prior to assesment was 2.26±2.02 and the amount of time fatigued each day was 2.75±2.44 (0 = none of the day and 10 = the entire day) . Mean score of fatigue interference were 2.27±2.09. Ranking fatigue interference scores in descending order, the seven dimensions were fatigue interfered with general activity level, enjoyment of life, mood, relations with others, ability to concentrate, work activity, and ability to bathe and dress.

Table 2. Liver transplant recipients' scores on the FSI

	Range	Mean	SD
Intensity ratings (sub-scale score)		3.07	2.05
Most fatigue	0~10	4.47	2.85
Least fatigue	0~9	1.93	1.97
Average fatigue	0~9	3.15	2.13
Fatigue at the point of assesment	0~10	2.73	2.42
Duration ratings			
Number of days fatigued	0~7	2.26	2.02
Amount of time fatigued	0~10	2.75	2.44
Interference scale (sub-scale score)		2.27	2.09
General activity level	0~10	2.78	2.62
Ability to bathe and dress	0~10	1.39	2.13
Work activity	0~10	2.12	2.42
Ability to concentrate	0~10	2.21	2.22
Relations with others	0~9	2.26	2.34
Enjoyment of life	0~10	2.61	2.70
Mood	0~10	2.48	2.59

Considering that LT recipients who had longer time after liver transplantation may have better functional recovery and less fatigue than those who had liver transplantation in the short time, we divided 285 LT recipients into early post transplant recipient group (time after LT $\leqslant$ 5 years) and late post transplant recipient group (time after LT > 5 years). We compared the FSI 13-item scores between the two groups with Nonparametric Test (none of the scores obeyed the normal distribution), and it found that there were no significant differences between the two groups scores (Table 3).

Table 3. FSI scores in early and late post transplant recipient groups

	Mean Rank (early post group, *n* =157)	Mean Rank (late post group, *n* =128)	*Z*	*P*
Intensity ratings				
Most fatigue	140.51	146.05	-0.569	0.569
Least fatigue	139.66	147.09	-0.775	0.438
Average fatigue	139.25	147.61	-0.860	0.390
Fatigue at the point of assesment	137.83	149.34	-1.187	0.235
Duration ratings				
Number of days fatigued	143.32	142.61	-0.073	0.942
Amount of time fatigued	143.92	141.88	-0.226	0.822
Interference scale				
General activity level	149.65	134.84	-1.551	0.121

Ability to bathe and dress	143.78	142.05	-0.180	0.857
Work activity	141.29	145.10	-0.397	0.692
Ability to concentrate	143.21	142.74	-0.049	0.961
Relations with others	143.93	141.86	-0.215	0.830
Enjoyment of life	144.66	140.97	-0.383	0.702
Mood	146.38	138.86	-0.776	0.437

Association between fatigue and other variables

Neither the scores of fatigue intensity or fatigue interference obeyed the normal distribution, Spearman Correlation Analysis was adopted to find the association between fatigue and other variables. The correlations between fatigue intensity/interference and other variables are shown in Table 4. Fatigue intensity was significantly and positively correlated with anxiety (r_s = 0.454, P<0.001), depression(r_s = 0.429, P<0.001), and insomnia (r_s = 0.561, P<0.001), while fatigue interference was significantly and positively correlated with gender (r_s = 0.119, P = 0.044), anxiety (r_s = 0.534, P<0.001), depression (r_s = 0.489, P<0.001), and insomnia (r_s = 0.541, P<0.001). There were no significant correlation between fatigue with age, BMI, employment status, duration after LT, and social support from others (P>0.05).

Table 4. Correlations between fatigue scores and scores on other variables

	Fatigue intensity		Fatigue interference	
	r_s	P	r_s	P
Age	-0.002	0.978	-0.013	0.821
Gender(1=male, 2=female)	0.101	0.088	0.119	0.044*
BMI	-0.032	0.594	-0.106	0.073
Employment	0.043	0.469	0.056	0.342
Duration after LT	0.073	0.219	-0.037	0.529
Anxiety	0.454	0.000*	0.534	0.000*
Depression	0.429	0.000*	0.489	0.000*
Insomnia	0.561	0.000*	0.541	0.000*
Family support	-0.062	0.301	-0.055	0.355
Friends support	-0.038	0.520	-0.094	0.114
Significant other support	-0.088	0.138	-0.089	0.132

* P<0.05

Influencing factors of fatigue

A multiple linear regression analysis was conducted to determine the influencing factors of fatigue as assessed by FSI intensity score and interference score. Variables which were significant correlated with fatigue intensity and fatigue interference in the Spearman correlation analysis (Table 4, anxiety, depression, and insomnia were associated with fatigue intensity; gender, anxiety, depression, and insomnia were associated with fatigue interference) entered into the regression analysis as independent variables. Through the backward and forward methods, it found that anxiety and insomnia were included in the linear regression model of fatigue intensity, and

insomnia, depression and anxiety were included in the linear regression model of fatigue interference (Table 5 and Table 6). The variables explained 31.3% (fatigue intensity: R = 0.560, R^2 = 0.313) and 36.2% (fatigue interference: R = 0.602, R^2 = 0.362) of the total variance, and each made a significant contribution to the prediction of fatigue (P<0.001 for each variable). F value were 64.352 (fatigue intensity, P<0.05) and 53.103 (fatigue interference, P<0.05), indicating that the linear regression equations were statistically significant.

Table 5. Regression analysis of fatigue intensity in liver transplant recipients

	B	SE	β'	*t*	*P*
Constant	1.350	0.182	—	7.409	0.000*
Insomnia	0.209	0.029	0.418	7.278	0.000*
Anxiety	0.135	0.036	0.216	3.754	0.000*

* P<0.05

Table 6. Regression analysis of fatigue interference in liver transplant recipients

	B	SE	β'	*t*	*P*
Constant	0.397	0.181	—	2.196	0.029*
Insomnia	0.167	0.029	0.326	5.836	0.000*
Depression	0.134	0.047	0.207	2.885	0.004*
Anxiety	0.118	0.048	0.184	2.463	0.014*

* P<0.05

Discussion

Fatigue is common among liver transplant recipients

Fatigue is often experienced after liver transplantation. In our study, 87.0% liver transplant recipients reported fatigue on the average in the week prior to assesment, indicating a high prevalence of fatigue in LT recipients. The result is in agreement with those from previously published studies (66%~76%) [17,27]. The average score of fatigue intensity during the previous week before assesment was 3.07 (10 = extreme fatigue) and there were 2.26 days in the week prior to assesment recipients experienced fatigue, indicating a frequent and mild fatigue the LT recipients experienced. Even three years after LT, fatigue was still the third most frequent and distressing symptom [28]. In our study, there were no significant differences between early and late post transplant recipient groups in FSI 13-item scores, indicating that recipients' fatigue symptom persisted for a long time after LT. Although compared to the pretransplant patients, LT recipients had more slight fatigue, but they still had a greater load of fatigue compared to normal individuals [13-14]. It's reported that apart from hepatic mechanism, extra-hepatic mechanism may lead to fatigue in patients with liver diseases, including autonomic nervous system dysfunction, progesterone metabolites, psychological elements, mitochondrial dysfunction, cytokines and adipokines as well as structural cerebral abnormalities [16]. Extra-hepatic mechanism and the persistent organic brain injury caused by liver diseases before LT may explain why patients' fatigue persisted after liver transplantation.

Interference of fatigue on recipients' quality of life and daily activities

Fatigue has a major impact on quality of life and daily activities [29]. Berbke's research found that patients with more severe complaints of fatigue had larger deficits in cardiorespiratory fitness than patients with less severe complaints of fatigue, implying that cardiorespiratory fitness and body composition were impaired in liver transplant recipients and that fitness was related with severity of fatigue and quality of life [30]. It reported that liver transplant recipients experience physical fatigue and had reduced activity rather than mental fatigue and reduced motivation [17,31]. In our study, we found that fatigue among LT recipients had moderate interference on their quality of life, and general activity level was the most affected aspect. This was similar to previous studies results. Fatigue is a complex symptom and makes people feel malaise, exhaustion, lethargy, and loss of motivation and social interest [15], which had an impact on recipients' enjoyment of life, mood, relations with others, ability to concentrate and work activity.

Factors influencing fatigue intensity and interference in LT recipients

Several studies have found that sleep quality of LT recipients was associated with fatigue [32], patients with high fatigue severity were significantly more likely to have been taking sleep medication than do patients with low fatigue severity [27]. In our study, insomnia was moderate positively correlated with fatigue intensity and fatigue interference, and the result of linear regression showed that insomnia was the influencing factors of fatigue among LT recipients, indicating that poor sleep quality are at increased risk of fatigue intensity and interference post-transplantation. Having poor sleep quality at night, recipients often felt tired and found it hard to concentrate in the daytime; their exercise decreased, finally affecting their physiological function and complaining more weakness and fatigue.

Another influencing factor of fatigue among LT recipients was mood disturbance. It reported that high fatigue severity was associated with higher total mood disturbance [27,32]. We found that both anxiety and depression were positively correlated with fatigue intensity and fatigue interference, and the result of linear regression showed that anxiety was the influencing factor of fatigue intensity while anxiety and depression was the influencing factors of fatigue interference among LT recipients. Anxiety and depression in LT recipients may be due to recipients' experience of a major life event or because they have adopted the "sick role" and have difficulty readjusting to a healthy role [33]. These negative emotions make recipients lose interest and enthusiasm for life, and may lead to recipients' mental and emotional fatigue. In addition to this, mood disturbance and insomnia often interact and aggravate each other, which may lead to patients' physical fatigue. Insomnia, anxiety, and depression, these factors often co-exist with fatigue and should be targeted by health care providers' interventions designed to reduce fatigue in LT recipients.

In our study, gender was correlated to fatigue interference, indicating that female recipients obtained more fatigue interference on their quality of life than male recipients. This result met with van den Berg‐Emons and his colleagues' research [17], which found women were more severely fatigued than men. No relation were found between fatigue with age, employment status, and duration after LT in our study, however, there were different results in previous studies. It found that the older recipients were more severely fatigued than younger recipients [17]; working and having undergone LT 4 to 5 years previously were associated with less physical fatigue than

not working and having undergone LT 1 to 3 years previously [31]. The difference in results may be due to differences in sampling groups. In our study, recipients who had a liver transplantation less than 3 months were excluded, considering their condition was not stable. These excluded recipients might have different fatigue sense comparing with those included in the study. Berg-Emons included recipients who were discharged 3 weeks or more [17], and Aadahl excluded recipients who received their liver transplant less than 1 year because they are not long-time survivors [31].

Conclusion

The current study showed that fatigue is common among liver transplant recipient in China and fatigue negatively influences the recipient's quality of life and daily activities. Anxiety, depression, and insomnia were the influencing factors of fatigue intensity and fatigue interference. The recipients who had severe insomnia and mood disorders, felt severer fatigue and greater influence caused by fatigue. It suggests that health care providers should not only pay more attention on recipients' fatigue but also on other co-exist symptoms. Some intervention, such as rehabilitation program, antidepressant drugs treatment, and sleep medicine, may be necessary and helpful.

Limitations and Recommendations

This study had certain limitations such as being a single-center cross-sectional survey. Additional longitudinal studies of fatigue in liver transplant recipients are needed. We only measured LT recipients' BMI, and other indices of their nutritional and sarcopenic status were not assessed and measured. Also, we did not report LT recipients' indications, MELD scores and post-transplant status which might be associated with their fatigue. More influencing factors, such as recipients' nutritional status, sarcopenic status, renal function, cardiorespiratoty fitness, anemia, primary disease diagnosis, and pre-transplant and post-transplant status should be considered and explored in the future research.

Acknowledgments

Special thanks to the LT recipients who participated in this study.

Competing interests

There is no conflict of interest. The results presented in this paper have not been published previously.

Data sharing statement

No additional data available.

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Contributors

X-H. Lin participated in the data collection and data analysis and drafted the manuscript. H-X. Liu designed the study and revised the manuscript. Y-J. Zang, L. Wang and J. Zhang participated in the

data collection. J. Zhang provided suggestions for the manuscript. S. Teng, and Y-B. Shang executed the scheme and collected data. All authors read and approved the final manuscript.

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Manuscript Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Yes, Page 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Yes, Page 2
Introduction			
Background /rationale	2	Explain the scientific background and rationale for the investigation being reported	Yes, Page 3
Objectives	3	State specific objectives, including any prespecified hypotheses	Yes, Page 3
Methods			
Study design	4	Present key elements of study design early in the paper	Yes, Page 3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Yes, Page 4-5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	Yes, Page 4
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Yes, Page 4-5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Yes, Page 4-5
Bias	9	Describe any efforts to address potential sources of bias	No
Study size	10	Explain how the study size was arrived at	No
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Yes, Page 6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Yes, Page 6
		(*b*) Describe any methods used to examine subgroups and interactions	Yes, Page 6
		(*c*) Explain how missing data were addressed	No
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	No
		(*e*) Describe any sensitivity analyses	

Continued on next page

Results			
Participants	13 *	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Yes, Page 6
		(b) Give reasons for non-participation at each stage	No
		(c) Consider use of a flow diagram	No
Descriptive data	14 *	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Yes, Page 6-7
		(b) Indicate number of participants with missing data for each variable of interest	No
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15 *	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	Yes, Page 7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Yes, Page 7-9
		(*b*) Report category boundaries when continuous variables were categorized	Not categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	No
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Yes, Page 9
Discussion			
Key results	18	Summarise key results with reference to study objectives	Yes, Page 9-10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Yes, Page 11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Yes, Page 11
Generalisability	21	Discuss the generalisability (external validity) of the study results	Yes, Page 11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Yes, Page 11

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Correction: *Fatigue and its associated factors in liver transplant recipients in Beijing: a cross-sectional study*

Lin X, Teng S, Wang L, *et al*. Fatigue and its associated factors in liver transplant recipients in Beijing: a cross-sectional study. *BMJ Open* 2017;7:e011840. doi: 10.1136/bmjopen-2016-011840

Th correct Ethical considerations for this article is:
Ethical considerations:

Ethical approval had been obtained from the hospital and university ethics committee, which requires processes to ensure the confidentiality of all data. The purpose, risks and benefits of this study were explained to the patients before they were asked to participate. The patients were assured that participation was voluntary, and that choosing not to participate would not influence their clinical care. The organs of the liver transplant cases involved in this study are from citizens who underwent cardiac death, and were not from executed prisoners. Authors have provided BMJ Open with a note from their hospital to indicate this.

BMJ Open 2019;**9**:e011840corr1. doi:10.1136/bmjopen-2016-011840corr1