

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: <http://www.elsevier.com/locate/medici>

Review

Health-related quality of life measurement in chronic liver disease patients

Jolanta Šumskienė^a, Limas Kupčinskas^a, Linas Šumskas^{b,c,*}

^aDepartment of Gastroenterology, Medical Academy, Lithuanian University of Health Sciences, Kaunas, Lithuania

^bDepartment of Preventive Medicine, Faculty of Public Health, Medical Academy, Lithuanian University of Health Sciences, Kaunas, Lithuania

^cInstitute of Health Research, Faculty of Public Health, Medical Academy, Lithuanian University of Health Sciences, Kaunas, Lithuania

ARTICLE INFO

Article history:

Received 24 April 2014

Accepted 13 June 2015

Available online 1 August 2015

Keywords:

Health-related quality of life

Liver cirrhosis

Chronic liver disease

Liver transplantation

ABSTRACT

Background and objective: Health-related quality of life (HRQOL) is an important health indicator in medical outcome research and clinical practice. This issue tends to attract even more attention with the recent improvements of patient survival after liver transplantation. This review article aims at providing a deeper insight into practices used for evaluating HRQOL in chronic liver diseases (CLDs) and especially cirrhosis patients during different stages of the disease including liver transplantation.

Materials and methods: A systematic review of the MEDLINE database and Cochrane library was conducted. A search using the Medical Subject Headings (MeSH) major terms “liver disease” AND “quality of life” was applied for the period from 1966 to 2012.

Results: Our review identified 1483 publications. The searched showed that significant increase of publications (from 362 to 1018) was observed during last decade (period 2003–2012) in comparison with previous. The majority of publications were in English ($n = 1179$). The literature search and analysis provided information on the most common generic and disease-specific HRQOL instruments, which are used in CLD patients: Medical Outcomes Study Short Form-36, the National Institute of Diabetes and Digestive and Kidney Diseases Quality of Life questionnaire, the Chronic Liver Disease questionnaire, the Liver Disease Quality of Life questionnaire, and other.

Conclusions: Quality of life instruments are potentially powerful tools for evaluating the functional status, presenting gains of treatment and reflecting patients' ability to return to a normal lifestyle in CLD patients. More attention should be paid by clinicians for integrated use of clinical tests together with HRQOL instruments in liver transplantation for establishing the reference levels of mental, physical, and role-social functioning.

© 2015 Lithuanian University of Health Sciences. Production and hosting by Elsevier

Sp. z o.o. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

* Corresponding author at: Department of Preventive Medicine, Faculty of Public Health, Medical Academy, Lithuanian University of Health Sciences, A. Mickevičiaus 9, 44307 Kaunas, Lithuania.

E-mail address: linas.sumskas@ismuni.lt (L. Šumskas).

Peer review under the responsibility of the Lithuanian University of Health Sciences.



Production and hosting by Elsevier

<http://dx.doi.org/10.1016/j.medici.2015.06.006>

1010-660X/© 2015 Lithuanian University of Health Sciences. Production and hosting by Elsevier Sp. z o.o. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

A significant increase in the prevalence of chronic liver diseases (CLDs) has been observed during the recent decades globally in contrast to a decrease in morbidity and mortality from cardiovascular diseases which dominated in many industrial countries (in the Nordic, Northwestern European countries as well as in Australia and the United States) during the second half of the 20th century [1–3]. It has been estimated that in countries such as the United Kingdom more people may die from cirrhosis and other CLDs than from cardiovascular diseases by the year 2030 [4].

CLDs now are considered as a major public health problem in Europe and worldwide. These diseases are the fifth leading cause of mortality in England. In the United States, they are among the 15 most prevalent causes of death in the past decade with the estimated adjusted mortality rate being 10.3 per 100,000 inhabitants in 2010 [5]. In Canada, 2748 deaths were attributed to CLDs in 2008, 1809 (66%) of which occurred among men [6]. Such determinants as excessive alcohol consumption, also viral hepatitis B and C, metabolic syndrome are the key causes of cirrhosis and liver cancer in Europe [7]. Available data suggest that 29 million persons in the European Union are affected by chronic liver conditions, and about 0.1% of the European population suffers from cirrhosis. It corresponds to 170,000 deaths per year [8]. The consequences of cirrhosis and other CLDs negatively affect all aspects of well-being and health-related quality of life (HRQOL). These patients are exposed to inability to function at work, fatigue, anxiety, loss of self-esteem, depression, and other emotional problems [9–11].

The assessment of HRQOL can be an efficient tool of patients care and in clinical outcomes research. HRQOL shows how the changing health status of patient has an impact on the quality of life. The majority of definitions of HRQOL focus mainly on the effects of disease and treatment methods as well as on physical, psychological, social role, emotional, and cognitive functioning. An important reason to measure the HRQOL is establishing and expanding information about the range of problems that affect patient. Combined application of generic and disease-specific instruments can result in more accurate assessment of both the global aspects and the specific domains of HRQOL in rehabilitation, clinical trials, surgical interventions, and palliative care [12].

Liver transplantation has recently become a life-saving intervention for the majority of patients with cirrhosis and other life threatening end-stage CLDs [13]. Evident progress in graft and patient survival as well as re-establishment of quality of life of patients have been achieved during the last 20 years [14]. The HRQOL measure provides a set of useful practical information about the patients' health status during liver transplantation. The development of HRQOL assessment tools specific to transplantation could lead for more accurate assessment of factors that influence pretransplantation and posttransplantation HRQOL scores [15].

In this review article, we aimed to get a deeper insight into methodology and the instruments applied to assess HRQOL in the adult CLD patients and especially in liver cirrhosis, which constitutes the major segment of CLDs in the population. Also

we focused our analysis on the properties, characteristics of the existing HRQOL instruments, their particular advantages, limitations in evaluating patients with CLD. Conducting the systematic literature search was one of our objectives and primary step of the literature analysis.

2. Materials and methods

The search of the relevant articles related with cirrhosis, CLD and HRQOL was conducted in the MEDLINE database and the Cochrane library (period 1966–2012 included). In order to identify any topic of interest related articles, a search using the Medical Subject Headings (MeSH) major terms “liver disease” AND “quality of life” was applied. In order to get more detailed insight also other combinations of search keywords were used: “liver cirrhosis” AND “quality of life”; “liver failure” AND “quality of life”; liver transplantation” AND “quality of life”; liver transplantation” AND “waiting lists” AND “quality of life”. Quotations related to the keywords “QOL”, “HRQOL”, OR “HRQOL” were also included. The search was not limited to only original journal articles published in English but also covered other languages: Chinese, Dutch, French, German, Italian, Japanese, Spanish, Polish, Russian, and other.

Publications were included into analysis if they used a patient-reported quality of life assessment in CLD patients and if HRQOL instruments were mentioned. Also the article had to be focused more on HRQOL rather than on the general definition of quality of life. The search of the sources was performed by the experienced staff of the university's library. The final review and the text of literature review were performed by the researchers, i.e., the authors of this paper.

3. Results

3.1. Search of literature on chronic liver diseases and quality of life

In the primary stage of search, the most general headings (by MeSH) “liver disease” AND “quality of life” were selected. We identified 1483 publications (period 1966–2012), which included combination of these headings (Table 1). Majority of

Table 1 – Results of search in the MEDLINE and Cochrane library for publications on “liver disease”, “liver cirrhosis”, “liver failure” AND “quality of life”: results of search in the MEDLINE and Cochrane library, 1993–2012.

Time period by decades (years)	“Liver disease” AND “quality of life”	
	All languages	In English
2003–2012	1018	818
1993–2002	362	292
1983–1992	84	55
1973–1982	18	13
1963–1972	1 ^a	1 ^a
Total	1483	1179

^a First publication in 1966.

publications were in English (n = 1179). Therefore, articles in other languages such as Japanese (n = 116), German (n = 45), French (n = 33) and Chinese (n = 33) were less numerous. Therefore, evident increase of papers published in Chinese (from 2 to 31) and Japanese (from 34 to 82) was observed (Table 2). The analysis showed that a significant increase in the number of publications was observed during the last analyzed decade (2003–2012) and it has tripled in comparison with the previous (1993–2002) period (Table 1).

Table 3 presents the results of search on five categories, which were related to cirrhosis and has been selected by the library experts and medical professionals from the field. Heading of “liver transplantation” and its combination with “quality of life” were the most common (n = 661) among the publications. Headings such as “chronic hepatitis” (n = 307) also “liver cirrhosis” (n = 268) in combination with the headings “quality of life” were also highly prevalent among publications. “Liver failure” and “quality of life” were less prevalent among the topics – 150 articles were published on this issue during 2003–2012. The results also indicate on the global increase of research on “liver transplantation” (rise from 8 to 27, two last decades compared) in relation to the heading “waiting lists” of liver disease patients.

3.2. HRQOL assessment in CLD patients

The concept of HRQOL has been developing through the last 5 decades. HRQOL has originated from the more overall and wider concept of “quality of life.” Nowadays quality-of-life concepts range from the measurement of an exclusively physical state of health to embodying the patient's perceptions and social aspects of disease to the concept of quality of life – from economic to environmental, medical definitions, depending on professionals in respective fields. It is now becoming approved and appropriate for medical doctors and researchers studying chronic illness to use more often the HRQOL instruments that measure the patients reported health outcomes.

It is generally agreed that HRQOL involves 3 core domains: physical functioning, psychological functioning (well-being and emotional status), and social functioning [16]. This concept and definition of HRQOL are related with the impact of disease and the clinical perspective. Therefore, despite the evident increase of HRQOL investigations worldwide presented in the previous chapter, their acceptance and incorporation into clinical practice go on the slower pace.

Table 2 – The number of publications on “liver disease” AND “quality of life” by language: results of search in the MEDLINE and Cochrane library, 1963–2012.

Languages	“Liver disease” AND “quality of life”					Total
	1963–1972	1973–1982	1983–1992	1993–2002	2003–2012	
English	1	13	55	292	818	1179
Japanese	0	0	10	24	82	116
German	0	0	9	11	25	45
French	0	1	3	18*	11	33
Chinese	0	0	0	2	31	33
Russian	0	0	0	4	17	21
Spanish	0	0	2	4	7	13
Italian	0	2	1	3	3*	9
Polish	0	0	0	3	6	9
Dutch	0	2	3	0	1	6
Other languages	0	0	1	2*	19	22
Total	1	18	84	361 (363)	1019 (1020)	1483 (1486)

Note: * – 3 articles were published in two languages and this resulted in an increase in the total number (see in brackets) from 1483 to 1486

Table 3 – The results of search for publications on five categories of “liver disease” AND “quality of life”: MEDLINE and Cochrane library data, 1963–2012.

Time period by decades (years)	“Liver transplantation” AND “quality of life”	“Chronic hepatitis” AND “quality of life”	“Liver cirrhosis” AND “quality of life”	“Liver failure” AND “quality of life”	“Liver transplantation” AND “waiting list” AND “quality of life”
2003–2012	375	245	174	110	27
1993–2002	211	62 ^b	70	31	8 ^e
1983–1992	72	0	18	6	0
1973–1982	3 ^a	0	6 ^c	2	0
1963–1972	0	0	0	1 ^d	0
Total	661	307	268	150	35

^a First publication in 1979.

^b First publication in 1994.

^c First publication in 1978.

^d First publication in 1966.

^e First publication in 1998.

CLDs have demonstrated a substantial impact on the well-being of patients and contribute to a significant burden of morbidity associated with these conditions. The clinicians show that these people experience substantial deterioration in their HRQOL. Therefore, they continue to incorporate HRQOL measures into their practice. Professional associations of liver disease experts suggest following the main applications of HRQOL assessments in the health care practices: conducting treatment evaluations in clinical trials; providing epidemiological studies of HRQOL in different groups of population; investigating in health economics for determining the balanced use of health care spending; selecting treatment options in the individual patient care; evaluating of side effects of antiviral and other therapies [16,17]. More recent research evidence indicates on widening the scope of application of concepts of HRQOL for clinical trials and activities in management of liver transplantation patients [18].

3.3. Use of generic questionnaires in chronic liver disease patients

Both the generic and disease-specific instruments recently are applied in patients with CLD. Generic HRQOL questionnaires as a rule include a number of domains of HRQOL that could be applied to various populations of people. The generic questionnaires have some advantages – the scoring of the different groups of patients can be compared with the scoring of other patient population or with a healthy reference population. A weakness is that generic instruments are not designed to identify disease-specific domains that may be important to establish and track clinical changes. Three most commonly used generic HRQOL instruments (according to other research done and by our current MEDLINE and Cochrane library review) are: the Medical Outcomes Study Short Form-36 (SF-36), the Nottingham Health Profile (NHP), and the Sickness Impact Profile (SIP) [19–21]. The SF-36 (36 items, 8 domains) is currently the most used HRQOL instrument in CLD and other diseases studies worldwide [12,16,22]. It focuses on a wider range of disease severity and has sufficient sensitivity for variety of health conditions [23]. The NHP has 38 items and covers 6 domains and focuses on more severe stages of diseases. This questionnaire is less sensitive in relatively mild condition and for minor changes. The tool is considered as concise and practical generic instrument, which could be used in liver disease patients. The SIP has a wide coverage of domains. Therefore, due to its 136 items, this questionnaire is very long for completing by patients and is used less frequently.

3.4. Use of disease-specific questionnaires in CLD patients

Disease-specific questionnaires are designed to measure symptoms likely to occur in patients with a specific disease. These instruments have the advantage due to offering greater sensitivity and specificity [18]. They measure the impact of the symptoms of a particular disease on patient's well-being. Disease-specific questionnaires define responses to treatment, or burden of disease if compared to norms. As a rule they do not apply to other health disorders and are not designed to cover all the rest domains of health [24]. The scores

of good disease-specific HRQOL instrument (questionnaire) should correlate with disease severity, i.e., Child-Turcotte-Pugh (CTP), MELD score, and proportionally reflects the influence of concomitant complications of cirrhosis (ascites, fatigue, hepatic encephalopathy, etc.) on a patient's well-being [12].

Four most frequently applied disease-specific HRQOL questionnaires for CLD patients have been created during the last two decades. The first liver disease-specific HRQOL questionnaire (the Hepatitis Quality of Life Questionnaire, HQLQ) was presented in 1998 [25]. Very soon, in 1999 and 2000, another two more universal instruments the Chronic Liver Disease Questionnaire (CLDQ) and also the Liver Disease Quality Of Life questionnaire (LDQOL), were implemented [26,27]. Later, in 2004, the Liver Disease Symptom Index 2.0 (LDSI 2.0) was developed [28].

All mentioned instruments have advantages and weaknesses. The HQLQ instrument covers also questions from the generic, widely validated SF-36 questionnaire. In addition, 5 disease-specific subscales are added. Therefore, the HQLQ is not suitable for patients with other CLD than hepatitis. The application of CLDQ is more universal and covers variety of CLD. This short questionnaire is practical in use and can be considered as one of the most recognized instruments. Therefore, researchers see some limitations of CLDQ when use it in more advanced stages of disease. Other frequently used instrument in liver diseases is LDQOL. This questionnaire is focused on the broad range of liver diseases. It covers a variety of domains (111 items included), but it makes the instrument very long for completing especially in case the other additional questionnaires are being suggested to complete [16]. The LDSI 2.0 was elaborated as a short questionnaire. It evaluates 9 liver disease-specific symptoms and measures malaise inconveniences that patients suffer. The instrument sometimes is criticized as too narrow and focused more on measuring symptoms rather than quality of life, which could not affected significantly in liver disease patients.

3.5. HRQOL instruments used in liver transplantation

Cirrhosis is the most frequent indication for liver transplantation: 52% of such surgeries are performed due to cirrhosis in Europe [29]. With steady rise of numbers of liver transplantation, which has reached over 21,602 globally (2010 data) and improvements in patient survival after this radical treatment, more attention has been given not for mortality and morbidity characteristics but to quality-of-life profiles before transplantation and after this life-saving intervention [30,31]. Until now, more than 50 generic and disease-specific instruments have been applied to measure HRQOL in liver transplant candidates or recipients [18].

3.6. Generic HRQOL instruments in liver transplant recipients

The following generic quality of life evaluation instruments are the most commonly applied: the Medical Outcomes Study Short Form-36 (SF-36), the Hospital Anxiety and Depression Scale (HADS), the Beck Depression Inventory (BDI), the EuroQOL-5D (EQ-5D), and the Sickness Impact Profile (SIP)

[18]. These generic HRQOL instruments allow making comparisons between three groups of patients: CLD patients, liver transplant recipients, and the individuals from the general population. The SF-36 is most popular instrument. It was used for the first time for measuring HRQOL in liver transplant patients in 1993 and remains an important tool for monitoring, comparing groups of liver transplant patients with other clinical groups [18,29]. First validation studies of the generic quality of life instruments showed strong psychometric properties. Therefore, the generic instruments were not elaborated especially for the liver transplant recipients. This means that only limited data were collected on their consistency, reliability and validity in liver patient population. Due to that circumstances there are published very few publications on this issue. Despite scarcity of such studies, some researcher have demonstrated good measuring properties (good construct validity and high internal consistency) of the SF-36 in a group of patients referred for liver transplantation [18,27,32].

3.7. Disease-specific HRQOL instruments in liver transplant recipients

Three targeted quality of life questionnaires are used in liver transplantation most frequently: the National Institute of Diabetes and Digestive and Kidney Diseases Quality of Life questionnaire (NIDDK QOL), the Liver Disease Quality of Life questionnaire (LDQOL), and the Chronic Liver Disease questionnaire (CLDQ). It is worth noting that these instruments have been developed for the assessment of HRQOL in patients with CLDs rather than patients after liver transplantation. The NIDDK QOL questionnaire was created in the framework of the 7-year NIDDK multi-center program for liver transplant recipients [33,34]. This questionnaire was applied consistently in four studies published in 2003–2004 [18].

The LDQOL is a disease-specific instrument, which involves 8 domains of the SF-36 tool, plus additional items comprising 12 multi-item scales are added. The 12 domains cover the following: symptoms of liver disease, concentration, memory, sleep, hopelessness, loneliness, effects of liver disease, quality of social interaction, health distress, stigma of liver disease, sexual functioning, and social interaction [35]. Evaluation of validity of this instrument was conducted during a multi-center study of patients referred for liver transplant evaluation and showed the positive results [36].

Another instrument – CLDQ – is an evaluation tool of 29 items, which was developed by Younossi et al. in 1999 in order to measure of the main features of HRQOL in patients CLDs [26]. It covers items representing six domains for evaluating activity, fatigue, emotional function, worry, abdominal symptoms, and systemic symptoms. Later, in 2005, this instrument was started to be applied as a tool also for evaluation HRQOL in the studies of liver transplant recipients.

Some years ago the clinicians expressed their expectations about the need of creating totally new more disease-specific and only liver transplantation focused questionnaires that could be routinely applied in liver transplant candidates and recipients. Evidence shows that the previously available instruments which measuring HRQOL are somewhat lack of practicality. Such innovative instrument could be extremely

essential today, when longer survival and lower levels of lethality in liver transplantation medicine open a new era. Therefore, only recently such group of instruments was started to be developed and tested [14].

3.8. HRQOL in patients awaiting liver transplantation

Health outcomes of patients awaiting liver transplantation can be considered in context of prediction of survival, quality of life (including cognitive and psychological outcome) and cost of intervention [37]. Prognosis of survival and quality of life are the key focus issues related with liver transplantation. Decisions on selecting livers for transplantation is currently based on MELD score. The MELD score includes results of three laboratory tests – International Normalized Ratio (INR), serum bilirubine and serum creatinine. It allows making prognosis on the short-term for liver disease [38]. The higher score predicts more advanced liver disease. The serum sodium concentration has been considered also as an additional significant prognostic factor in patients with liver cirrhosis on a waiting list [39]. Common complications such as ascites and hepatic encephalopathy, which are the part of the Child-Turcotte-Pugh (CTP) score and which can influence quality of life, are not calculated in the MELD score. The studies conducted have showed that severity of liver disease as assessed by the CTP score is related to worsening quality of life [27,40,41]. Although patients may have medium MELD scores, their quality of life may be deteriorated due to liver disease complications. Therefore, the perceived symptoms and quality of life could be a part of framework for evaluating the survival and the need of liver transplantation. In addition, assessing the effect of liver disease severity on quality of life should lead for studying additional subscales of the validated instruments. It means that future investigations in patients awaiting liver transplantation should incorporate quality of life indicators as well as scoring of survival.

Both generic and liver disease-specific HRQOL instruments have been applied and validated for assessing HRQOL in liver transplantation patients. It was mentioned before that HRQOL instruments measure physical, mental, functional, psychological, social, and some liver disease-specific domains [35]. However, the association between these domains of HRQOL and survival in liver transplant patients has not been investigated extensively yet.

The study, which was published by Tanikella and co-authors, analyzed the properties of the LDQOL in liver transplant patients [42]. This group of researchers has demonstrated that liver-specific scales but not the generic Short Form 36 (SF-36) scales, as a part of LDQOL instrument, were associated with survival in patients with severe liver disease. This contradicts with the findings of other authors, who proved that the Mental Component Summary (MCS) and the Physical Component Summary (PCS) scales could be considered as the independent predictors of mortality in other chronic conditions [43,44].

Other studies have demonstrated different levels of correlation between HRQOL measured in candidates awaiting liver transplantation and disease severity evaluated by the MELD scores [44,45]. Therefore, in the study by Tanikella et al., the PCS scale had a moderate relation to the MELD scores [42].

In addition, other authors found that survival is most strongly associated with health distress, perceived disease stigma, sleep disturbance and activities of daily living [45]. Despite some controversies in research findings, from a purely medical perspective it is evident that the self-reported physical quality of life of liver transplant patients and other measures of psychosocial functioning are the important prognostic indicators, which could complement the MELD score.

Recently researchers from Mayo clinic made attempt to include the objective evaluation of physical capacity by introducing the 6-min walking test for patients on a waiting list [46]. Their prospective study demonstrated that this test is a good predictor of mortality in candidates for liver transplantation. It supports the considerations that this test may be an additional tool which could be used in conjunction with the MELD when patients at risk of death before transplantation are being predicted.

In summary, despite MELD and HRQOL are different concepts the research and practice evidence show that each has independent capacity to predict the risk of mortality and finally to forecast the success of liver transplantation. Adding HRQOL information could improve the discriminative ability of the MELD-based model. Only HRQOL data, which have a subjective nature, are not suitable for use in making liver awaiting decisions. These data might certainly be useful for clinical practice as complement for MELD as a predictor of mortality and a tool for better risk stratification of patients with end-stage cirrhosis or other CLD [44,45]. In addition, data on various domains of quality of life could be applied in providing the tracking of a waiting list of patients, in addressing the nursing, nutritional status issues and implementing enhanced focus on well-being [47,48].

4. Discussion

Our review article aimed at providing a deeper insight into the instruments and practices used for evaluating HRQOL in CLD patients and especially cirrhosis during different stages of the disease including the liver transplantation. The systematic review in MEDLINE database and Cochrane, which was conducted during our survey, showed that the number of publications on CLD and quality of life has tripled during period 2003-2012 in comparison with the previous decade. Heading of "liver transplantation" and its combination with "quality of life" were the most common among the publications. These results coincide with similar observations of other investigators [49]. Headings such as "chronic hepatitis" ($n = 307$) also "liver cirrhosis" ($n = 268$) in combination with the headings "quality of life" were also highly prevalent among publications.

In this paper, the main focus was concentrated on review of the recent state of art in the area that examines quality of life instruments applied in liver diseases. It was showed by this analysis and review of literature, that majority of leading researchers emphasizes the need of introduction of the holistic paradigm, which could be applied in the clinical practices. Many authors also conclude that the effects of the treatment methods on quality of life domains in physical, social, psychological and emotional, also cognitive functioning are extremely important for modern clinicians. Research

evidence shows that each of these domains could be affected significantly by the disease or treatment [49]. This is why different strategies of CLD management should be under consideration. The routine administration of HRQOL questionnaires in general practice and in specialists' consultations showed that such systematic approach could provide additional information on variety of physical, social and psychological issues and lead for improved treatment and compliance. In addition, many obstacles should be overcome in the clinical practice for implementation of the HRQOL assessment as a routine and everyday procedure due to lack of human resources, extra time needed, additional costs and ignorance of good practices in this field [16].

Some achievements in the treatment of CLDs and cirrhosis could be observed during last decades. The successful development of effective antiviral treatments, nutrition therapy, radiological and endoscopic management of portal hypertension, and especially liver transplantation has improved survival and quality of life in this group of patients. This is why further research of patients awaiting liver transplantation should be in the focus of the researchers. It means that future studies in patients awaiting liver transplantation should include not only simplified (such as MELD) scores but also quality of life evaluation and more advanced innovative approaches such as physical capacity, nutritional status evaluation and possibly other innovative measures [48]. It is evident that the complex improvement of their HRQOL together with diminishing their dependence on basic and instrumental activities of daily living should be in focus of the researchers.

Another challenge for researchers also is development of new improved and targeted instruments with high discriminate ability for liver transplantation. The lack of a valid and reliable HRQOL instrument for liver transplant patients is a barrier for further cross-study comparisons [18]. We consider that the elaboration of HRQOL questionnaires dedicated specifically for liver transplant patients will improve HRQOL assessment in this clinical group and could lead to a more complete understanding of the well-being determinants in transplant recipients [49,50].

Some limitations of this review must be mentioned. Language bias could be introduced in the review because some part of articles was in Japanese ($n = 116$), German ($n = 45$), French ($n = 33$), Chinese ($n = 33$) and other languages. We did not concentrate extensively on such important indices necessary to measure the psychometric properties. Also responsiveness over time and reliability for many of the instruments were not the special focus of this review. It seems that these shortcomings are an inherited gap of the current state of art in the liver transplantation and HRQOL literature. The main strength of the review is an attempt of more systematic revealing look on the most significant instruments used, with particular attention for their properties, advantages and weaknesses in measuring HRQOL in chronic liver disease patients.

5. Conclusions

This review shows that quality-of-life instruments are potentially powerful tools for evaluating the functional status,

presenting gains of treatment and reflecting patients' ability to return to a normal lifestyle in CLD patients. More attention to be paid in the future by clinicians for integrated use of clinical tests together with HRQOL instruments in liver transplantation for establishing the reference levels of physical, mental, role-social functioning (in work, family or in other health setting) including relationships, life satisfaction, perceptions of health, fitness and well-being. Integrated use of clinical scores and tests together with HRQOL instruments also is strongly advised. Clinicians should concentrate more attention on the future prospects of the patient, and on the holistic health understanding. Further investigations are required to provide for defining the determinants of good HRQOL outcomes and to develop the strategies for improvement of well-being.

Conflict of interest

The authors state no conflict of interest.

Acknowledgements

The authors express their gratitude to the staff of the Library and Information Centre, Lithuanian University of Health Sciences, and especially to Mrs. Lina Šaferienė, who contributed a lot by advises and personal involvement in search for the literature sources.

REFERENCES

- [1] World Health Organisation. WHO European health for all database; 2012 [updated July 2013]. Available from <http://data.euro.who.int/hfad> [accessed 11.12.13].
- [2] Mirzaei M, Truswell AS, Taylor R, Leeder SR. Coronary heart disease epidemics: not all the same. *Heart* 2009;95:740–6.
- [3] Institute of Medicine (US) Committee on Preventing the Global Epidemic of Cardiovascular Disease: Meeting the Challenges in Developing Countries. In: Fuster V, Kelly BB, editors. *Promoting cardiovascular health in the developing world: a critical challenge to achieve global health*. Washington (DC): National Academies Press (US); 2010. Available from <http://www.ncbi.nlm.nih.gov/books/NBK45693/>.
- [4] Moore K, Sheron N. Why we need a national strategy for liver disease. *Br J Hosp Med (Lond)* 2009;70:674–5.
- [5] Murphy SL, Xu JQ, Kochanek KD. Deaths: preliminary data for 2010. *Natl Vital Stat Rep* 2012;60:1–52.
- [6] Mortality, summary list of causes 2008. Frequency: annual. Ottawa (ON): Statistics Canada; 2011 [Statistics Canada, Catalogue No.: 84F0209X]. Available from <http://www.statcan.gc.ca/pub/84f0209x/84f0209x2008000-eng.pdf>.
- [7] Blachier M, Leleu H, Peck-Radosavljevic M, Valla DC, Roudot-Thoraval F. The burden of liver disease in Europe: a review of available epidemiological data. *J Hepatol* 2013;58:593–608.
- [8] Zatonski WA, Sulkowska U, Manczuk M, Rehm J, Boffetta P, Lowenfels AB, et al. Liver cirrhosis mortality in Europe, with special attention to Central and Eastern Europe. *Eur Addict Res* 2010;16:193–201.
- [9] Les I, Doval E, Flavià M, Jacas C, Cárdenas G, Esteban R, et al. Quality of life in cirrhosis is related to potentially treatable factors. *Eur J Gastroenterol Hepatol* 2010;22:221–7.
- [10] Gao R, Gao F, Li G, Hao JY. Health-related quality of life in Chinese patients with chronic liver disease. *Gastroenterol Res Pract* 2012;2012. <http://dx.doi.org/10.1155/2012/516140>. Article ID 516140, 7 pages. Available from <http://www.hindawi.com/journals/grp/2012/516140/>
- [11] Mahmood S, Kida T, Izumi A, Sasaki C, Okamoto H, Kobayashi H, et al. Assessment of Health Related Quality of life in chronic liver disease patients using the Japanese versions of CLDQ and SF-36. *Open Gastroenterol J* 2008; 2:57–63. Available from <http://www.benthamscience.com/open/togasj/articles/V002/57TOGASJ.pdf>.
- [12] Loria A, Escheik C, Gerber NL, Younossi ZM. Quality of life in cirrhosis. *Curr Gastroenterol Rep* 2013;15:301.
- [13] Braun F, Teren K, Wilms P, Gunther R, Allmann J, Broering DC, et al. Quality of life after liver transplantation. *Transplant Proc* 2009;41:2564–6.
- [14] Yekta ZP, Tayebi Z, Shahsavari H, Ebadi A, Tayebi R, Bolourchifard F, et al. Liver transplant recipients quality of life instrument: development and psychometric testing. *Hepat Mon* 2013;13(10):e9701.
- [15] Bownik H, Saab S. Health-related quality of life after liver transplantation for adult recipients. *Liver Transpl* 2009; 15(Suppl. 2):S42–9.
- [16] Gutteling JJ, de Man RA, Busschbach JJ, Darlington AS. Overview of research on health-related quality of life in patients with chronic liver disease. *Neth J Med* 2007; 65:227–34.
- [17] Rodger AJ, Jolley D, Thompson SC, Lanigan A, Crofts N. The impact of diagnosis of hepatitis C virus on quality of life. *Hepatology* 1999;30:1299–301.
- [18] Jay CL, Butt Z, Ladner DP, Skaro AI, Abecassis MM. A review of quality of life instruments used in liver transplantation. *J Hepatol* 2009;51:949–59.
- [19] Bergner M, Bobbitt RA, Carter WB, Gilson BS. The Sickness Impact Profile: development and final revision of a health status measure. *Med Care* 1981;19:787–805.
- [20] Hunt SM, McEwen J, McKenna SP. Measuring health status: a new tool for clinicians and epidemiologists. *J R Coll Gen Pract* 1985;35:185–8.
- [21] Ware Jr JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). Conceptual framework and item selection. *Med Care* 1992;30:473–83.
- [22] Garratt A, Schmidt L, Mackintosh A, Fitzpatrick R. Quality of life measurement: bibliographic study of patient assessed health outcome measures. *BMJ* 2002;324(7351):1417–21.
- [23] Brazier JE, Harper R, Jones NM, et al. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. *BMJ* 1992;305(6846):160–4.
- [24] Fryback GD. Measuring health-related quality of life. Workshop on advancing social science theory: the importance of common metrics. Washington, DC: The National Academies, Division of Behavioral and Social Sciences and Education; 2010.
- [25] Bayliss MS, Gandek B, Bungay KM, Sugano D, Hsu MA, Ware Jr JE. A questionnaire to assess the generic and disease-specific health outcomes of patients with chronic hepatitis C. *Qual Life Res* 1998;7:39–55.
- [26] Younossi ZM, Guyatt G, Kiwi M, Boparai N, King D. Development of a disease specific questionnaire to measure health related quality of life in patients with chronic liver disease. *Gut* 1999;45:295–300.
- [27] Gralnek IM, Hays RD, Kilbourne A, Rosen HR, Keeffe EB, Artinian L, et al. Development and evaluation of the Liver Disease Quality of Life instrument in persons with advanced, chronic liver disease – the LDQOL 1.0. *Am J Gastroenterol* 2000;95:3552–65.

- [28] van der Plas SM, Hansen BE, de Boer JB, Stijnen T, Passchier J, de Man RA, et al. The Liver Disease Symptom Index 2.0; validation of a disease-specific questionnaire. *Qual Life Res* 2004;13:1469-81.
- [29] Adam R, Karam V, Delvart V, O'Grady J, Mirza D, Klempnauer J, et al., All contributing centers (www.eltr.org); European Liver and Intestine Transplant Association (ELITA). Evolution of indications and results of liver transplantation in Europe. A report from the European Liver Transplant Registry (ELTR). *J Hepatol* 2012;57:675-88.
- [30] Eurotransplant. Annual Report 2012. Leiden: Eurotransplant International Foundation; 2012, ISBN-EAN: 978-90-71658-31-0.
- [31] Global observatory on donation and transplantation (GODT). Global donation and transplantation activities; 2010, Available from <http://www.transplant-observatory.org/Pages/Data-Reports.aspx>.
- [32] Kousoulas L, Neipp M, Barg-Hock H, Jackobs S, Strassburg CP, Klempnauer J, et al. Health-related quality of life in adult transplant recipients more than 15 years after orthotopic liver transplantation. *Transpl Int* 2008;21:1052-8.
- [33] Cowling T, Jennings LW, Goldstein RM, Sanchez EQ, Chinnakotla S, Klintmalm GB, et al. Societal reintegration after liver transplantation: findings in alcohol-related and non-alcohol-related transplant recipients. *Ann Surg* 2004;239:93-8.
- [34] Cowling T, Jennings LW, Goldstein RM, Sanchez EQ, Chinnakotla S, Klintmalm GB, et al. Liver transplantation and health-related quality of life: scoring differences between men and women. *Liver Transpl* 2004;10:88-96.
- [35] Santos JR, Miyazaki MC, Domingos NA, Valerio NI, Silva RF, Silva RC. Patients undergoing liver transplantation: psychosocial characteristics, depressive symptoms, and quality of life. *Transplant Proc* 2008;40:802-4.
- [36] Goetzmann L, Ruegg L, Stamm M, Ambühl P, Boehler A, Halter J, et al. Psychosocial profiles after transplantation: a 24-month follow-up of heart, lung, liver, kidney and allogeneic bone-marrow patients. *Transplantation* 2008;86:662-8.
- [37] Senzolo M, Pizzolato G, Ferronato C, Chierichetti F, Boccagni P, Dam M, et al. Long-term evaluation of cognitive function and cerebral metabolism in liver transplanted patients. *Transplant Proc* 2009;41:1295-6.
- [38] Sumskiene J, Sumskas L, Petrauskas D, Kupcinskas L. Disease-specific health-related quality of life and its determinants in liver cirrhosis patients in Lithuania. *World J Gastroenterol* 2006;12:7792-7.
- [39] Kim WR, Biggins SW, Kremers WK, Wiesner RH, Kamath PS, Benson JT, et al. Hyponatremia and mortality among patients on the liver-transplant waiting list. *N Engl J Med* 2008;359:1018-26.
- [40] Younossi ZM, Kiwi ML, Boparai N, Price LL, Guyatt G. Cholestatic liver diseases and health-related quality of life. *Am J Gastroenterol* 2000;95:497-502.
- [41] Marchesini G, Bianchi G, Amodio P, Salerno F, Merli M, Panella C, et al., and the Italian Study Group for Quality of Life in Cirrhosis. Factors associated with poor health-related quality of life of patients with cirrhosis. *Gastroenterology* 2001;120:170-8.
- [42] Tanikella R, Kawut SM, Brown Jr RS, Krowka JM, Reinen J, Dinasarapu CR, et al. Health-related quality of life and survival in liver transplant candidates. *Liver Transpl* 2010;16:238-45.
- [43] Ong SC, Mak B, Aung MO, Li SC, Lim SG. Health-related quality of life in chronic hepatitis B patients. *Hepatology* 2008;47:1108-17.
- [44] Saab S, Ibrahim AB, Shpaner A, Younossi ZM, Lee C, Durazo F, et al. MELD fails to measure quality of life in liver transplant candidates. *Liver Transpl* 2005;11:218-23.
- [45] Kanwal F, Gralnek IM, Hays RD, Zeringue A, Durazo F, Han SB, et al. Health related quality of life predicts mortality in patients with advanced chronic liver disease. *Clin Gastroenterol Hepatol* 2009;7:793-9.
- [46] Carey EJ, Steidley DE, Aqel BA, Byrne TJ, Mekeel KL, Rakela J, et al. Six-minute walk distance predicts mortality in liver transplant candidates. *Liver Transpl* 2010;16:1373-8.
- [47] Fukushima K, Ueno Y, Kawagishi N, Kondo Y, Inoue J, Kakazu E, et al. The nutritional index 'CONUT' is useful for predicting long-term prognosis of patients with end-stage liver diseases. *Tohoku J Exp Med* 2011;224(3):215-9.
- [48] García-Rodríguez MT, Piñón-Villar MC, López-Calviño B, Otero-Ferreiro A, Suárez-López F, Gómez-Gutiérrez M, et al. Assessment of nutritional status and health-related quality of life before and after liver transplantation. *BMC Gastroenterol* 2015;15:6.
- [49] Yang LS, Shan LL, Saxena A, Morris DL. Liver transplantation: a systematic review of long-term quality of life. *Liver Int* 2014;34:1298-313.
- [50] Aberg F, Hockerstedt K, Roine RP, Sintonen H, Isoniemi H. Influence of liver-disease etiology on long-term quality of life and employment after liver transplantation. *Clin Transpl* 2012;26:729-35.