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World Journal of Hepatology (*World J Hepatol*, *WJH*, online ISSN 1948-5182, DOI: 10.4254), is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJH covers topics concerning liver biology/pathology, cirrhosis and its complications, liver fibrosis, liver failure, portal hypertension, hepatitis B and C and inflammatory disorders, steatohepatitis and metabolic liver disease, hepatocellular carcinoma, biliary tract disease, autoimmune disease, cholestatic and biliary disease, transplantation, genetics, epidemiology, microbiology, molecular and cell biology, nutrition, geriatric and pediatric hepatology, diagnosis and screening, endoscopy, imaging, and advanced technology. Priority publication will be given to articles concerning diagnosis and treatment of hepatology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

We encourage authors to submit their manuscripts to *WJH*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great basic and clinical significance.

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Value of quality of life analysis in liver cancer: A clinician's perspective

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Abstract

Health related quality of life (HRQOL) is increasingly

recognized as an important clinical parameter and research endpoint in patients with hepatocellular carcinoma (HCC). HRQOL in HCC patients is multifaceted and affected by medical factor which encompasses HCC and its complications, oncological and palliative treatment for HCC, underlying liver disease, as well as the psychological, social or spiritual reaction to the disease. Many patients presented late with advanced disease and limited survival, plagued with multiple symptoms, rendering QOL a very important aspect in their general well being. Various instruments have been developed and validated to measure and report HRQOL in HCC patients, these included general HRQOL instruments, *e.g.*, Short form (SF)-36, SF-12, EuroQoL-5D, World Health Organization Quality of Life Assessment 100 (WHOQOL-100), World Health Organization Quality of Life Assessment abbreviated version; general cancer HRQOL instruments, *e.g.*, the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30, Functional Assessment of Cancer Therapy (FACT)-General, Spitzer Quality of Life Index; and liver-cancer specific HRQOL instruments, *e.g.*, EORTC QLQ-HCC18, FACT-Hepatobiliary (FACT-Hep), FACT-Hep Symptom Index, Trial Outcome Index. Important utilization of HRQOL in HCC patients included description of symptomatology and HRQOL of patients, treatment endpoint in clinical trial, prognostication of survival, benchmarking of palliative care service and health care valuation. In this review, difficulties regarding the use of HRQOL data in research and clinical practice, including choosing a suitable instrument, problems of missing data, data interpretation, analysis and presentation are examined. Potential solutions are also discussed.

Key words: Hepatocellular carcinoma; Health related quality of life; Palliative care; Prognosis; Survival; The European Organisation for Research and Treatment of Cancer QLQ-C30; QLQ-HCC18; Index score; Functional Assessment of Cancer Therapy; EQ-5D; Spitzer; Short form 36; FHSI-8; World Health Organization Quality of Life Assessment

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Core tip: Health related quality of life (HRQOL) is an important clinical parameter and research endpoint in hepatocellular carcinoma (HCC) patients. Instruments discussed are short form (SF)-36, SF-12, EQ-5D, World Health Organization Quality of Life Assessment (WHOQOL) 100, WHOQOL-BREF, the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30, Functional Assessment of Cancer Therapy (FACT)-G, Spitzer QoL index, EORTC QLQ-HCC18, FACT-Hep, FHSI-8, TOI. Important utilization of HRQOL included measurement and monitoring of HRQOL, treatment endpoint in clinical trial, prognostication of survival, benchmarking of palliative care service and health care valuation. Various difficulties in using HRQOL data in research and clinical practice, including choosing a suitable instrument, missing data, data interpretation, analysis and presentation are explained. Potential solutions are also discussed.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is a common and aggressive cancer that arises usually in a cirrhotic liver. Etiological pattern differs between Caucasians (mostly alcoholic liver disease and hepatitis C viral infection) and Asians (predominantly chronic hepatitis B)^[1,2]. HCC carries high morbidity and mortality, since many patients present only when symptomatic. Patients with early disease are typically asymptomatic and their diseases are usually detected by regular HCC screening or incidental finding during investigation for other diseases^[3]. Advanced disease at presentation is common and patients suffer from symptoms resulting from large space occupying lesion(s) in the liver or associated hepatic dysfunction/failure.

Early diseases are potentially curable by complete surgical extirpation^[4,5]. Local tumor ablation, for example radiofrequency ablation (RFA), is a reasonable alternative to partial hepatectomy for small HCC^[6,7]. Liver transplantation is considered if the disease falls within the Milan criteria but the anticipated residual liver function is not adequate^[8]. Liver directed therapies, such as transarterial chemoembolisation (TACE) and selective internal radiation therapy (SIRT), are palliative treatment for patients with higher tumor burden that is confined to the liver^[9-11]. For patients with advanced disease palliative treatment with systemic targeted agents, namely sorafenib and regorafenib, were demonstrated to improve their overall survival (OS)^[12-14]. However, in the two phase III trials of

first-line sorafenib in advanced HCC patients, the improvement in median OS was modest at 2-3 mo^[12,13] when compared to placebo. Similar magnitude of benefit was observed in the second-line setting using regorafenib when compared to placebo^[14].

In most clinical trials on patients with advanced HCC, the endpoints of interest are disease-free survival (DFS), progression-free survival (PFS) and OS. However in this poor prognostic group, treatment is mainly palliative and the survival benefit is modest. Hence, apart from survival improvement, health related quality of life (HRQOL) becomes very relevant. Thus, increasing number of phase III HCC trials have adopted QOL as additional study endpoints. HRQOL therefore has become an important monitoring parameter and treatment goal in clinical research and practice.

HRQOL in HCC patients is a complicated and multidimensional issue that involves medical, psychological, social and spiritual factors. Apart from symptoms arising from HCC and its complications, underlying liver disease and oncological treatment are intertwined with other factors including palliative care service, social and spiritual support, individual's coping skill, patients' function and general well being as well as cultural background, educational level and health literacy.

Therefore HRQOL intrinsically is a multifaceted and complex assessment of human life. Assessment of HRQOL should be comprehensive. Various instruments have been developed to measure and report HRQOL in these patients, they also serve as a means to communicate and reflect on patient's overall well being.

HRQOL INSTRUMENTS UTILIZED TO ASSESS HCC PATIENTS

HRQOL assessment using general tools

HRQOL in HCC patients could be measured using general cancer QOL instruments, *e.g.*, the European Organization for Research and Treatment of Cancer QLQ-C30^[15], Functional Assessment of Cancer Therapy - General^[16], Spitzer Quality of Life Index^[17]; as well as general disease QOL instruments, *e.g.*, Short Form 36^[18], short form (SF) 12^[19], World Health Organization Quality of Life Assessment 100^[20], World Health Organization Quality of Life Assessment abbreviated version^[21], EuroQoL-5D^[22,23]. These are described in Table 1.

HRQOL assessment using liver-cancer specific tools

Since HCC patients commonly have symptoms related to concomitant underlying liver disease in addition to the tumor(s) within the liver, liver-cancer specific HRQOL instruments have been developed to address symptoms in relation to the malignancy as well as chronic liver disease. These include the European Organization for Research and Treatment of Cancer QLQ-HCC18^[24], Functional Assessment of Cancer Therapy-Hepatobiliary^[25], Functional Assessment of

Table 1 Health related quality of life instruments commonly used in hepatocellular carcinoma studies

General instruments	
European Organization for Research and Treatment of Cancer QLQ-C30	EORTC QLQ-C30 is a general cancer instrument containing multiple items, measured in multiple-point Likert scales, that reflect the multidimensionality of HRQOL construct ^[15] . It includes five functional domains (physical, role, cognitive, emotional and social), three symptom domains (fatigue, pain, nausea/vomiting), and a global health and QOL domain. Six single items assess common symptoms in cancer patients (dyspnea, appetite loss, sleep disturbance, constipation and diarrhea) and financial problem. All scales and domains are transformed to scores ranging from 0 to 100. A lower score for a functional or global QOL scale reflects a relatively poorer functioning level or global QOL, a higher score for a symptom/problem scale reflects a more disturbing symptom/problem
Functional Assessment of Cancer Therapy - General	The FACT-G questionnaire is a commonly used tool for HRQOL assessment in general cancer patients ^[16] . It consists of 27 items for assessment of symptoms and four domains of HRQOL: (1) physical well being (PWB) containing seven items with a subscale score ranging from 0 to 28 points; (2) socio-family well being (SFWB) containing seven items with a subscale score of 0-28 points; (3) emotional well being (EWB) containing six items with a subscale score of 0-24 points; and (4) functional well being (FWB) containing seven items with a subscale score of 0-28 points. Patients were asked to score each item according to how true each statement was to them during the past week on a 5-point ordinal scale, from 0 indicating "not at all" to 4 indicating "very much". The FACT-G total score is the summation of the four subscales (PWB, FWB, SFWB and EWB) scores and can range from 0 to 108. Higher scores reflect better HRQOL
Spitzer Quality of Life Index (Spitzer QoL index)	Spitzer QoL index is a general cancer HRQOL measurement ^[17] . A score of 0 (worst QOL) to 10 (best QoL) was calculated after the patient answered five items of the questionnaire in the areas of activity, daily life, health perceptions, social support and behavior. Each item is rated on a 3-point Likert scale
Short form 36	SF-36 is a general disease questionnaire to measure the following 8 domains of health: General health, bodily pain, social functioning, role-physical, physical functioning, vitality, role-emotional and mental health ^[18] . The raw scores of each subscale are converted to scores that range from 0 to 100, with higher scores indicating higher levels of functioning or well being. Scores representing overall physical functioning and mental functioning were calculated from the subscales and are grouped as the physical component summary scale and mental component summary scale
Short form 12	SF-12 is a shortened version of SF-36. It contains a 12-item generic measure of health status developed from SF-36 ^[19] . It also yields scores for eight domains: Physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. It likewise provides overall summaries of the physical and mental components
World Health Organization Quality of Life Assessment 100	The WHOQOL-100 questionnaire comprises of 100 items grouped into 25 facets ^[20] . One of the facets measures overall quality of life/health. The remaining 24 facets are organized in 6 domains: (1) physical health; (2) psychological health; (3) level of independence; (4) social relationships; (5) environment; and (6) spirituality/religion/personal beliefs. Each facet includes four items, rated on a 5-point Likert scale, with higher scores indicating more positive evaluations. Domain and facet raw scores can also be transformed onto a 0 to 100 scale. Higher scores denote higher HRQOL
World Health Organization Quality of Life Assessment abbreviated version	The original 6-domain structure of WHOQOL-100 was subsequently reduced into 4 comprehensive domains by the WHOQOL Group, comprising: (1) physical health (merging the level of independence domain); (2) psychological health (merging the spirituality/religion/personal beliefs domain); (3) social relationships; and (4) environment ^[21] . It contains a total of 26 questions. Attributes incorporated within the physical health domain of the WHOQOL-BREF include: activities of daily living, dependence on medicines or medical aids, energy and fatigue, mobility, pain and discomfort, sleep and rest and work capacity. Attributes incorporated within the psychological health domain are: body image and appearance, negative and positive feelings, self-esteem, spirituality, religion and personal beliefs, thinking, learning, memory and concentration. Measurements of social health domain include personal relationships, social support and sexual activity. Features incorporated in the environmental health domain are: Financial resources, freedom, physical safety and security, health and social care, home environment, opportunities for acquiring the new information and skills, participation in and opportunities for recreation, physical environment and transportation. Higher scores denote higher HRQOL
EuroQoL-5D	EQ-5D is a general disease instrument for describing and valuing HRQOL developed by the EuroQoL Group ^[22,23] . The questionnaire consists of 2 sections: The EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The descriptive system contains one question in each of the 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). In the 3-point Likert version (EQ-5D-3L), each question has three levels of response: No problems, some problems or extreme problems. A specific value (weight) is attached to each response of each question according to that country's specific value sets. Studies have been conducted to elicit preferences from general population samples to derive these value sets. A summary score is calculated by deducting all values of the 5 responses from the full mark of 1. A summary score of 1 represents perfect health, 0 represents death, below 0 represents a state being worse than dead. This summary score could be used for quality adjusted life-year (QALY) calculations. Thus EQ-5D is an important tool for economic valuation. The EQ VAS lets the respondent place an "x" on a vertical VAS to reflect his/her self rated health. The endpoints are labeled "best imaginable health state" at 100 and "worst imaginable health state" at 0

Liver-cancer specific instruments	
European Organization for Research and Treatment of Cancer QLQ-HCC18	EORTC QLQ-HCC18 includes eighteen multiple item scales organized into six domains (fatigue, body image, jaundice, nutrition, pain and fever) and two items (abdominal swelling and sex life) ^[24] . All scales are grouped and transformed to score ranging from 0 to 100. A lower score represents a less severe symptom/problem. EORTC QLQ-HCC18 is used together with EORTC QLQ-C30
Functional Assessment of Cancer Therapy-Hepatobiliary	The FACT-Hep questionnaire is a 45-item instrument for measuring HRQOL in patients with hepatobiliary cancers (liver, bile duct and pancreas) ^[25] . FACT-Hep is used together with FACT-G. It consists of the 27 items (PWB, FWB, SFWB and EWB domains) in FACT-G together with an 18-item disease-specific hepatobiliary cancer subscale (HepCS) which address specific symptoms of hepatobiliary carcinoma, such as back/stomach pain, gastrointestinal symptoms, anorexia, weight loss, jaundice, as well as side-effects of treatment. An aggregate HepCS score could be obtained. The FACT-G and HepCS scores are summed to form the FACT-Hep total score. Higher scores on all scales of the FACT-Hep reflect better HRQOL or fewer symptoms
Functional Assessment of Cancer Therapy-Hepatobiliary Symptom Index	FHSI-8 is a subset of FACT-Hep. It includes eight items from the FACT-Hep that measure specific symptoms of patient priority concern and side effects of hepatobiliary carcinoma ^[26] . Higher scores on all items of the FHSI-8 reflect fewer symptoms
Trial Outcome Index	TOI is also a subset of FACT-Hep. It consists of the summation of the PWB, FWB and HepCS subscales ^[25] . Higher scores reflect better HRQOL and fewer symptoms

EORTC QLQ-C30: European Organization for Research and Treatment of Cancer QLQ-C30; FACT-G: Functional Assessment of Cancer Therapy - General; QoL: Quality of Life; SF-36: Short form 36; SF-12: Short form 12; WHOQOL-100: World Health Organization Quality of Life Assessment 100; FACT-Hep: Functional Assessment of Cancer Therapy-Hepatobiliary; FHSI-8: Functional Assessment of Cancer Therapy - Hepatobiliary Symptom Index; TOI: Trial Outcome Index; HCC: Hepatocellular carcinoma; HRQOL: Health related quality of life.

Cancer Therapy-Hepatobiliary Symptom Index^[26] and Trial Outcome Index^[25]. Liver specific tools are used together with their general counterparts. See Table 1 for description of each instrument.

Validation of HRQOL instruments

All the above instruments were validated, many were widely validated in patients of different languages and cultural backgrounds^[15-17,19-21,25-30].

Validation of an HRQOL instrument encompasses reliability and validity analyses. Internal consistency reliability determines if there is satisfactory correlation between items within the same multi-item scale. Test-retest reliability assesses if there is good correlation between measurements of the same patient at 2 closely separated time points when major QOL discrepancy is not expected. Convergent validity tests for adequate correlation between conceptually related scales within the same instrument or a different validated instrument. Discriminant validity evaluates the ability to differentiate between patients of different clinical statuses. Responsiveness to change looks for significant change in score corresponding to patient's improvement or deterioration in condition with time. Good convergence and discrimination are required for scaling success to support the hypothesized scale structure. These are the essential statistical analyses to validate QOL instruments.

UTILIZATION OF HRQOL INSTRUMENTS

HRQOL assessments have been conducted in HCC patients in different settings, and these are listed in Table 2.

To describe symptomatology and HRQOL of HCC patients

Baseline QOL at HCC diagnosis: HRQOL instruments

were frequently used in HCC studies to assess baseline symptomatology and QOL of patients at presentation (Table 2). For instance, a case-control study compared baseline HRQOL of HCC patients at diagnosis with that of normal population^[31]. HCC patients had significantly worse physical domain QOL but better environmental QOL of WHOQOL-BREF compared to healthy controls. Another case-control study reported bodily pain, role limitation-physical and physical component summary of SF-36 were significantly worse in HCC patients compared to matched cirrhotic control^[32]. Similarly, another report found significantly worse physical, functional, emotional, social-family well-being and overall QOL of FACT-Hep in HCC patients when compared to general population; it also found significantly worse functional well-being and overall QOL in HCC patients when compared to controls with chronic liver disease^[33].

Observational studies with QOL assessment during treatment: Many case series on HCC patients undergoing surgical resection, liver transplantation, local ablation, SIRT or transarterial chemoembolisation (TACE) for HCC also reported patients' QOL.

HCC patients after curative intent treatment, for example partial hepatectomy, typically had transient deterioration in QOL followed by improvement of QOL. For long term survivors, their QOL could be comparable to that of control cirrhotic patients but worse than that of general population^[34-37]. Patients with recurrent disease after curative treatment had deterioration in QOL^[34].

In a prospective cohort study, 388 patients with solitary HCC of ≤ 3 cm were treated with either surgical resection or percutaneous RFA, there was no difference in DFS or OS between the 2 groups. However, FACT-Hep total scores at 3, 6, 12, 24, 36 mo post treatment were significantly better in percutaneous RFA group compared to resection group^[38].

Table 2 Clinical studies in hepatocellular carcinoma that involved health related quality of life assessment

Ref.	Year	Study type	n	HCC status	Intervention(s)	HRQOL instruments used	HRQOL assessment time point(s)	Remarks
Poon <i>et al.</i> ^[34]	2001	Cohort	76	Resectable and unresectable	Resection (66) <i>vs</i> TACE (10)	FACT-G	Baseline, 3, 6, 7, 12, 18 and 24 mo	Observational study with QOL assessment during treatment
Brans <i>et al.</i> ^[40]	2002	Cohort	26	Unresectable	SIRT (14) <i>vs</i> TACE (14)	EORTC QLQ-C30	Baseline, 1 and 3 mo	Observational study with QOL assessment during treatment
Bianchi <i>et al.</i> ^[32]	2002	Case-control	101	Any stage	NA	SF-36	Baseline	To describe symptomatology and/or HRQOL of HCC patients - HRQOL of HCC patients compared to 202 matched cirrhotic patients
Chow <i>et al.</i> ^[39]	2002	Phase III trial	329	Unresectable	Tamoxifen 120 mg/d (121) <i>vs</i> tamoxifen 60 mg/d (76) <i>vs</i> placebo (132)	Global QOL domain of EORTC QLQ-C30	Baseline, then every 1 mo	Phase III trial with HRQOL endpoint
Steel <i>et al.</i> ^[46]	2004	Cohort	28	Allocated to SIRT or TACE	SIRT (14) <i>vs</i> TACE (14)	FACT-Hep, HepCS, TOL, FHS18	Baseline, 3, 6 and 12 mo	Observational study with QOL assessment during treatment.
Poon <i>et al.</i> ^[47]	2004	Randomized phase II trial	88	Allocated to TACE	Branched chained amino acid <i>vs</i> control	FACT-G	Baseline, 3, 6, 9 and 12 mo	Included in ^[97] Phase II trial with HRQOL endpoint
Steel <i>et al.</i> ^[84]	2005	Cohort	82	Any stage	Various treatments	FACT-Hep, HepCS, TOL, FHS18	Baseline, 3 and 6 mo	To describe symptomatology and/or HRQOL of HCC patients - Compared HRQOL between patients and proxy-raters.
Steel <i>et al.</i> ^[86]	2005	Case-control	21	TNM stage III or IV	NA	FACT-Hep, Sexual History Questionnaire	Baseline	Included in ^[97] To describe symptomatology and/or HRQOL of HCC patients - Included 23 patients with chronic liver disease
Barbare <i>et al.</i> ^[88]	2005	Phase III trial	420	Not eligible for resection or local treatment	Tamoxifen (210) <i>vs</i> control (210)	Spitzer QoL index	Baseline, then every 3 mo	Phase III trial with HRQOL endpoint
Kirchhoff <i>et al.</i> ^[48]	2005	Randomized phase II trial	70	Eligible for TACE	TACE with microspheres (35) <i>vs</i> TACE (35)	Global QOL of EORTC QLQ-C30	Baseline, then every 6 mo	Phase II trial with HRQOL endpoint
Steel <i>et al.</i> ^[97]	2006	Combined analysis of 3 studies	157	Mixed patient populations from 3 studies	Various treatments	FACT-Hep, HepCS, TOL, FHS18	Baseline, 3 and 6 mo	Observational study with QOL assessment during treatment - evaluates minimally important difference in HRQOL
Eid <i>et al.</i> ^[36]	2006	Cohort	7	Allocated to hepatic ablation or resection	Hepatic ablation (3) <i>vs</i> resection (4)	EORTC QLQ-C30, FACT-Hep, FHS18, Profile of Mood States (POMS)	Baseline, postoperative visit, 1.5, 3 and 6 mo	Observational study with QOL assessment during treatment. Study included other liver tumor types (33 patients)
Yeo <i>et al.</i> ^[65]	2006	Combined analysis of 2 phase III trials	233	Unresectable or metastatic	Chemotherapy, hormonal therapy	EORTC QLQ-C30	Baseline	As prognostic tools for overall survival - baseline HRQOL was prognostic of overall survival in advanced HCC
Wang <i>et al.</i> ^[88]	2006	Cohort	83	Non-metastatic, 3 nodules or less	TACE + RFA (43) <i>vs</i> TACE (40)	FACT-G	Baseline, 3 mo	Observational study with QOL assessment during treatment
Cebon <i>et al.</i> ^[49]	2006	Phase I / II trial	63	Not eligible for standard therapies	Octreotide long acting release	FACT-Hep, patient disease and treatment assessment form (Pt DATA form), patient benefit form	Baseline, then every 1 mo	Phase I / II trial with HRQOL endpoint

	2006	Phase III trial	602	Not eligible for local treatment or had disease progression after surgery or local treatment	Sorafenib (299) <i>vs</i> placebo (303)	FHSL-8	Baseline then every 3 wk	Phase III trial with HRQOL endpoint
Lilovet <i>et al.</i> ^[12]								
Lee <i>et al.</i> ^[31]	2007	Case control	161	Any stage	Surgical, TACE, percutaneous ethanol injection, supportive care	EORTC QLQ-C30, WHOQOL-BREF	Cross sectional one-time assessment	To describe symptomatology and/or HRQOL of HCC patients - compared with national matched healthy controls
Kondo <i>et al.</i> ^[37]	2007	Case-control	97	Non-metastatic, 3 nodules or less	Percutaneous ablation	SF-36	Baseline	To describe symptomatology and/or HRQOL of HCC patients - HRQOL compared to 97 matched chronic liver disease controls, and normal population values
Steel <i>et al.</i> ^[33]	2007	Case-control	83	Any stage	NA	FACT-Hep	Baseline	To describe symptomatology and/or HRQOL of HCC patients - HRQOL compared to 51 matched chronic liver disease controls, and 138 controls from general population
Martin <i>et al.</i> ^[35]	2007	Cohort	4	Resectable	Resection	EORTC QLQ-C30, FACT-Hep, FHSL-8	Baseline, discharge, postoperative visit, 1.5, 3, 6 and 12 mo	Observational study with QOL assessment during treatment.
Becker <i>et al.</i> ^[50]	2007	Randomized phase II trial	120	Not eligible for resection or local treatment	Octreotide (61) <i>vs</i> placebo (59)	EORTC QLQ-C30	Baseline, 1, 3 mo, then every 3 mo	Included 28 patients with other liver tumors
Dimitroulopoulos <i>et al.</i> ^[51]	2007	Randomized phase II trial	127	Advanced stage. Somatostatin receptor overexpression for randomisation	Octreotide (31) <i>vs</i> placebo (30) observation (66)	EORTC QLQ-C30	Baseline then every 1 mo	Phase II trial with HRQOL endpoint
Sun <i>et al.</i> ^[99]	2008	Cohort	22	Mainly advanced disease	Various treatments	FACT-Hep, Functional assessment of chronic illness therapy spirituality subscale (FACIT-Sp-12)	Baseline, 1, 2 and 3 mo	Observational study with QOL assessment during treatment.
Méndez Romero <i>et al.</i> ^[52]	2008	Phase I / II trial	9	Not eligible for other local treatments	SBRT	EORTC QLQ-C30 EQ-5D VAS	Baseline, 1, 3 and 6 mo	Included 23 patients with pancreatic cancer
Bonnetain <i>et al.</i> ^[66]	2008	Combined analysis of 2 phase III trials ^[99,100]	538	Not eligible for resection, transplantation or percutaneous ablation	Tamoxifen <i>vs</i> supportive care; TACE + tamoxifen <i>vs</i> tamoxifen	Spitzer QoL index	Baseline	Observational study with QOL assessment during treatment. Included 19 patients with liver metastases. Phase I / II trial with HRQOL endpoint
Doffoël <i>et al.</i> ^[100]	2008	Phase III trial	138	Eligible for TACE	TACE + tamoxifen (70) <i>vs</i> tamoxifen (68)	Spitzer QoL index	Baseline, then every 2 mo during treatment, every 3 mo after treatment	As prognostic tools for overall survival - baseline HRQOL was prognostic of overall survival in advanced HCC
Barbare <i>et al.</i> ^[60]	2009	Phase III trial	272	Not eligible for curative treatment	Octreotide (135) <i>vs</i> placebo (137)	EORTC QLQ-C30	Baseline, then every 1 mo during treatment, every 3 mo after treatment	Phase III trial with HRQOL endpoint
Cheng <i>et al.</i> ^[13]	2009	Phase III trial	271	Unresectable or metastatic, no prior systemic therapy	Sorafenib (150) <i>vs</i> placebo (76)	FHSL-8, Physical well being domain of FACT-Hep	Baseline then every 3 wk	Phase III trial with HRQOL endpoint
Wible <i>et al.</i> ^[44]	2010	Cohort	73	Allocated to TACE	TACE	SF-36	Baseline, 4, 8 and 12 mo	Observational study with QOL assessment during treatment

Dollinger <i>et al</i> ^[101]	2010	Phase III trial	135	Locally advanced or metastatic	Thymostimulin (67) <i>vs</i> placebo (68)	FACT = Hep	Baseline then every 3 mo	Phase III trial with HRQOL endpoint
Chow <i>et al</i> ^[61]	2011	Phase III trial	204	Advanced disease, not eligible for standard therapies	Megestrol acetate (195) <i>vs</i> placebo (69)	EORTC QLQ-C30	Baseline, then every 1 mo during treatment, then every 3 mo after treatment completed	Phase III trial with HRQOL endpoint
Shun <i>et al</i> ^[102]	2012	Cohort	89	Allocated to TACE	TACE	SF-12, Symptom Distress Scale, Hospital Anxiety and Depression Scale	3 d before discharge, 1 and 2 mo	Observational study with QOL assessment during treatment
Qiao <i>et al</i> ^[103]	2012	Observational	140	Any stage	NANANAdadsfna	FACT-epHep	Baseline	To describe symptomatology and/or HRQOL of HCC patients - HRQOL worsens with advancing stage
Eltawil <i>et al</i> ^[45]	2012	Cohort	48	Allocated to TACE	TACE	WHOQOL-BREF	Baseline then every 3-4 mo	Observational study with QOL assessment during treatment
Fan <i>et al</i> ^[104]	2012	Cross sectional	286	Any stage		EORTC QLQ-C30, EORTC QLQ-HCC18	Baseline	To describe symptomatology and/or HRQOL of HCC patients - HRQOL compared with population norms. Correlation between HRQOL and coping and illness perception
Diouf <i>et al</i> ^[67]	2013	Reanalysis of a phase III trial ^[61]	215	Not eligible for curative treatment, baseline HRQOL data available	Octreotide <i>vs</i> placebo	EORTC QLQ-C30	Baseline	As prognostic tools for overall survival - baseline HRQOL was prognostic of overall survival in advanced HCC. HRQOL data may improve existing staging systems
Soliman <i>et al</i> ^[81]	2013	Phase II trial	21	Not eligible for or refractory to standard therapies, symptomatic	Liver radiotherapy	EORTC QLQ-C30, FACT-Hep, HepCS, TOL, FACT-G	Baseline, 1, 3 and 6 mo	Phase II trial with HRQOL endpoint. Included 20 patients with liver metastasis
Salem <i>et al</i> ^[41]	2013	Cohort	56	Allocated to SIRT or TACE	SIRT (29), TACE (27)	FACT-Hep	Baseline, 2 and 4 wk	Observational study with QOL assessment during treatment
Brunocilla <i>et al</i> ^[105]	2013	Cohort	36	Allocated to sorafenib	Sorafenib	FACT-Hep, FHSI-8, FACT-G	Baseline, 1 wk, 1 and 2 mo	Observational study with QOL assessment during treatment
Johnson <i>et al</i> ^[62]	2013	Phase III trial	1150	Not eligible for resection or local treatment, no prior systemic treatment	Brivanib (577) <i>vs</i> sorafenib (578)	Physical function and role function of EORTC QLQ-C30	Baseline then every 6 wk	Phase III trial with HRQOL endpoint
Meyer <i>et al</i> ^[63]	2013	Phase II / III trial	86	Unresectable, non-metastatic	TACE <i>vs</i> TAE	EORTC QLQ-C30, EORTC QLQ-HCC18	Baseline, 1.5, 3 and 6 mo	Phase II trial with HRQOL endpoint
Mise <i>et al</i> ^[106]	2014	Cohort	69	Allocated to resection	Resection	SF-36	Baseline then every 3 mo	Observational study with QOL assessment during treatment
Huang <i>et al</i> ^[88]	2014	Cohort	388	Solitary HCC ≤ 3 cm	Resection, radiofrequency ablation	FACT-Hep, HepCS, TOL, FACT-G	Baseline, 3, 6, 12, 24 and 36 mo	Observational study with QOL assessment during treatment
Zhu <i>et al</i> ^[64]	2014	Phase III trial	564	Progressive disease during or after sorafenib	Everolimus (362) <i>vs</i> placebo (184)	Global QOL and physical function of EORTC QLQ-C30	Baseline, then multiple reassessments	Phase III trial with HRQOL endpoint
Palmieri <i>et al</i> ^[107]	2015	Case control	24	Any stage	NA	SF-36	Baseline	To describe symptomatology and/or HRQOL of HCC patients - evaluates relationship between psychological profile and HRQOL in HCC. Included 22 cirrhotic patients without HCC, 20 control subjects
Chie <i>et al</i> ^[108]	2015	Cohort	171	Allocated to respective treatments	Surgery (53), ablation (53), TACE (65)	EORTC QLQ-C30, EORTC QLQ-HCC18	Baseline, then 4-6 wk for post-ablation/post-TACE, 12-15 wk post-operation	Observational study with QOL assessment during treatment

Heits <i>et al</i> ^[109]	2015	Cross sectional	173	Allocated to liver transplantation	liver transplantation	EORTC QLQ-C30	At one variable time point post-transplantation	To describe symptomatology and/or HRQOL of HCC patients
Xie <i>et al</i> ^[110]	2015	Cohort	102	Allocated to resection or TACE	resection (58), TACE (44)	SF-36	Baseline, 1, 3, 6, 12 and 24 mo	Observational study with QOL assessment during treatment
Xing <i>et al</i> ^[111]	2015	Cohort	118	Allocated to TACE	TACE with doxorubicin eluted beads	SF-36	Baseline, 1-3, 6 and 12 mo	Observational study with QOL assessment during treatment
Kolligs <i>et al</i> ^[54]	2015	Randomized phase II trial	28	Allocated to SIRT or TACE	SIRT (13), TACE (15)	FACT-Hep	Baseline, then every 6 wk	Phase II trial with HRQOL endpoint
Klein <i>et al</i> ^[42]	2015	Combined analysis of prior phase I/II trials	98	Allocated to SBRT	SBRT	EORTC QLQ-C30, FACT-Hep	Baseline, 1, 3, 6 and 12 mo	Phase I/II trial with HRQOL endpoint
Kensinger <i>et al</i> ^[48]	2016	Case-control	139	Allocated to priority liver transplantation	Liver transplantation	SF-36	Baseline, post transplantation	Observational study with QOL assessment during treatment - included 362 subjects without HCC
Lei <i>et al</i> ^[39]	2016	Cohort	205	Allocated to resection or transplantation	Liver transplantation (110), resection (95)	SF-36	Baseline, then every 1-2 mo for the first 6 mo, then every 2-3 mo for the next 6 mo, then every 6 mo	Observational study with QOL assessment during treatment
Yang <i>et al</i> ^[112]	2016	Cohort	17	Portal vein thrombosis	TACE and transarterial ethanol ablation	EORTC QLQ-C30	Baseline then every 1 mo	Observational study with QOL assessment during treatment
Anota <i>et al</i> ^[63]	2016	Phase I trial	21	Not eligible for curative treatment	TACE with idarubicin eluted beads	EORTC QLQ-C30	Baseline, 15, 30 and 60 d	Phase I trial with HRQOL endpoint
Chie <i>et al</i> ^[88]	2016	Case-control	227	Any stage	Various treatments	EORTC QLQ-C30, EORTC QLQ-HCC18	Baseline, post-treatment	Observational study with QOL assessment during treatment - Compared HRQOL between Asian and European HCC patients
Lv <i>et al</i> ^[56]	2016	Randomized phase II trial	120	Allocated to TACE	COX2 inhibitor (60) <i>vs</i> placebo (60)	Locally developed questionnaire	Baseline, 24 and 48 h	Phase II trial with HRQOL endpoint
Koeberle <i>et al</i> ^[57]	2016	Randomized phase II trial	106	Unresectable or metastatic	Sorafenib + everolimus (60) <i>vs</i> sorafenib (46)	FACT-HepCS, EQ-VAS	Baseline, then every 2 wk until week 12	Phase II trial with HRQOL endpoint
Shomura <i>et al</i> ^[113]	2016	Cohort	54	TNM stage IV	Sorafenib	SF-36	Baseline, then every 3 mo	Observational study with QOL assessment during treatment
Bruix <i>et al</i> ^[14]	2016	Phase III trial	573	Progressive disease during sorafenib	Regorafenib (379) <i>vs</i> placebo (193)	FACT-Hep, TOI, FACT-G, EQ-5D, EQ-VAS	Baseline, then multiple reassessments	Phase III trial with HRQOL endpoint
Li <i>et al</i> ^[69]	2017	Cohort	472	Any stage	Various treatments	EORTC QLQ-C30, EORTC QLQ-HCC18, C30 index score, HCC18 index score	Baseline	As prognostic tools for overall survival - baseline HRQOL was prognostic of overall survival in advanced HCC. QOL derived scoring system resembles a staging system

EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: EuroQoL-5D; FACT-G: Functional Assessment of Cancer Therapy - General; FACT-Hep: Functional Assessment of Cancer Therapy - Hepatobiliary; FHSI-8: Functional Assessment of Cancer Therapy - Hepatobiliary Symptom Index; HCC: Hepatocellular carcinoma; HepCS: Hepatobiliary cancer subscale; HRQOL: Health related quality of life; *n*: Sample size; NA: Not applicable; RFA: Radiofrequency ablation; SBRT: Stereotactic body radiation therapy; SF-12: Short Form 12; SF-36: Short Form 36; SIRT: Selective internal radiation therapy; Spitzer QoL Index: Spitzer Quality of Life Index; TACE: Transarterial chemoembolization; TOI: Trial Outcome Index; VAS: Visual analogue scale; WHOQOL-BREF: World Health Organization Quality of Life Assessment abbreviated version.

A surgical series compared post operative QOL using SF-36 between liver transplantation (*n* = 95) and resection (*n* = 110) in HCC patients fulfilling Milan's criteria. It reported no significant difference in all domains, physical component summary scale and mental component summary scale between these 2 cohorts. However it did not correlate with survival outcomes^[39].

Patients received palliative locoregional therapies, *e.g.*, TACE, SIRT, stereotactic body radiation therapy (SBRT) commonly reported early deterioration of HRQOL, which could be attributable to treatment toxicity^[40-43].

A case series reported HRQOL (SF-36) of HCC patients who received TACE^[44]. Overall patients' mental component summary scale improved at 4 mo after TACE. For patients received more than 2 cycles of TACE, their mental component summary scale improved after the initial 2 cycles of TACE, and their bodily pain score also improved. Another TACE series observed deterioration of physical health domain of WHOQOL-BREF that coincided with HCC progression^[45]. A cohort study using FACT-Hep reported better functional well-being and overall QOL in HCC patients after treatment with SIRT when compared to TACE^[46].

As clinical trials endpoint

HRQOL has been increasingly used as secondary endpoint in HCC clinical trials. Phase I / II trials put emphasis on treatment tolerability or toxicity, and thus QOL impact is a logical endpoint of interest. Quite a number of phase I / II HCC trials have QOL as secondary endpoints^[47-57] (Table 2).

QOL analysis in phase I / II clinical trials: A phase I / II trial assessed the use of octreotide in 63 untreatable HCC patients^[49]. Grade 3/4 toxicities were uncommon and responses were rare. QOL assessment using FACT-Hep was performed at baseline and every 1 mo afterwards. There was no significant change in reassessment QOL compared to baseline.

A combined analysis of 3 phase I / II trials of SBRT addressed the QOL of 98 HCC, 86 liver metastasis and 21 intrahepatic cholangiocarcinoma patients^[42]. EORTC QLQ-C30 and FACT-Hep were used for QOL assessment, which was scheduled at baseline, 1, 3, 6 and 12 mo. Overall the QOL deteriorated at 1 mo after SBRT, then recovered at 3 mo. Patients with liver metastasis had significantly better QOL at 1 and 6 mo than patients with primary liver cancer.

A randomized phase II trial evaluated TACE with microspheres vs TACE in 70 HCC patients^[48]. G4 toxicities were rare in both arms. Global QOL domain of EORTC QLQ-C30 was used for QOL monitoring, which was measured at baseline and every 3 mo afterwards. There was no significant difference in QOL in both arms.

QOL analysis in phase III clinical trials: Although phase III trials focus on evaluation of treatment efficacy, there is an increasing trend for these phase III clinical trials to incorporate HRQOL as a study endpoint. Effective treatment could improve QOL, whereas treatment-related toxicity, disease progression with ineffective treatment could worsen QOL. Thus it is important to investigate whether a treatment could

provide a net QOL benefit. Capturing HRQOL data in clinical trials could provide valuable information to guide clinicians in treatment decision. Commonly used tools included EORTC QLQ-C30, EORTC QLQ-HCC18, Spitzer QoL index, FACT-G, FACT-Hep, FHSI-8^[12-14,58-64] (Table 2). Some trials defined *a priori* 1-2 scales of interest within an HRQOL instrument as study endpoint, *e.g.*, global QOL or physical functioning domain of EORTC QLQ-C30^[59,60,64].

A phase III trial comparing first-line tamoxifen vs best supportive care alone in advanced HCC patients found no significant difference in OS in both arms. HRQOL, measured using Spitzer QoL index, decreased in both groups of patients with time^[58].

A phase III trial compared first-line megestrol acetate vs placebo in advanced HCC patients^[61]. There was no significant impact on OS with megestrol acetate. However, patients received megestrol acetate had significantly better scores in EORTC QLQ-C30 appetite loss, nausea/vomiting and emotional functioning scales compared to placebo. Such prospective randomized HRQOL data might provide rationale in using megestrol acetate for palliative symptom relief in advanced HCC patients.

The SHARP study and the phase III trial reported by Cheng *et al.*^[13] were pivotal trials demonstrating PFS and OS benefits of first-line sorafenib in advanced HCC patients compared to placebo^[12]. Drug related serious adverse events were more frequent in sorafenib arm than placebo arm in both studies. Both trials employed deterioration in FHSI-8 score as one of the definitions of symptomatic progression. In both trials, median time to symptomatic progression was not significantly different between sorafenib and placebo arms.

The phase III BRISK-FL study randomized 1150 advanced HCC patients to first-line brivanib or sorafenib^[62]. There was no significant difference in OS, time to tumor progression or response rate between the 2 arms. The overall incidence of serious adverse events was 56% for brivanib arm and 48% for sorafenib arm. The study used EORTC QLQ-C30 physical and role functioning domains as HRQOL endpoint. There was no significant difference in HRQOL at baseline between the 2 arms. The mean scores for physical and role functions declined at 12 wk in both brivanib and sorafenib patients, but the deterioration was significantly worse in brivanib arm. The objective of non-inferiority in OS was not met for brivanib. Should the objective be met, the available QOL could potentially be a key in guiding clinicians on the use of a more tolerable agent (in this case sorafenib) which has less impairment in QOL.

From these first-line trials on tyrosine kinase inhibitors, it appears that the toxicity profile of brivanib was worse than sorafenib, while that of sorafenib was worse than placebo. The deterioration in QOL may be due to treatment-related toxicities, which can be offset by improvement in QOL due to disease control by a more effective treatment. This postulation could

Table 3 Algorithm of C30 and HCC18 index scores

QOL Index scores for survival prognostication	
C30 index score	$\sum [(100\text{-Physical functioning}), (100\text{-Role functioning}), (100\text{-Emotional functioning}), (100\text{-Cognitive functioning}), (100\text{-Social functioning}), (100\text{-global QOL}), \text{scores of Fatigue, Nausea/vomiting, Pain, Dyspnoea, Insomnia, Appetite loss, Constipation, Diarrhea, Financial Difficulty}]/15$
HCC18 index score	$\sum (\text{scores of Fatigue, Body Image, Jaundice, Nutrition, Pain, Fever, Sex life, Abdominal distension})/8$

QOL: Quality of life.

theoretically be explored in a meta-analysis of these studies, however, the usage of different HRQOL instruments across studies precluded such an attempt.

In the EVOLVE-1 trial, HCC patients who failed sorafenib were treated with everolimus or placebo^[64]. Disease control rate was significantly better in the everolimus arm, but there was no significant difference in PFS or OS between the 2 arms. On the other hand, the time to definitive deterioration in EORTC QLQ-C30 physical functioning was significantly shorter in the everolimus arm. This might be related to the significantly increased incidence in grade 3/4 adverse events in the everolimus arm compared to the placebo arm. This study again exemplified the importance in inclusion of HRQOL assessment in clinical trial because the intervention itself could have negative effect on QOL.

The phase III RESORCE trial evaluated second-line regorafenib vs placebo in advanced HCC patients with prior sorafenib. Compared to placebo arm, patients randomized to regorafenib had significantly longer OS and PFS (using modified Response Evaluation Criteria in Solid Tumors for HCC), and reported more drug related adverse events. HRQOL was assessed using FACT-G, FACT-Hep, TOI, EQ-5D and EQ-VAS. The FACT-Hep total score and TOI were significantly lower in regorafenib arm than placebo arm, while FACT-G, EQ-5D and EQ-VAS were not significantly different^[14]. Cost-effectiveness analysis of this expensive intervention is essential in parts of the world where medical resources are particularly limited, the use of EQ-5D will allow such analysis to be conducted.

As prognostic tools for overall survival

One interesting use of HRQOL data in HCC patients is prognostication for OS. Three studies showed that in advanced HCC patients, baseline HRQOL at diagnosis was prognostic for OS^[65-67]. Our group reported the prognostic significance of EORTC QLQ-C30 in advanced HCC patients, where worse scores in appetite loss, physical function and role function domains were independent risk factors for shorter OS^[65]. In another study using EORTC QLQ-C30, better baseline role function score was found to be a significant prognostic factor for longer OS in advanced HCC patients^[67]. Baseline Spitzer QoL index was also reported to be prognostic of survival in 538 advanced HCC patients, where higher baseline Spitzer QoL index score was associated with longer OS^[66]. However, a study recruiting HCC patients

of all stages reported FACT-G was not prognostic of overall survival^[68].

Our group subsequently evaluated the prognostic value of baseline EORTC QLQ-C30 and QLQ-HCC18 in a cohort of newly diagnosed HCC patients including all stages and found both were significant prognostic factors for OS irrespective of stage of disease^[69]. Better scores in QLQ-C30 pain, QLQ-C30 physical functioning, QLQ-HCC18 pain, QLQ-HCC18 fatigue scales at diagnosis were significant independent prognostic factors for longer OS. In order to enhance the user-friendliness of these instruments, two summative scoring systems, the C30 index score and HCC18 index score, were derived. See Table 3 for the formulae.

Both of these scores were found to be highly significant factors for OS and their prognostic values resemble that of a staging system.

For C30 index score of 0-20, 21-40, 41-60, 61-100, the median OS were 16.4, 7.3, 3.1, 1.8 mo respectively ($P < 0.0001$). For HCC18 index score of 0-20, 21-40, 41-60, 61-100, the median OS were 16.4, 6.0, 2.8, 1.8 mo respectively ($P < 0.0001$).

Attempts have been made to enhance existing staging systems with HRQOL data^[66,67]. Addition of EORTC QLQ-C30 data has been shown to improve the performance of the Cancer of the Liver Italian Program (CLIP)^[70,71], the Barcelona Clinic Liver Cancer system^[72], the Groupe d'Étude et de Traitement du Carcinome Hépatocellulaire system^[73]. Spitzer QoL index could improve the prognostic value of CLIP^[66].

Valuation of health care service

Cost-effectiveness studies analyze the cost per outcome (effectiveness) of health care interventions, and compare this with reference to the country's willingness to pay threshold. In cancer setting, this outcome is commonly QALY. HRQOL measurement allows valuation of HRQOL specific to the population. When this is combined with time, QALY could be calculated^[74]. A popular instrument for this purpose is EQ-5D.

Certain treatments for HCC, such as liver transplantation and tyrosine kinase inhibitors, carry significant economic burden due to high utility and cost, particularly in areas with endemic hepatitis B viral infection. Cost-effectiveness analysis is therefore important to assist societal economic consideration by policy makers in health care service. A number of cost-effectiveness analyses in HCC have been carried out in this regard^[75-80].

Palliative care service benchmark

HRQOL is an important benchmark for palliative care service and clinical trial^[81]. Palliative care in cancer setting aims to improve QOL of cancer patients. It involves prevention, early identification and relief of sufferings (physical, psychological, social and spiritual) of cancer patients during the whole course of their illnesses. Therefore effective palliative care could be reflected in improvement in QOL.

Palliative care trials commonly recruit patients with a wide range of malignant diseases, including HCC. A prospective study conducted in Germany assessed the change in HRQOL using EORTC QLQ-C30 in cancer patients admitted to a hospital unit or palliative home care service where palliative treatment was given for symptoms relief^[82]. Of all the patients who received palliative service for 7 d, 57% had a better rating in symptom domains and 42% had a better rating in functional domains when compared to their rating before receiving the service.

DIFFICULTIES IN UTILIZATION OF HRQOL IN CLINICAL TRIAL AND PRACTICE

Prospective study design

Although retrospective analysis of QOL can be conducted, HRQOL data have to be prospectively collected to be usable. Unless an institute has routine HRQOL assessment for all patients, a retrospective study is impossible to have HRQOL as a parameter.

Choosing a suitable tool

Choosing a suitable HRQOL instrument for a study could be challenging. Although the majority of the mentioned instruments were extensively validated, which instrument prevails over another is largely unknown. The aim of a study and the characteristics of individual HRQOL instruments should be considered. If the symptom aspect of HRQOL was of interest, one may favor an instrument housing more liver-cancer related symptoms, for example, EORTC QLQ-C30 plus QLQ-HCC18, or FACT-Hep. One should also take into account the instrument's responsiveness to change with clinical condition in order to accurately capture significant HRQOL deterioration or improvement in subsequent reassessment time points. If follow-up cost-effectiveness analysis of an intervention is anticipated, the study needs to include an instrument with QOL valuation ability, for example, EQ-5D.

Missing data

Missing data is common in HRQOL studies, and inadequate reporting and handling of missing data are also common^[83]. Analysis of incomplete data could give biased results. Therefore missing data should be prevented, identified and handled appropriately.

Prevention of missing data should be planned before a study begins. As opposed to survival data

that could be captured even when patients have succumbed, follow-up QOL assessment relies mainly on active participation of patients. They need to have adequate physical and cognitive function and motivation to answer relevant questionnaires. This could be demanding to patients with deteriorated clinical status. This proves particularly challenging in clinical trial involving advanced HCC patients because their PFS generally is short and the clinical downhill course can be rapid. More frequent HRQOL reassessment may maximize the capture of HRQOL data before significant clinical deterioration occurs. Proxy (treating clinicians or patients' care-giver) filled questionnaires could be a reasonable substitute^[84] but still creates significant bias because HRQOL is a personal and subjective measurement. Computerized questionnaire during follow up visit could be programmed to forbid submission of incomplete questionnaire. Patients may forget to return reassessment questionnaires by mail if such system is utilized. Some studies employed reminder system to reduce this non-compliance.

When missing data occurred, it is essential to identify the mechanism of missing data and tackle it accordingly. There are 3 mechanisms of missing data: (1) missing completely at random (MCAR): MCAR is said to occur if the reason of missing data is unrelated to any variable of the study. For example, an on-site hand-held device for HRQOL assessment broke down for a certain period of time; (2) missing at random (MAR): If the reason of missing data was related to non-QOL data, MAR is present. For example, elderly patients are more prone to forget returning the reassessment questionnaire by mail than younger patients; and (3) missing not at random (MNAR): MNAR is assumed when the reason of missing data is related to the QOL data. For example, severely ill patients with the worse QOL may feel too weak to complete reassessment questionnaires.

MCAR and MAR are categorized as ignorable missingness. Whereas MNAR is categorized as non-ignorable missingness, because the observed (available) QOL data are typically biased. Therefore it is important to investigate the mechanism of missing data in order to employ specific method of handling. Various statistical methods have been established to investigate the mechanism of missing data^[85]. Nevertheless, confirmation of the underlying mechanism may not be possible. Once assumption of the mechanism is made, appropriate method to deal with missing data follows^[86].

The following are the methods to handle missing data: (1) complete case analysis: Patients with missing data are excluded from the analysis; (2) single imputation: Single imputation replaces a missing value by a single value and analysis is carried out as if all data are observed. The replacement value could be the mean or mode of observed data, last observed value carried forward, baseline observed value carried forward, or predicted value from a regression equation based on information from observed data. Single imputation

may have a higher risk of biasing the analysis because the uncertainty of imputed values was not addressed; (3) multiple imputation: Multiple imputation generates multiple copies of the original dataset by replacing missing values using a specified regression model. Analysis is then performed for each dataset and the results are pooled into one estimate with standard error taking into account the uncertainty of the imputation process; and (4) statistical models: Mixed models and generalized estimating equations could be used to allow for missing data without imputation, making assumptions about their relationships with the observed data.

Option (1) will only be unbiased in case of MCAR or MAR. For MNAR, options (2-4) are more appropriate. Sensitivity analysis is then carried out. It involves separate analysis of every dataset generated by various imputation methods and comparison of the results. Sensitivity analysis reflects whether an analysis is robust (insignificant distortion of conclusion) after handling of missing data^[87]. These are the key steps to minimize the detrimental effect of missing data on the results of QOL studies.

Population related difference in HRQOL

HRQOL changes significantly across different diseases, cultures and ethnicities. For example, in Chinese culture people take endurance as a merit, they often minimize the verbalization or expression of discomfort, thus symptoms scales might underestimate their symptomatology. Oriental culture tends not to discuss sex issue openly, therefore missing data rate in the sexual problem scale could be particularly high. Different languages and dialects could also affect patient's interpretation of the intended questions. Therefore HRQOL instruments need validation in different countries, since HRQOL data from one country may not be applicable to another.

This is evident in a study that compared HRQOL between Asian and European HCC patients^[88]. It reported significantly better scores in emotional functioning and insomnia (based on EORTC QLQ-C30) and sexual interest (based on EORTC QLQ-HCC18) in Asian when compared to European patients, after adjusting for demographic and clinical variables.

Data interpretation

Most HRQOL instruments consist of a collection of scores in various domains. How can one define a domain score being significantly good or bad? How can one define a clinically significant change in a domain score? Attempts have been made to evaluate minimally important differences in HRQOL measurements by comparing the scores among different patient groups stratified according to various clinical anchors, for example, stage of disease, performance status, *etc*^[89-92]. This permits meaningful interpretation of HRQOL data. Studies sometimes employed these findings to

define their HRQOL endpoints. However caution has to be exercised as these cutoffs or thresholds might be population- or disease-specific and might not be applicable to all.

Data analysis

Raw HRQOL ordinal data are commonly used as continuous variables in data analysis. Analysis is usually in the form of comparison of mean domain score between 2 patient groups or 2 time points within the same group. The situation is complicated by the fact that when all domain scores are included in a multivariate analysis model, the numerous raw HRQOL data could cause excessive multiple comparisons and instability of model^[93,94].

Studies using limited number of domains within an HRQOL instrument may have avoided such problem, but may sacrifice potentially significant HRQOL variables.

Diouf *et al*^[67] dichotomized all EORTC QLQ-C30 scale scores using 50 as an empirical cut-off for analysis. This may prevent overfitting and multi-collinearity and allows clinicians to understand HRQOL data in a simpler manner. As these cut-offs were supposed to be population-specific, another analysis was performed and reported the real cut-off for various scales^[95].

Another way of HRQOL data analysis while avoiding multi-collinearity, yet without sacrificing any QOL data, is to use 1 score to represent all scales in the whole instrument. As discussed earlier, by transforming the EORTC QLQ-C30 into C30 index score, and EORTC QLQ-HCC18 into HCC18 index score for data analysis, our group has shown that these index scores were the most significant independent factors for OS among all the individual HRQOL variables, whether continuous or dichotomized^[69].

Different studies used different HRQOL instruments. QOL data, unlike survival data or response assessment, are not unified to allow cross trial communication. Cross study comparison of HRQOL result is not usually possible. Performing meta-analysis on HRQOL studies is therefore difficult.

Limitation for use in clinical practice

Measurement of HRQOL in clinical practice is desirable. QOL changes over time in HCC patients when their diseases improve or progress, or when treatment complications arise. Deterioration in QOL reflects the need for palliative care intervention. However routine capturing of QOL data is difficult. Filling in the instruments, calculating all domain and total scores could be cumbersome in the clinical setting. Difficulty in interpretation of a collection of numerical scores also deters a clinician from welcoming it. Modern hand-held device might help patients to self-administer the questionnaires during waiting time, it can help generate all domain and total scores automatically, as well as support interpretation of individual score according to published local reference values.

CONCLUSION

Quality of life could be as important as survival in HCC patients because majority of them have advanced disease and limited survival. QOL measurement provides valuable information in clinical practice and research. Future research into utilization in clinical trials as well as routine clinical practice are warranted.

REFERENCES

- Chin PL, Chu DZ, Clarke KG, Odom-Maryon T, Yen Y, Wagman LD. Ethnic differences in the behavior of hepatocellular carcinoma. *Cancer* 1999; **85**: 1931-1936 [PMID: 10223232 DOI: 10.1002/(SICI)1097-0142(19990501)85:9<1931::AID-CNCR8>3.0.CO;2-O]
- Hsu C, Shen YC, Cheng CC, Hu FC, Cheng AL. Geographic difference in survival outcome for advanced hepatocellular carcinoma: implications on future clinical trial design. *Contemp Clin Trials* 2010; **31**: 55-61 [PMID: 19737631 DOI: 10.1016/j.cct.2009.08.002]
- Zhang BH, Yang BH, Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma. *J Cancer Res Clin Oncol* 2004; **130**: 417-422 [PMID: 15042359 DOI: 10.1007/s00432-004-0552-0]
- Regimbeau JM, Kianmanesh R, Farges O, Dondero F, Sauvanet A, Belghiti J. Extent of liver resection influences the outcome in patients with cirrhosis and small hepatocellular carcinoma. *Surgery* 2002; **131**: 311-317 [PMID: 11894036]
- Marubashi S, Gotoh K, Akita H, Takahashi H, Ito Y, Yano M, Ishikawa O, Sakon M. Anatomical versus non-anatomical resection for hepatocellular carcinoma. *Br J Surg* 2015; **102**: 776-784 [PMID: 25847111 DOI: 10.1002/bjs.9815]
- Sala M, Llovet JM, Vilana R, Bianchi L, Solé M, Ayuso C, Brú C, Bruix J. Initial response to percutaneous ablation predicts survival in patients with hepatocellular carcinoma. *Hepatology* 2004; **40**: 1352-1360 [PMID: 15565564 DOI: 10.1002/hep.20465]
- Chen MS, Li JQ, Zheng Y, Guo RP, Liang HH, Zhang YQ, Lin XJ, Lau WY. A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma. *Ann Surg* 2006; **243**: 321-328 [PMID: 16495695 DOI: 10.1097/01.sla.0000201480.65519.b8]
- Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, Montalto F, Ammatuna M, Morabito A, Gennari L. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996; **334**: 693-699 [PMID: 8594428 DOI: 10.1056/nejm199603143341104]
- Llovet JM, Real MI, Montaña X, Planas R, Coll S, Aponte J, Ayuso C, Sala M, Muchart J, Solà R, Rodés J, Bruix J. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet* 2002; **359**: 1734-1739 [PMID: 12049862 DOI: 10.1016/S0140-6736(02)08649-X]
- Lo CM, Ngan H, Tso WK, Liu CL, Lam CM, Poon RT, Fan ST, Wong J. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. *Hepatology* 2002; **35**: 1164-1171 [PMID: 11981766 DOI: 10.1053/jhep.2002.33156]
- Sangro B, Salem R, Kennedy A, Coldwell D, Wasan H. Radioembolization for hepatocellular carcinoma: a review of the evidence and treatment recommendations. *Am J Clin Oncol* 2011; **34**: 422-431 [PMID: 20622645 DOI: 10.1097/COC.0b013e3181df0a50]
- Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, Santoro A, Raoul JL, Forner A, Schwartz M, Porta C, Zeuzem S, Bolondi L, Greten TF, Galle PR, Seitz JF, Borbath I, Häussinger D, Giannaris T, Shan M, Moscovici M, Voliotis D, Bruix J. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008; **359**: 378-390 [PMID: 18650514 DOI: 10.1056/NEJMoa0708857]
- Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, Luo R, Feng J, Ye S, Yang TS, Xu J, Sun Y, Liang H, Liu J, Wang J, Tak WY, Pan H, Burock K, Zou J, Voliotis D, Guan Z. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 2009; **10**: 25-34 [PMID: 19095497 DOI: 10.1016/s1470-2045(08)70285-7]
- Bruix J, Qin S, Merle P, Granito A, Huang YH, Bodoky G, Pracht M, Yokosuka O, Rosmorduc O, Breder V, Gerolami R, Masi G, Ross PJ, Song T, Bronowicki JP, Ollivier-Hourmand I, Kudo M, Cheng AL, Llovet JM, Finn RS, LeBerre MA, Baumhauer A, Meinhardt G, Han G. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2017; **389**: 56-66 [PMID: 27932229 DOI: 10.1016/s0140-6736(16)32453-9]
- Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, Filiberti A, Flechtner H, Fleishman SB, de Haes JC. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993; **85**: 365-376 [PMID: 8433390]
- Cella DF, Tulskey DS, Gray G, Sarafian B, Linn E, Bonomi A, Silberman M, Yellen SB, Winicour P, Brannon J. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *J Clin Oncol* 1993; **11**: 570-579 [PMID: 8445433]
- Spitzer WO, Dobson AJ, Hall J, Chesterman E, Levi J, Shepherd R, Battista RN, Catchlove BR. Measuring the quality of life of cancer patients: a concise QL-index for use by physicians. *J Chronic Dis* 1981; **34**: 585-597 [PMID: 7309824]
- Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992; **30**: 473-483 [PMID: 1593914]
- Ware J, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med Care* 1996; **34**: 220-233 [PMID: 8628042]
- The World Health Organization Quality of Life Assessment (WHOQOL): development and general psychometric properties. *Soc Sci Med* 1998; **46**: 1569-1585 [PMID: 9672396]
- Development of the World Health Organization WHOQOL-BREF quality of life assessment. The WHOQOL Group. *Psychol Med* 1998; **28**: 551-558 [PMID: 9626712]
- EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. *Health Policy* 1990; **16**: 199-208 [PMID: 10109801]
- Brooks R. EuroQol: the current state of play. *Health Policy* 1996; **37**: 53-72 [PMID: 10158943]
- Blazeby JM, Currie E, Zee BC, Chie WC, Poon RT, Garden OJ. Development of a questionnaire module to supplement the EORTC QLQ-C30 to assess quality of life in patients with hepatocellular carcinoma, the EORTC QLQ-HCC18. *Eur J Cancer* 2004; **40**: 2439-2444 [PMID: 15519517 DOI: 10.1016/j.ejca.2004.06.033]
- Heffernan N, Cella D, Webster K, Odom L, Martone M, Passik S, Bookbinder M, Fong Y, Jarnagin W, Blumgart L. Measuring health-related quality of life in patients with hepatobiliary cancers: the functional assessment of cancer therapy-hepatobiliary questionnaire. *J Clin Oncol* 2002; **20**: 2229-2239 [PMID: 11980994]
- Yount S, Cella D, Webster K, Heffernan N, Chang C, Odom L, van Gool R. Assessment of patient-reported clinical outcome in pancreatic and other hepatobiliary cancers: the FACT Hepatobiliary Symptom Index. *J Pain Symptom Manage* 2002; **24**: 32-44 [PMID: 12183093 DOI: 10.1016/S0885-3924(02)00422-0]
- Chie WC, Blazeby JM, Hsiao CF, Chiu HC, Poon RT, Mikoshiba N, Al-Kadhimi G, Heaton N, Calara J, Collins P, Caddick K, Costantini A, Vilgrain V, Trinquart L, Chiang C. International cross-cultural field validation of an European Organization for Research and Treatment of Cancer questionnaire module for patients with primary liver cancer, the European Organization for

- Research and Treatment of Cancer quality-of-life questionnaire HCC18. *Hepatology* 2012; **55**: 1122-1129 [PMID: 22105642 DOI: 10.1002/hep.24798]
- 28 **Mikoshiba N**, Tateishi R, Tanaka M, Sakai T, Blazeby JM, Kokudo N, Koike K, Kazuma K. Validation of the Japanese version of the EORTC hepatocellular carcinoma-specific quality of life questionnaire module (QLQ-HCC18). *Health Qual Life Outcomes* 2012; **10**: 58 [PMID: 22651810 DOI: 10.1186/1477-7525-10-58]
 - 29 **Ware JE**. SF-36 health survey update. *Spine (Phila Pa 1976)* 2000; **25**: 3130-3139 [PMID: 11124729]
 - 30 **Pickard AS**, Wilke CT, Lin HW, Lloyd A. Health utilities using the EQ-5D in studies of cancer. *Pharmacoeconomics* 2007; **25**: 365-384 [PMID: 17488136]
 - 31 **Lee LJ**, Chen CH, Yao G, Chung CW, Sheu JC, Lee PH, Tsai YJ, Wang JD. Quality of life in patients with hepatocellular carcinoma received surgical resection. *J Surg Oncol* 2007; **95**: 34-39 [PMID: 17192864 DOI: 10.1002/jso.20374]
 - 32 **Bianchi G**, Loguercio C, Sgarbi D, Abbiati R, Brunetti N, De Simone T, Zoli M, Marchesini G. Reduced quality of life of patients with hepatocellular carcinoma. *Dig Liver Dis* 2003; **35**: 46-54 [PMID: 12725608]
 - 33 **Steel JL**, Chopra K, Olek MC, Carr BI. Health-related quality of life: Hepatocellular carcinoma, chronic liver disease, and the general population. *Qual Life Res* 2007; **16**: 203-215 [PMID: 17119847 DOI: 10.1007/s11136-006-9111-2]
 - 34 **Poon RT**, Fan ST, Yu WC, Lam BK, Chan FY, Wong J. A prospective longitudinal study of quality of life after resection of hepatocellular carcinoma. *Arch Surg* 2001; **136**: 693-699 [PMID: 11387012]
 - 35 **Martin RC**, Eid S, Scoggins CR, McMasters KM. Health-related quality of life: return to baseline after major and minor liver resection. *Surgery* 2007; **142**: 676-684 [PMID: 17981187 DOI: 10.1016/j.surg.2007.04.026]
 - 36 **Eid S**, Stromberg AJ, Ames S, Ellis S, McMasters KM, Martin RC. Assessment of symptom experience in patients undergoing hepatic resection or ablation. *Cancer* 2006; **107**: 2715-2722 [PMID: 17075874 DOI: 10.1002/cncr.22297]
 - 37 **Kondo Y**, Yoshida H, Tateishi R, Shiina S, Mine N, Yamashiki N, Sato S, Kato N, Kanai F, Yanase M, Yoshida H, Akamatsu M, Teratani T, Kawabe T, Omata M. Health-related quality of life of chronic liver disease patients with and without hepatocellular carcinoma. *J Gastroenterol Hepatol* 2007; **22**: 197-203 [PMID: 17295871 DOI: 10.1111/j.1440-1746.2006.04456.x]
 - 38 **Huang G**, Chen X, Lau WY, Shen F, Wang RY, Yuan SX, Geng WX, Zhou WP. Quality of life after surgical resection compared with radiofrequency ablation for small hepatocellular carcinomas. *Br J Surg* 2014; **101**: 1006-1015 [PMID: 24863168 DOI: 10.1002/bjs.9539]
 - 39 **Lei JY**, Yan LN, Wang WT, Zhu JQ, Li DJ. Health-Related Quality of Life and Psychological Distress in Patients With Early-Stage Hepatocellular Carcinoma After Hepatic Resection or Transplantation. *Transplant Proc* 2016; **48**: 2107-2111 [PMID: 27569954 DOI: 10.1016/j.transproceed.2016.04.012]
 - 40 **Brans B**, Lambert B, De Beule E, De Winter F, Van Belle S, Van Vlierberghe H, de Hemptinne B, Dierckx RA. Quality of life assessment in radionuclide therapy: a feasibility study of the EORTC QLQ-C30 questionnaire in palliative (131)I-lipiodol therapy. *Eur J Nucl Med Mol Imaging* 2002; **29**: 1374-1379 [PMID: 12271421 DOI: 10.1007/s00259-002-0918-y]
 - 41 **Salem R**, Gilbertsen M, Butt Z, Memon K, Vouche M, Hickey R, Baker T, Abecassis MM, Atassi R, Riaz A, Cella D, Burns JL, Ganger D, Benson AB, Mulcahy MF, Kulik L, Lewandowski R. Increased quality of life among hepatocellular carcinoma patients treated with radioembolization, compared with chemoembolization. *Clin Gastroenterol Hepatol* 2013; **11**: 1358-1365.e1 [PMID: 23644386 DOI: 10.1016/j.cgh.2013.04.028]
 - 42 **Klein J**, Dawson LA, Jiang H, Kim J, Dinniwell R, Brierley J, Wong R, Lockwood G, Ringash J. Prospective Longitudinal Assessment of Quality of Life for Liver Cancer Patients Treated With Stereotactic Body Radiation Therapy. *Int J Radiat Oncol Biol Phys* 2015; **93**: 16-25 [PMID: 26279020 DOI: 10.1016/j.ijrobp.2015.04.016]
 - 43 **Ahmed S**, de Souza NN, Qiao W, Kasai M, Keem LJ, Shelat VG. Quality of life in HCC Patients Treated with Transarterial Chemoembolization. *HPB Surg* 2016; **2016**: 6120143 [PMID: 27143815 DOI: 10.1155/2016/6120143]
 - 44 **Wible BC**, Rilling WS, Drescher P, Hieb RA, Saeian K, Frangakis C, Chen Y, Eastwood D, Kim HS. Longitudinal quality of life assessment of patients with hepatocellular carcinoma after primary transarterial chemoembolization. *J Vasc Interv Radiol* 2010; **21**: 1024-1030 [PMID: 20621715 DOI: 10.1016/j.jvir.2010.03.005]
 - 45 **Eltawil KM**, Berry R, Abdoell M, Molinari M. Quality of life and survival analysis of patients undergoing transarterial chemoembolization for primary hepatic malignancies: a prospective cohort study. *HPB (Oxford)* 2012; **14**: 341-350 [PMID: 22487072 DOI: 10.1111/j.1477-2574.2012.00455.x]
 - 46 **Steel J**, Baum A, Carr B. Quality of life in patients diagnosed with primary hepatocellular carcinoma: hepatic arterial infusion of Cisplatin versus 90-Yttrium microspheres (Therasphere). *Psychooncology* 2004; **13**: 73-79 [PMID: 14872525 DOI: 10.1002/pon.725]
 - 47 **Poon RT**, Yu WC, Fan ST, Wong J. Long-term oral branched chain amino acids in patients undergoing chemoembolization for hepatocellular carcinoma: a randomized trial. *Aliment Pharmacol Ther* 2004; **19**: 779-788 [PMID: 15043519 DOI: 10.1111/j.1365-2036.2004.01920.x]
 - 48 **Kirchhoff TD**, Rudolph KL, Layer G, Chavan A, Greten TF, Rosenthal H, Kubicka S, Galanski M, Manns MP, Schild H, Gallkowski U. Chemoocclusion vs chemoperfusion for treatment of advanced hepatocellular carcinoma: a randomised trial. *Eur J Surg Oncol* 2006; **32**: 201-207 [PMID: 16373084 DOI: 10.1016/j.ejso.2005.11.003]
 - 49 **Cebon J**, Findlay M, Hargreaves C, Stockler M, Thompson P, Boyer M, Roberts S, Poon A, Scott AM, Kalff V, Garas G, Dowling A, Crawford D, Ring J, Bassar R, Strickland A, Macdonald G, Green M, Nowak A, Dickman B, Dhillon H, GebSKI V. Somatostatin receptor expression, tumour response, and quality of life in patients with advanced hepatocellular carcinoma treated with long-acting octreotide. *Br J Cancer* 2006; **95**: 853-861 [PMID: 16953241 DOI: 10.1038/sj.bjc.6603325]
 - 50 **Becker G**, Allgaier HP, Olschewski M, Zähringer A, Blum HE. Long-acting octreotide versus placebo for treatment of advanced HCC: a randomized controlled double-blind study. *Hepatology* 2007; **45**: 9-15 [PMID: 17187405 DOI: 10.1002/hep.21468]
 - 51 **Dimitroulopoulos D**, Xinopoulos D, Tsamakidis K, Zisimopoulos A, Andriotis E, Panagiotakos D, Fotopoulou A, Chrysoshoou C, Bazinis A, Daskalopoulou D, Paraskevas E. Long acting octreotide in the treatment of advanced hepatocellular cancer and overexpression of somatostatin receptors: randomized placebo-controlled trial. *World J Gastroenterol* 2007; **13**: 3164-3170 [PMID: 17589893 DOI: 10.3748/wjg.v13.i13.3164]
 - 52 **Méndez Romero A**, Wunderink W, van Os RM, Nowak PJ, Heijmen BJ, Nuytens JJ, Brandwijk RP, Verhoef C, Ijzermans JN, Levendag PC. Quality of life after stereotactic body radiation therapy for primary and metastatic liver tumors. *Int J Radiat Oncol Biol Phys* 2008; **70**: 1447-1452 [PMID: 17996394 DOI: 10.1016/j.ijrobp.2007.08.058]
 - 53 **Soliman H**, Ringash J, Jiang H, Singh K, Kim J, Dinniwell R, Brade A, Wong R, Brierley J, Cummings B, Zimmermann C, Dawson LA. Phase II trial of palliative radiotherapy for hepatocellular carcinoma and liver metastases. *J Clin Oncol* 2013; **31**: 3980-3986 [PMID: 24062394 DOI: 10.1200/jco.2013.49.9202]
 - 54 **Kolligs FT**, Bilbao JJ, Jakobs T, Iñárraiaegui M, Nagel JM, Rodriguez M, Haug A, D'Avola D, op den Winkel M, Martínez-Cuesta A, Trumm C, Benito A, Tatsch K, Zech CJ, Hoffmann RT, Sangro B. Pilot randomized trial of selective internal radiation therapy vs. chemoembolization in unresectable hepatocellular carcinoma. *Liver Int* 2015; **35**: 1715-1721 [PMID: 25443863 DOI: 10.1111/liv.12750]
 - 55 **Anota A**, Boulin M, Dabakuyo-Yonli S, Hillon P, Cercueil JP,

- Minello A, Jouve JL, Paoletti X, Bedenne L, Guieu B, Bonnetain F. An explorative study to assess the association between health-related quality of life and the recommended phase II dose in a phase I trial: idarubicin-loaded beads for chemoembolisation of hepatocellular carcinoma. *BMJ Open* 2016; **6**: e010696 [PMID: 27342239 DOI: 10.1136/bmjopen-2015-010696]
- 56 **Lv N**, Kong Y, Mu L, Pan T, Xie Q, Zhao M. Effect of perioperative parecoxib sodium on postoperative pain control for transcatheter arterial chemoembolization for inoperable hepatocellular carcinoma: a prospective randomized trial. *Eur Radiol* 2016; **26**: 3492-3499 [PMID: 26801163 DOI: 10.1007/s00330-016-4207-8]
- 57 **Koeberle D**, Dufour JF, Demeter G, Li Q, Ribi K, Samaras P, Saletti P, Roth AD, Horber D, Buehlmann M, Wagner AD, Montemurro M, Lakatos G, Feilchenfeldt J, Peck-Radosavljevic M, Rauch D, Tschanz B, Bodoky G. Sorafenib with or without everolimus in patients with advanced hepatocellular carcinoma (HCC): a randomized multicenter, multinational phase II trial (SAKK 77/08 and SASL 29). *Ann Oncol* 2016; **27**: 856-861 [PMID: 26884590 DOI: 10.1093/annonc/mdw054]
- 58 **Barbare JC**, Bouché O, Bonnetain F, Raoul JL, Rougier P, Abergel A, Boige V, Denis B, Blanchi A, Pariente A, Milan C, Bedenne L. Randomized controlled trial of tamoxifen in advanced hepatocellular carcinoma. *J Clin Oncol* 2005; **23**: 4338-4346 [PMID: 15994145 DOI: 10.1200/jco.2005.05.470]
- 59 **Chow PK**, Tai BC, Tan CK, Machin D, Win KM, Johnson PJ, Soo KC. High-dose tamoxifen in the treatment of inoperable hepatocellular carcinoma: A multicenter randomized controlled trial. *Hepatology* 2002; **36**: 1221-1226 [PMID: 12395333 DOI: 10.1053/jhep.2002.36824]
- 60 **Barbare JC**, Bouché O, Bonnetain F, Dahan L, Lombard-Bohas C, Faroux R, Raoul JL, Cattani S, Lemoine A, Blanc JF, Bronowicki JP, Zarski JP, Cazorla S, Gargot D, Thevenot T, Diaz E, Bastie A, Aparicio T, Bedenne L. Treatment of advanced hepatocellular carcinoma with long-acting octreotide: a phase III multicentre, randomised, double blind placebo-controlled study. *Eur J Cancer* 2009; **45**: 1788-1797 [PMID: 19303768 DOI: 10.1016/j.ejca.2009.02.018]
- 61 **Chow PK**, Machin D, Chen Y, Zhang X, Win KM, Hoang HH, Nguyen BD, Jin MY, Lobo R, Findlay M, Lim CH, Tan SB, Gandhi M, Soo KC. Randomised double-blind trial of megestrol acetate vs placebo in treatment-naive advanced hepatocellular carcinoma. *Br J Cancer* 2011; **105**: 945-952 [PMID: 21863030 DOI: 10.1038/bjc.2011.333]
- 62 **Johnson PJ**, Qin S, Park JW, Poon RT, Raoul JL, Philip PA, Hsu CH, Hu TH, Heo J, Xu J, Lu L, Chao Y, Boucher E, Han KH, Paik SW, Robles-Aviña J, Kudo M, Yan L, Sobhonslidsuk A, Komov D, Decaens T, Tak WY, Jeng LB, Liu D, Ezzeddine R, Walters I, Cheng AL. Brivanib versus sorafenib as first-line therapy in patients with unresectable, advanced hepatocellular carcinoma: results from the randomized phase III BRISK-FL study. *J Clin Oncol* 2013; **31**: 3517-3524 [PMID: 23980084 DOI: 10.1200/jco.2012.48.4410]
- 63 **Meyer T**, Kirkwood A, Roughton M, Beare S, Tsochatzis E, Yu D, Davies N, Williams E, Pereira SP, Hochhauser D, Mayer A, Gillmore R, O'Beirne J, Patch D, Burroughs AK. A randomised phase II/III trial of 3-weekly cisplatin-based sequential transarterial chemoembolisation vs embolisation alone for hepatocellular carcinoma. *Br J Cancer* 2013; **108**: 1252-1259 [PMID: 23449352 DOI: 10.1038/bjc.2013.85]
- 64 **Zhu AX**, Kudo M, Assenat E, Cattani S, Kang YK, Lim HY, Poon RT, Blanc JF, Vogel A, Chen CL, Dorval E, Peck-Radosavljevic M, Santoro A, Daniele B, Furuse J, Jappe A, Perraud K, Anak O, Sellami DB, Chen LT. Effect of everolimus on survival in advanced hepatocellular carcinoma after failure of sorafenib: the EVOLVE-1 randomized clinical trial. *JAMA* 2014; **312**: 57-67 [PMID: 25058218 DOI: 10.1001/jama.2014.7189]
- 65 **Yeo W**, Mo FK, Koh J, Chan AT, Leung T, Hui P, Chan L, Tang A, Lee JJ, Mok TS, Lai PB, Johnson PJ, Zee B. Quality of life is predictive of survival in patients with unresectable hepatocellular carcinoma. *Ann Oncol* 2006; **17**: 1083-1089 [PMID: 16600982 DOI: 10.1093/annonc/mdl065]
- 66 **Bonnetain F**, Paoletti X, Collette S, Doffoel M, Bouché O, Raoul JL, Rougier P, Masskouri F, Barbare JC, Bedenne L. Quality of life as a prognostic factor of overall survival in patients with advanced hepatocellular carcinoma: results from two French clinical trials. *Qual Life Res* 2008; **17**: 831-843 [PMID: 18618292 DOI: 10.1007/s11136-008-9365-y]
- 67 **Diouf M**, Filleron T, Barbare JC, Fin L, Picard C, Bouché O, Dahan L, Paoletti X, Bonnetain F. The added value of quality of life (QoL) for prognosis of overall survival in patients with palliative hepatocellular carcinoma. *J Hepatol* 2013; **58**: 509-521 [PMID: 23178978 DOI: 10.1016/j.jhep.2012.11.019]
- 68 **Fielding R**, Wong WS. Quality of life as a predictor of cancer survival among Chinese liver and lung cancer patients. *Eur J Cancer* 2007; **43**: 1723-1730 [PMID: 17588741 DOI: 10.1016/j.ejca.2007.05.002]
- 69 **Li L**, Mo FK, Chan SL, Hui EP, Tang NS, Koh J, Leung LK, Poon AN, Hui J, Chu CM, Lee KF, Ma BB, Lai PB, Chan AT, Yu SC, Yeo W. Prognostic values of EORTC QLQ-C30 and QLQ-HCC18 index-scores in patients with hepatocellular carcinoma - clinical application of health-related quality-of-life data. *BMC Cancer* 2017; **17**: 8 [PMID: 28052758 DOI: 10.1186/s12885-016-2995-5]
- 70 [No authors listed]. A new prognostic system for hepatocellular carcinoma: a retrospective study of 435 patients: the Cancer of the Liver Italian Program (CLIP) investigators. *Hepatology* 1998; **28**: 751-755 [PMID: 9731568 DOI: 10.1002/hep.510280322]
- 71 [No authors listed]. Prospective validation of the CLIP score: a new prognostic system for patients with cirrhosis and hepatocellular carcinoma. The Cancer of the Liver Italian Program (CLIP) Investigators. *Hepatology* 2000; **31**: 840-845 [PMID: 10733537 DOI: 10.1053/he.2000.5628]
- 72 **Llovet JM**, Brú C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. *Semin Liver Dis* 1999; **19**: 329-338 [PMID: 10518312]
- 73 **Chevret S**, Trinchet JC, Mathieu D, Rached AA, Beaugrand M, Chastang C. A new prognostic classification for predicting survival in patients with hepatocellular carcinoma. Groupe d'Etude et de Traitement du Carcinome Hépatocellulaire. *J Hepatol* 1999; **31**: 133-141 [PMID: 10424293 DOI: 10.1016/S0168-8278(99)80173-1]
- 74 **Rabin R**, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. *Ann Med* 2001; **33**: 337-343 [PMID: 11491192]
- 75 **Cucchetti A**, Trevisani F, Cappelli A, Mosconi C, Renzulli M, Pinna AD, Golfieri R. Cost-effectiveness of doxorubicin-eluting beads versus conventional trans-arterial chemo-embolization for hepatocellular carcinoma. *Dig Liver Dis* 2016; **48**: 798-805 [PMID: 27263056 DOI: 10.1016/j.dld.2016.03.031]
- 76 **Leung HW**, Liu CF, Chan AL. Cost-effectiveness of sorafenib versus SBRT for unresectable advanced hepatocellular carcinoma. *Radiat Oncol* 2016; **11**: 69 [PMID: 27193904 DOI: 10.1186/s13014-016-0644-4]
- 77 **Lim KC**, Wang VW, Siddiqui FJ, Shi L, Chan ES, Oh HC, Tan SB, Chow PK. Cost-effectiveness analysis of liver resection versus transplantation for early hepatocellular carcinoma within the Milan criteria. *Hepatology* 2015; **61**: 227-237 [PMID: 24638991 DOI: 10.1002/hep.27135]
- 78 **Spolverato G**, Vitale A, Ejaz A, Kim Y, Maithel SK, Cosgrove DP, Pawlik TM. The relative net health benefit of liver resection, ablation, and transplantation for early hepatocellular carcinoma. *World J Surg* 2015; **39**: 1474-1484 [PMID: 25665675 DOI: 10.1007/s00268-015-2987-7]
- 79 **Zhang P**, Yang Y, Wen F, He X, Tang R, Du Z, Zhou J, Zhang J, Li Q. Cost-effectiveness of sorafenib as a first-line treatment for advanced hepatocellular carcinoma. *Eur J Gastroenterol Hepatol* 2015; **27**: 853-859 [PMID: 25919775 DOI: 10.1097/meg.0000000000000373]
- 80 **Zhang P**, Wen F, Li Q. FOLFOX4 or sorafenib as the first-line treatments for advanced hepatocellular carcinoma: A cost-effectiveness analysis. *Dig Liver Dis* 2016; **48**: 1492-1497 [PMID: 27486048 DOI: 10.1016/j.dld.2016.07.007]
- 81 **Kaasa S**, Loge JH. Quality-of-life assessment in palliative care.

- Lancet Oncol* 2002; **3**: 175-182 [PMID: 11902505]
- 82 **Jocham HR**, Dassen T, Widdershoven G, Halfens RJ. Quality-of-life assessment in a palliative care setting in Germany: an outcome evaluation. *Int J Palliat Nurs* 2009; **15**: 338-345 [PMID: 19648849 DOI: 10.12968/ijpn.2009.15.7.43424]
 - 83 **Fielding S**, Ogbuagu A, Sivasubramaniam S, MacLennan G, Ramsay CR. Reporting and dealing with missing quality of life data in RCTs: has the picture changed in the last decade? *Qual Life Res* 2016; **25**: 2977-2983 [PMID: 27650288 DOI: 10.1007/s11136-016-1411-6]
 - 84 **Steel JL**, Geller DA, Carr BI. Proxy ratings of health related quality of life in patients with hepatocellular carcinoma. *Qual Life Res* 2005; **14**: 1025-1033 [PMID: 16041898]
 - 85 **Fielding S**, Fayers PM, Ramsay CR. Investigating the missing data mechanism in quality of life outcomes: a comparison of approaches. *Health Qual Life Outcomes* 2009; **7**: 57 [PMID: 19545408 DOI: 10.1186/1477-7525-7-57]
 - 86 **Bell ML**, Fiero M, Horton NJ, Hsu CH. Handling missing data in RCTs; a review of the top medical journals. *BMC Med Res Methodol* 2014; **14**: 118 [PMID: 25407057 DOI: 10.1186/1471-2288-14-118]
 - 87 **Thabane L**, Mbuagbaw L, Zhang S, Samaan Z, Marcucci M, Ye C, Thabane M, Giangregorio L, Dennis B, Kosa D, Borg Debono V, Dillenburg R, Fruci V, Bawor M, Lee J, Wells G, Goldsmith CH. A tutorial on sensitivity analyses in clinical trials: the what, why, when and how. *BMC Med Res Methodol* 2013; **13**: 92 [PMID: 23855337 DOI: 10.1186/1471-2288-13-92]
 - 88 **Chie WC**, Blazeby JM, Hsiao CF, Chiu HC, Poon RT, Mikoshiba N, Al-Kadhim G, Heaton N, Calara J, Collins P, Caddick K, Costantini A, Vilgrain V. Differences in health-related quality of life between European and Asian patients with hepatocellular carcinoma. *Asia Pac J Clin Oncol* 2016; Epub ahead of print [PMID: 27038366 DOI: 10.1111/ajco.12464]
 - 89 **King MT**. The interpretation of scores from the EORTC quality of life questionnaire QLQ-C30. *Qual Life Res* 1996; **5**: 555-567 [PMID: 8993101]
 - 90 **Osoha D**, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol* 1998; **16**: 139-144 [PMID: 9440735 DOI: 10.1200/jco.1998.16.1.139]
 - 91 **Cella D**, Hahn EA, Dineen K. Meaningful change in cancer-specific quality of life scores: differences between improvement and worsening. *Qual Life Res* 2002; **11**: 207-221 [PMID: 12074259]
 - 92 **Pickard AS**, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. *Health Qual Life Outcomes* 2007; **5**: 70 [PMID: 18154669 DOI: 10.1186/1477-7525-5-70]
 - 93 **Van Steen K**, Curran R, Kramer J, Molenberghs G, Van Vreckem A, Bottomley A, Sylvester R. Multicollinearity in prognostic factor analyses using the EORTC QLQ-C30: identification and impact on model selection. *Stat Med* 2002; **21**: 3865-3884 [PMID: 12483772 DOI: 10.1002/sim.1358]
 - 94 **Gotay CC**, Kawamoto CT, Bottomley A, Efficace F. The prognostic significance of patient-reported outcomes in cancer clinical trials. *J Clin Oncol* 2008; **1355**-1363
 - 95 **Diouf M**, Bonnetain F, Barbare JC, Bouché O, Dahan L, Paoletti X, Filleron T. Optimal cut points for quality of life questionnaire-core 30 (QLQ-C30) scales: utility for clinical trials and updates of prognostic systems in advanced hepatocellular carcinoma. *Oncologist* 2015; **20**: 62-71 [PMID: 25542450 DOI: 10.1634/theoncologist.2014-0175]
 - 96 **Steel J**, Hess SA, Tunke L, Chopra K, Carr BI. Sexual functioning in patients with hepatocellular carcinoma. *Cancer* 2005; **104**: 2234-2243 [PMID: 16220558 DOI: 10.1002/cncr.21450]
 - 97 **Steel JL**, Eton DT, Cella D, Olek MC, Carr BI. Clinically meaningful changes in health-related quality of life in patients diagnosed with hepatobiliary carcinoma. *Ann Oncol* 2006; **17**: 304-312 [PMID: 16357021 DOI: 10.1093/annonc/mdj072]
 - 98 **Wang YB**, Chen MH, Yan K, Yang W, Dai Y, Yin SS. Quality of life after radiofrequency ablation combined with transcatheter arterial chemoembolization for hepatocellular carcinoma: comparison with transcatheter arterial chemoembolization alone. *Qual Life Res* 2007; **16**: 389-397 [PMID: 17111232 DOI: 10.1007/s11136-006-9133-9]
 - 99 **Sun V**, Ferrell B, Juarez G, Wagman LD, Yen Y, Chung V. Symptom concerns and quality of life in hepatobiliary cancers. *Oncol Nurs Forum* 2008; **35**: E45-E52 [PMID: 18467279 DOI: 10.1188/08.onf.e45-e52]
 - 100 **Doffoël M**, Bonnetain F, Bouché O, Vetter D, Abergel A, Fratté S, Grangé JD, Stremsdoerfer N, Blanchi A, Bronowicki JP, Caroli-Bosc FX, Causse X, Masskouri F, Rougier P, Bedenne L. Multicentre randomised phase III trial comparing Tamoxifen alone or with Transarterial Lipiodol Chemoembolisation for unresectable hepatocellular carcinoma in cirrhotic patients (Fédération Francophone de Cancérologie Digestive 9402). *Eur J Cancer* 2008; **44**: 528-538 [PMID: 18242076 DOI: 10.1016/j.ejca.2008.01.004]
 - 101 **Dollinger MM**, Lautenschlaeger C, Lesske J, Tannapfel A, Wagner AD, Schoppmeyer K, Nehls O, Welker MW, Wiest R, Fleig WE. Thymostimulin versus placebo for palliative treatment of locally advanced or metastasised hepatocellular carcinoma: a phase III clinical trial. *BMC Cancer* 2010; **10**: 457 [PMID: 20735834 DOI: 10.1186/1471-2407-10-457]
 - 102 **Shun SC**, Chen CH, Sheu JC, Liang JD, Yang JC, Lai YH. Quality of life and its associated factors in patients with hepatocellular carcinoma receiving one course of transarterial chemoembolization treatment: a longitudinal study. *Oncologist* 2012; **17**: 732-739 [PMID: 22511265 DOI: 10.1634/theoncologist.2011-0368]
 - 103 **Qiao CX**, Zhai XF, Ling CQ, Lang QB, Dong HJ, Liu Q, Li MD. Health-related quality of life evaluated by tumor node metastasis staging system in patients with hepatocellular carcinoma. *World J Gastroenterol* 2012; **18**: 2689-2694 [PMID: 22690079 DOI: 10.3748/wjg.v18.i21.2689]
 - 104 **Fan SY**, Eiser C, Ho MC, Lin CY. Health-related quality of life in patients with hepatocellular carcinoma: the mediation effects of illness perceptions and coping. *Psychooncology* 2013; **22**: 1353-1360 [PMID: 22847677 DOI: 10.1002/pon.3146]
 - 105 **Brunocilla PR**, Brunello F, Carucci P, Gaia S, Rolle E, Cantamessa A, Castiglione A, Ciccone G, Rizzetto M. Sorafenib in hepatocellular carcinoma: prospective study on adverse events, quality of life, and related feasibility under daily conditions. *Med Oncol* 2013; **30**: 345 [PMID: 23263829 DOI: 10.1007/s12032-012-0345-2]
 - 106 **Mise Y**, Satou S, Ishizawa T, Kaneko J, Aoki T, Hasegawa K, Sugawara Y, Makuuchi M, Kokudo N. Impact of surgery on quality of life in patients with hepatocellular carcinoma. *World J Surg* 2014; **38**: 958-967 [PMID: 24305919 DOI: 10.1007/s00268-013-2342-9]
 - 107 **Palmieri VO**, Santovito D, Margari F, Lozupone M, Minerva F, Di Gennaro C, Todarello O, Palasciano G. Psychopathological profile and health-related quality of life (HRQOL) in patients with hepatocellular carcinoma (HCC) and cirrhosis. *Clin Exp Med* 2015; **15**: 65-72 [PMID: 24323278 DOI: 10.1007/s10238-013-0267-0]
 - 108 **Chie WC**, Yu F, Li M, Baccaglini L, Blazeby JM, Hsiao CF, Chiu HC, Poon RT, Mikoshiba N, Al-Kadhim G, Heaton N, Calara J, Collins P, Caddick K, Costantini A, Vilgrain V, Chiang C. Quality of life changes in patients undergoing treatment for hepatocellular carcinoma. *Qual Life Res* 2015; **24**: 2499-2506 [PMID: 25943170 DOI: 10.1007/s11136-015-0985-8]
 - 109 **Heits N**, Meer G, Bernsmeier A, Guenther R, Malchow B, Kuechler T, Becker T, Braun F. Mode of allocation and social demographic factors correlate with impaired quality of life after liver transplantation. *Health Qual Life Outcomes* 2015; **13**: 162 [PMID: 26420554 DOI: 10.1186/s12955-015-0360-z]
 - 110 **Xie ZR**, Luo YL, Xiao FM, Liu Q, Ma Y. Health-related quality of life of patients with intermediate hepatocellular carcinoma after liver resection or transcatheter arterial chemoembolization. *Asian Pac J Cancer Prev* 2015; **16**: 4451-4456 [PMID: 26028113]
 - 111 **Xing M**, Webber G, Prajapati HJ, Chen Z, El-Rayes B, Spivey JR, Pillai AA, Kim HS. Preservation of quality of life with doxorubicin drug-eluting bead transarterial chemoembolization for unresectable

- hepatocellular carcinoma: Longitudinal prospective study. *J Gastroenterol Hepatol* 2015; **30**: 1167-1174 [PMID: 25675849 DOI: 10.1111/jgh.12920]
- 112 **Yang B**, You X, Yuan ML, Qin TQ, Duan LJ, He J, Fei ZJ, Zhou X, Zan RY, Liao ZY. Transarterial Ethanol Ablation Combined with Transarterial Chemoembolization for Hepatocellular Carcinoma with Portal Vein Tumor Thrombus. *Hepat Mon* 2016; **16**: e37584 [PMID: 27799963 DOI: 10.5812/hepatmon.37584]
- 113 **Shomura M**, Kagawa T, Okabe H, Shiraishi K, Hirose S, Arase Y, Tsuruya K, Takahira S, Mine T. Longitudinal alterations in health-related quality of life and its impact on the clinical course of patients with advanced hepatocellular carcinoma receiving sorafenib treatment. *BMC Cancer* 2016; **16**: 878 [PMID: 27835949 DOI: 10.1186/s12885-016-2908-7]

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Retrospective Cohort Study

Impact of comorbidity on waiting list and post-transplant outcomes in patients undergoing liver retransplantation

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Abstract

AIM

To determine the impact of Charlson comorbidity index (CCI) on waiting list (WL) and post liver retransplantation (LRT) survival.

METHODS

Comparative study of all adult patients assessed for primary liver transplant (PLT) ($n = 1090$) and patients assessed for LRT ($n = 150$), 2000-2007 at our centre. Demographic, clinical and laboratory variables were recorded.

RESULTS

Median age for all patients was 53 years and 66% were men. Median model for end stage liver disease (MELD) score was 15. Median follow-up was 7-years. For retransplant patients, 84 (56%) had ≥ 1 comorbidity. The most common comorbidity was renal impairment in 66 (44.3%). WL mortality was higher in patients with ≥ 1 comorbidity (76% vs 53%, $P = 0.044$). CCI (OR = 2.688, 95%CI: 1.222-5.912, $P = 0.014$) was independently associated with WL mortality. Patients with MELD score ≥ 18 had inferior WL survival (Log-Rank 6.469, $P = 0.011$). On multivariate analysis,

CCI (OR = 2.823, 95%CI: 1.563-5.101, $P = 0.001$), MELD score ≥ 18 (OR 2.506, 95%CI: 1.044-6.018, $P = 0.04$), and requirement for organ support prior to LRT ($P < 0.05$) were associated with reduced post-LRT survival. Donor/graft parameters were not associated with survival ($P = \text{NS}$). Post-LRT mortality progressively increased according to the number of transplanted grafts (Log-Rank 18.455, $P < 0.001$). Post-LRT patient survival at 1-, 3- and 5-years were significantly inferior to those of PLT at 88% *vs* 73%, $P < 0.001$, 81% *vs* 71%, $P = 0.018$ and 69% *vs* 55%, $P = 0.006$, respectively.

CONCLUSION

Comorbidity increases WL and post-LRT mortality. Patients with MELD ≥ 18 have increased WL mortality. Patients with comorbidity or MELD ≥ 18 may benefit from earlier LRT. LRT for ≥ 3 grafts may not represent appropriate use of donated grafts.

Key words: Hepatic; Organ; Outcome; Diabetes; Renal

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Core tip: The prevalence and impact of comorbidity on waiting list (WL) and post-transplant survival is unknown in patients who had liver retransplantation. This study identified comorbidity(ies) were common (56%) in this cohort, most with renal impairment. WL mortality was higher in patients with ≥ 1 comorbidity and model for end stage liver disease (MELD) score ≥ 18 . Post-transplant survival was inferior in patients with ≥ 1 comorbidity, MELD score ≥ 18 and in patients who required organ support prior to retransplantation. Comorbidity increases WL and post-transplant mortality. Patients with comorbidity or MELD ≥ 18 may benefit from earlier retransplantation.

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INTRODUCTION

Liver retransplantation (LRT) represents the only viable option for survival for some patients who develop graft failure following primary liver transplant (PLT). Published reports on cohorts of patients who underwent LRT indicate inferior post-transplant survival in these patients^[1-5]. There has been an increase in the number of patients awaiting PLT which was not associated with increase in donated organs^[6]. Although transplant programmes have tried to compensate for this increase in demand by more liberal use of marginal grafts,

there is evidence that death on the waiting list (WL) for patients listed for PLT remains high^[7]. Therefore, the combination of increased WL mortality with increasing demand for PLT coupled with the known inferior outcomes of LRT; raises concerns and generates ethical debate in the transplant community on the use of scarce resource of donated organs for LRT^[8].

This debate has motivated researchers to identify predictors of survival following LRT to improve the selection of patients who might benefit most from LRT. Model for end-stage liver disease (MELD) score > 25 , recipient age, creatinine level, bilirubin level, indication for retransplantation, the urgency for LRT, coma episodes, haemoglobin (Hb) level and the number of fresh frozen plasma units transfused were identified as factors associated with reduced post-LRT survival in a number of studies^[3,5,9,10]. Death or graft loss was shown to increase gradually following LRT according to the timing of LRT with marked increase in risk between 4-38 d following LRT^[11-13]. Inferior survival was also observed according to increasing number of transplanted graft^[13].

Comorbidity as defined by the Charlson comorbidity index (CCI) was found to adversely affect post-transplant survival in patients who underwent PLT^[14]. Thuluvath *et al*^[7] analysed the data of the scientific registry of transplant recipients (SRTR) in the United States from 1999 to 2008. The prevalence of comorbidity such as diabetes mellitus (DM), renal impairment (RI) and obesity was found to have steadily increased in candidates listed for liver transplantation over the ten year period^[7]. However, the prevalence and impact of comorbidity on WL and post-transplant survival in patients listed for LRT have not been studied previously.

The aims of this study were three fold, firstly, to identify the prevalence of comorbidity according to CCI in patients listed for LRT, secondly, to study the impact of comorbidity on WL and post-LRT mortality, and finally, to identify other factors associated with reduced WL and post-LRT survival.

MATERIALS AND METHODS

Patients and design

This is a retrospective study of all patients referred to the liver unit at King's for LRT assessment between January 2000 and December 2007. There were 151 assessments for LRT on 137 patients over the 8 year period. One patient was excluded because of incomplete information. Data analysis was performed on 150 LRT assessments. We utilized a cohort of patients who underwent PLT over the same time period for comparison of outcomes of PLT and LRT ($n = 1332$). Patients assessed for acute liver failure ($n = 175$), familial amyloid polyneuropathy (43) and 24 with incomplete information were excluded. We analysed data on 1090 patients with end stage liver disease (ESLD) who were assessed for PLT.

Data

All patients assessed for liver transplantation at our centre had their clinical, laboratory, radiological and histological data as well as the outcome of transplant assessment entered at the time of liver transplant assessment into a prospective electronic database. This database was analysed in addition to electronic patient records and clinical notes to record demographic, clinical and laboratory variables of this cohort. Prognostic scores such as MELD and United Kingdom model for end-stage liver disease (UKELD) scores were calculated at the time of assessment and at the time of transplantation. MELD was calculated according to the UNOS adjustment^[15]. The UKELD score was calculated according to Barber *et al.*^[16]. Donor and graft variables were collected and donor risk index was calculated according to Feng *et al.*^[17]. Patient survival was recorded according to their survival status in our hospital information system and further confirmed using the National Health System electronic portal. This is a United Kingdom wide national database, where patient survival status is updated according to the generation of death certificates in the United Kingdom.

Definitions of outcome measures

WL outcome was defined for this study by death on WL or delisting because of significant deterioration or hepatocellular carcinoma (HCC) progression beyond Milan criteria whilst awaiting LT. To study the influence of comorbidity and other variables on listing outcome, we used the transplant free survival (defined as time from listing to death, time to delisting or time to transplant) to eliminate the artificial impact of transplantation on survival of this cohort. Post-transplant patient survival was defined as time from transplantation to death, and if alive, censored on 01/11/2011. Graft survival was defined as time from transplantation to retransplantation or death, and if alive censored on 01/11/2011. Patients who were lost to follow-up were censored as being alive at the date of their last follow-up. Post-LRT patient survival was defined as time from second or subsequent transplant to death, and if alive, censored on 01/11/2011. Post-LRT graft survival was defined as time from second or subsequent transplant to further retransplantation or death, and if alive censored on 01/11/2011. One-year post transplant patient survival was defined as time from LRT to death, and if alive, censored at 12 mo following transplantation. One-year post transplant graft survival was defined as time from transplantation to retransplantation or death, and if alive censored at 12 mo following transplantation. Marginal grafts were defined as graft with Donor Risk Index > 1.8 ^[7]. Cut off values for MELD score of 18 and 25 were chosen according to Rosen *et al.*^[18] and Edwards and Harper^[19].

Comorbidities

Nine comorbidities were prospectively defined according

to Volk *et al.*^[14]. These included congestive heart failure, coronary artery disease, DM, peripheral vascular disease, cerebro-vascular disease, chronic pulmonary disease, connective tissue disease, RI and malignancy. DM was defined as a chronic hyperglycaemia requiring medication use at any time during the month preceding transplant assessment. RI was defined as serum creatinine of ≥ 1.5 mg/dL (≥ 132 μ mol/L) on transplant assessment, being on renal replacement therapy or history of renal transplantation. Congestive heart failure was defined as documented decrease in left ventricular function on echocardiogram or left ventricle angiogram; or increased pulmonary artery pressure of ≥ 25 mmHg on echocardiogram or on invasive pulmonary artery pressure study, including patients with porto-pulmonary hypertension. Coronary artery disease was defined as documented history of myocardial infarction or abnormal coronary angiography. All patients underwent a functional cardiac assessment of ischemia either with Bruce protocol exercise tolerance test or cardio-pulmonary exercise test. Those with positive functional test but negative coronary angiogram were not considered as having coronary artery disease. Peripheral vascular disease was defined as documented history of peripheral ischaemia on angiography, abnormal ankle-brachial index or history of vascular bypass surgery. Cerebrovascular disease was defined as a history of stroke with residual neurological deficit. Chronic pulmonary disease was defined as chronic pulmonary disease requiring medication, a forced expiratory volume of < 1.5 L or history of intubation for respiratory failure. Connective tissue disease was defined as a rheumatologist diagnosis of rheumatoid arthritis, systemic lupus erythematosus, scleroderma or spondyloarthropathies excluding patients with arthralgia without evidence of inflammatory arthritis or those with osteoarthritis. Malignancy was defined as documented history of any malignancy excluding HCC or non melanoma skin cancers. To calculate the CCI, each comorbidity was assigned 1 point when present and was assigned 0 points when absent. The CCI was calculated as the sum of points of all 9 comorbidities. CCI was calculated at the time of assessment and at the time of transplantation.

Statistical analysis

Continuous variables were presented as median (range) and analysed using non-parametric methods (Mann Whitney-*U* or Kruskal Wallis test) for non-normally distributed data as appropriate. Categorical variables were presented as numbers (percentages) and analysed using χ^2 test or Fisher's exact test as appropriate. Cox proportional hazard analysis was used to identify factors associated with listing and transplant outcomes. Factors associated with outcome (*P*-value < 0.05) were entered into multivariate analysis. Collinearity diagnostics were used to determine whether variables

Table 1 Baseline characteristics for patients who had primary liver transplantation and those who had liver retransplantation

Variables	PLT (<i>n</i> = 1090)	LRT (<i>n</i> = 150)	<i>P</i> value
Demographic			
Age	54 (18-82)	46 (18-72)	< 0.001
Gender (male, %)	736 (67.5)	80 (53.3)	0.001
Etiology			
ALD (%)	345 (31.7)	18 (12.0)	< 0.001
Viral (%)	303 (27.8)	50 (33.3)	0.159
Cholestatic and autoimmune (%)	227 (20.8)	34 (22.7)	0.604
Clinical			
Na, mmol/L	135 (116-151)	138 (118-150)	< 0.001
Creatinine, mg/dL	1.0 (0.4-6.8)	1.3 (0.7-8.3)	< 0.001
Bilirubin, mg/dL	2.7 (0.2-68.4)	4.7 (0.4-56.3)	< 0.001
INR	1.3 (0.8-5.0)	1.2 (0.8-13.0)	0.078
MELD	14 (6-40)	20 (6-40)	< 0.001
UKELD	55 (43-77)	56 (44-79)	0.041
Ascites (%)	669 (62.9)	38 (25.5)	< 0.001
Encephalopathy (%)	350 (33.0)	52 (34.9)	0.637

ALD: Alcohol-related liver disease; INR: International normalised ratio; MELD: Model for end-stage liver disease; UKELD: United Kingdom end-stage liver disease model; PLT: Primary liver transplantation; LRT: Liver retransplantation.

entered into a model were collinear. MELD, UKELD, Child-Turcotte-Pugh (CTP), renal impairment and sodium level showed high collinearity (variance inflation factor - VIF > 5). Once MELD and UKELD were removed of the model, CTP, sodium level and renal impairment and all other individual comorbidities showed no collinearity (VIF < 3). Kaplan-Meier analysis was performed to assess survival outcomes. Statistical analyses were performed with SPSS software (SPSS® 17.0 for Windows ®SPSS Inc, Chicago, IL, United States).

RESULTS

Patient characteristics

One hundred and fifty assessments for LRT were examined and compared to a control group of 1090 patients assessed for PLT. Median follow-up was 7 years (3-12). There were 124 assessments for a second transplant, 21 assessments for a third transplant, 3 assessments for a fourth transplant, and 1 assessment each for a fifth and sixth transplant out of 150 LRT assessments. Out of these 150 assessments for LRT, six were not listed for LRT (two because of early referral, 1 because of alcohol abuse, 1 declined re-listing, 1 with complete porto-mesenteric thrombosis and 1 died during the assessment process. Only 121 patients received LRT of the 144 listed patients. Twenty three patients were delisted for the following reasons: 12 died awaiting a graft, 6 had significant clinical improvement and 5 were delisted because of significant clinical deterioration, whilst on WL. Information regarding mechanical ventilation, renal replacement therapy, vasopressor support and location of patient [home, hospital or intensive care unit (ICU)] prior to LRT was available on 113 patients. Thirty two patients (28%) received renal replacement therapy, 21 (19%) received mechanical ventilation and 20 (18%) received vasopressor support prior to LRT. Forty four patients

(36%) were transplanted from the hospital ward, 40 (33%) were transplanted from ICU and 28 (23%) were transplanted from home.

Table 1 summarises baseline characteristics according to PLT and LRT. LRT patients were significantly younger and were less likely to have ascites. However, this group were more likely to have higher median serum sodium levels (Na), creatinine values, bilirubin levels, MELD and UKELD scores ($P < 0.05$). There were no significant differences in proportion of patients with encephalopathy or median INR level between groups ($P = \text{NS}$).

Indications for LRT

The most common indication for LRT was vascular complications (thrombotic and non-thrombotic infarction of the graft) in 49 (33%) followed by graft rejection in 40 (27%), disease recurrence in 35 (23%), early graft dysfunction in 18 (12%) and 8 for other indications (5%). There were 30 patients (20%) who had biliary complications; however, only 3 (10%) patients developed graft failure secondary to biliary complications. Biliary strictures following PLT (anastomotic, hilar, papillary stenosis) were managed endoscopically, except for 2 patients who required per cutaneous biliary interventions. Eventually, 8 patients (27%) underwent biliary reconstruction for definitive management of post-transplant biliary complications. Thirty seven (78%) of patients with vascular-related complications had hepatic artery thrombosis, 9 (18%) had non thrombotic graft infarction, 1 (2%) had veno-occlusive disease and 1 (2%) had portal vein thrombosis resulting in graft infarction.

Comorbidities

There were 84 patients (56%) who had ≥ 1 comorbidity as defined by CCI. The most common comorbidity was RI in 66 (44.3%), followed by DM in 25 (16.8%),

Table 2 Factors associated with waiting list mortality in liver retransplantation patients on univariate and multivariate Cox proportional hazard analysis

Variable	Univariate			Multivariate		
	HR	95%CI	P value	HR	95%CI	P value
Age > 60 yr	2.959	0.550-3.896	0.048	3.102	1.015-9.484	0.047
DM	1.587	0.499-5.042	0.434			
Renal impairment	4.771	1.496-15.217	0.008	3.802	1.147-12.603	0.029
CCI continuous	3.121	1.589-6.130	0.001	2.688	1.222-5.912	0.014
CCI dichotomous	6.528	1.472-28.962	0.014	5.475	1.177-25.464	0.030
Hb, g/dL	0.755	0.545-1.047	0.092			
Platelet count, $\times 10^9$ /mL	0.994	0.986-1.001	0.090			
Bilirubin, mg/dL	1.012	0.979-1.045	0.481			
Creatinine, mg/dL	3.200	1.888-5.421	< 0.001	2.691	1.261-5.740	0.010
INR	1.489	1.055-2.102	0.024	1.406	0.967-2.044	0.075
Encephalopathy	2.049	0.620-6.770	0.239			
Ascites	2.781	1.006-7.682	0.049			
MELD	1.154	1.067-1.248	< 0.001	2.691	1.261-5.740	0.01
MELD ≥ 18	3.827	1.190-12.315	0.024	4.369	1.255-15.215	0.021
Na, mmol/L	0.945	0.870-1.027	0.180			
UKELD	1.121	1.029-1.220	0.009	1.117	1.037-1.204	0.003

DM: Diabetes mellitus; CCI: Charlson comorbidity index; Hb: Haemoglobin; INR: International normalised ratio; MELD: Model for end-stage liver disease; Na: Serum sodium; UKELD: United Kingdom end-stage liver disease model.

chronic pulmonary disease in 2 (1.3%) and 1 patient (0.7%) for each of cerebrovascular disease, connective tissue disease and history of previous malignancy. None of the patients had coronary artery disease, congestive heart failure or peripheral vascular disease according to CCI definitions. There was higher percentage of patients who died on the WL or delisted with ≥ 1 comorbidity compared to those without any comorbidity (76% vs 53%, $P = 0.044$). There was a higher percentage of patients with ≥ 1 comorbidity in those assessed for LRT compared to those assessed for PLT (56% vs 43%, $P = 0.002$). The CCI (HR = 2.688, 95%CI: 1.222-5.912, $P = 0.014$) and the presence of any comorbidity (HR = 5.475, 95%CI: 1.177-25.646, $P = 0.030$) were independently associated with WL mortality on Cox proportional hazard analysis (Table 2). Only DM and RI as individual comorbidities were included in the Cox model because of the infrequency of other comorbidities in this cohort. RI (HR = 3.802, 95%CI: 1.147-12.603, $P = 0.029$) was independently associated with WL mortality. WL mortality in patients with any comorbidity was higher compared to those without comorbidities as shown in Figure 1.

With regards to post-transplant outcomes, the CCI (HR = 2.823, 95%CI: 1.563-5.101, $P = 0.001$) and the presence of comorbidity (HR = 2.870, 95%CI: 1.306-6.307, $P = 0.009$) were independently associated with 12-mo patient and graft survival post-LRT on Cox proportional hazard analysis (Table 3).

WL mortality

Sixteen out of 144 patients (11%) died awaiting a graft. Eight had disease recurrence (of which 5 had HCV recurrence), 3 had vascular complications, 4 had graft rejection and 1 had other indication for LRT. None of the patients with early graft dysfunction died

awaiting a graft. WL mortality for PLT was significantly higher compared to LRT (24% vs 11%, $P < 0.001$). However, median waiting time was significantly shorter for LRT compared to PLT (16 d, range: 0-1118 d vs 100 d, range: 1-922, $P < 0.001$).

Table 2 summarises variables associated with WL mortality on univariate and multivariate analysis. Only age > 60 years and the presence of ascites were included as fixed variables in the multivariate model to prevent interaction of variables with similar clinical relevance (such as creatinine, MELD, RI, comorbidity). Factors which were independently associated with WL mortality were age > 60 years, RI, creatinine level, the presence of comorbidity, CCI, MELD score and UKELD score. Figure 2 illustrates significantly increased 12 mo WL mortality in patients with MELD score ≥ 18 on Kaplan Meier survival analysis (Log-Rank: 6.741, $P = 0.009$). Similar findings observed with MELD cut-off value of 25 (Log-Rank: 8.195, $P = 0.004$). WL mortality was not increased when comparing patients listed for their second graft ($n = 118$) to those listed for their third or more grafts ($n = 26$) (Log-Rank: 0.156, $P = 0.693$).

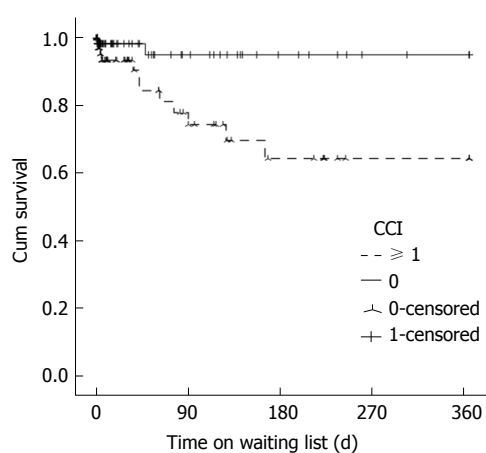
Post-transplant outcomes

The 1-, 3- and 5-year post-transplant patient and graft survival were significantly lower for patients who had LRT compared to those who had PLT. Figure 3 summarise these findings. In retransplanted patients, patient and graft survival were significantly different according to the number of grafts transplanted as analysed by Kaplan Meier survival method (Figure 4). The difference is mainly attributed to the inferior post-transplant survival of patients who had ≥ 3 transplants. There was no significant difference in patient or graft survival between patients who had

Table 3 Univariate and multivariate analysis of factors associated with 1-year post-transplant patient and graft survival of retransplanted patients on Cox proportional hazard analysis

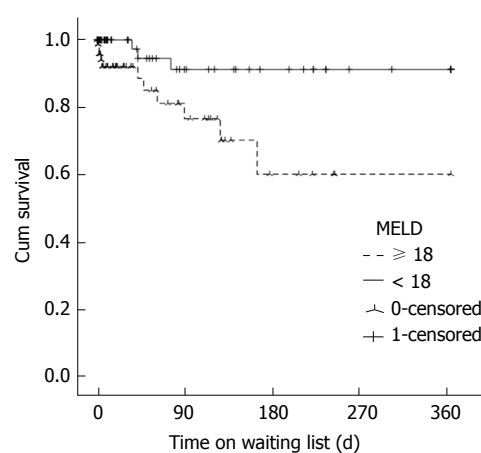
Variable	Patient survival			Graft survival		
	HR	95%CI	P value	HR	95%CI	P value
Univariate analysis						
Age	0.796	0.973-1.021	0.997	0.992	0.969-1.016	0.515
Early graft dysfunction	2.143	0.919-4.998	0.078	1.788	0.776-4.123	0.173
DM	2.242	0.961-5.228	0.062	2.004	0.869-4.618	0.103
Renal impairment	4.385	2.133-9.017	< 0.001	3.494	1.759-6.941	< 0.001
CCI continuous	3.344	1.949-5.738	< 0.001	2.755	1.638-4.633	< 0.001
CCI dichotomous	3.56	1.691-7.493	0.001	2.751	1.377-5.494	0.004
Pre-LRT mechanical ventilation	3.044	1.461-6.342	0.003	2.456	1.210-4.983	0.013
Pre-LRT vasopressor support	4.714	2.239-9.928	< 0.001	3.618	1.758-7.443	< 0.001
Pre-LRT renal replacement therapy	4.233	2.029-8.829	< 0.001	3.271	1.630-6.562	0.001
Transplant from ICU	2.744	1.318-5.712	0.007	2.101	1.049-4.206	0.036
MELD score ≥ 18	4.714	2.239-9.928	0.009	3.105	1.399-6.890	0.005
Encephalopathy at LRT	2.593	1.213-5.544	0.014	2.28	1.121-4.639	0.023
Hb, g/dL	0.791	0.629-0.994	0.044	0.792	0.636-0.985	0.037
ABO mismatch	2.37	1.015-5.532	0.046	2.338	1.053-5.190	0.037
Cold ischemia time (h)	1.113	0.987-1.255	0.082	1.081	0.962-1.216	0.191
DRI	0.68	0.236-1.963	0.476	0.693	0.250-1.918	0.476
DRI > 1.8	1.736	0.772-3.902	0.180	1.67	0.747-3.737	0.212
Multivariate analysis						
Renal impairment	3.215	1.147-12.603	0.005	2.543	1.160-5.573	0.020
CCI Continuous	2.823	1.563-5.101	0.001	2.350	1.331-4.148	0.003
CCI Dichotomous	2.87	1.306-6.307	0.009	2.223	1.067-4.633	0.033
Pre-LRT mechanical ventilation	2.52	1.126-5.637	0.024	2.099	0.968-4.552	0.060
Pre-LRT vasopressor support	4.004	1.554-10.314	0.004	3.023	1.216-7.514	0.017
Pre-LRT renal replacement therapy	2.691	1.261-5.740	0.01	2.441	1.107-5.383	0.027
Transplant from ICU	1.859	0.794-4.354	0.153	1.437	0.640-3.230	0.380
MELD score ≥ 18	2.506	1.044-6.018	0.04	2.512	1.098-5.743	0.029
Encephalopathy at LRT	1.922	0.856-4.315	0.113	1.626	0.752-3.515	0.217
Hb, g/dL at LRT	0.883	0.694-1.125	0.314	0.883	0.698-1.116	0.297
ABO mismatch	1.795	0.739-4.363	0.197	1.827	0.791-4.220	0.158

DM: Diabetes mellitus; LRT: Liver retransplant; ICU: Intensive care unit; CCI: Charlson comorbidity index; Hb: Haemoglobin; INR: International normalised ratio; MELD: Model for end-stage liver disease; DRI: Donor risk index.



No. at risk					
CCI = 0	63	60	60	60	60
CCI ≥ 1	81	60	53	53	53

Figure 1 One-year waiting list survival according to the presence or absence of comorbidity. Log-Rank = 6.798, $P = 0.009$. CCI: Charlson comorbidity index.



No. at risk					
CCI < 18	63	58	58	58	58
CCI ≥ 18	81	62	49	49	49

Figure 2 Waiting list survivals according to Model for end-stage liver disease score at listing (cut-off value of 18). Log-Rank = 6.741, $P = 0.009$. CCI: Charlson comorbidity index; MELD: Model for end stage liver disease.

PLT and patients who had a second transplant, Log-Rank = 1.741, $P = 0.187$ and Log-Rank = 2.225, $P = 0.136$, respectively. Patients who received ≥ 3 grafts had significantly decreased 5-year survival of 40%

compared to 72% in those who received 1 graft and 64% in patients who received 2 previous grafts (Log-Rank test: 13.737, $P < 0.001$).

With regards to the time interval between liver

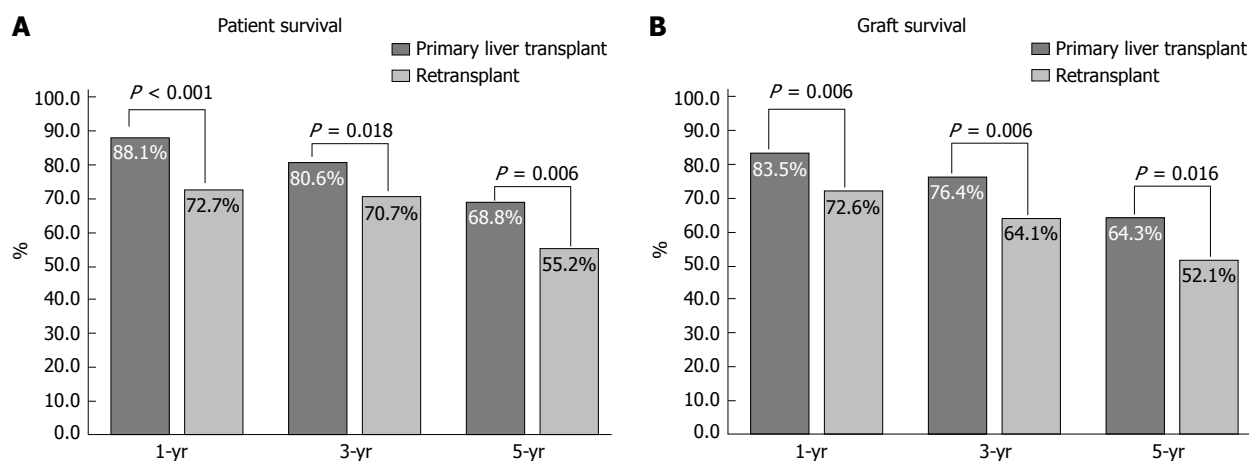


Figure 3 Post-transplant survival at 1, 3 and 5 years. A: Post-transplant patient survival for PLT and LRT; B: Post-transplant graft survival for PLT and LRT. LRT: Liver retransplantation; PLT: Primary liver transplantation.

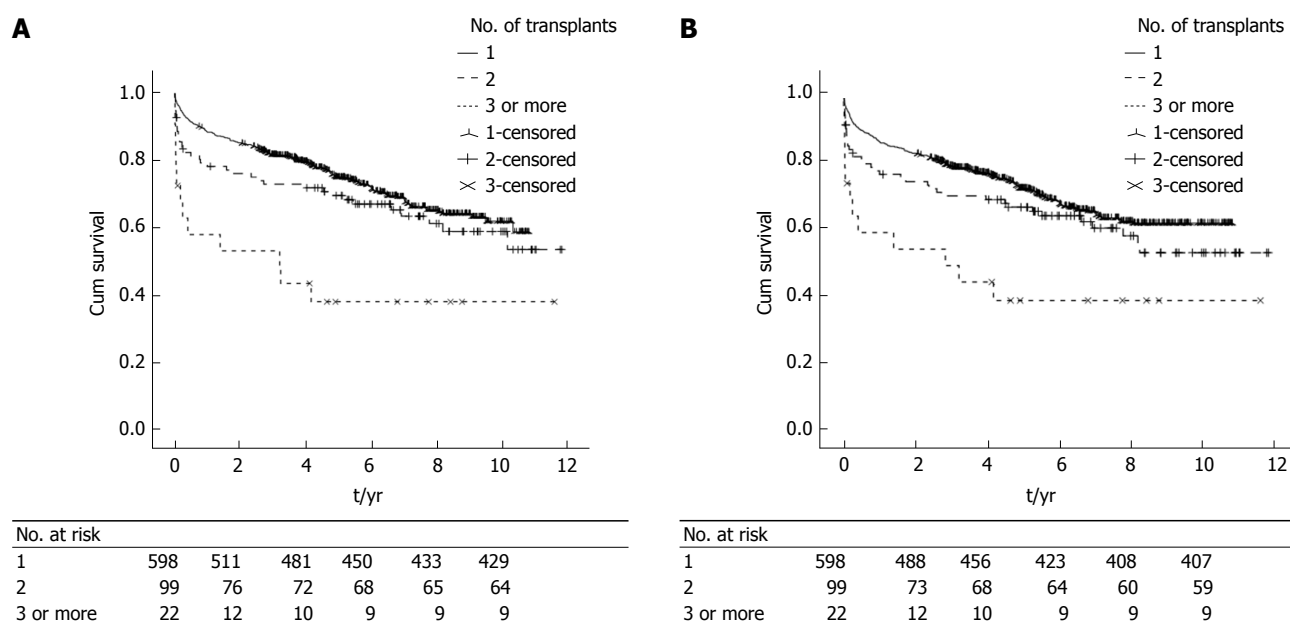


Figure 4 Post-transplant survival according to the number of transplants. A: Kaplan Meier survival analysis of post-transplant patient survival according to the number of transplants. Log-Rank = 18.455, $P < 0.001$; B: Kaplan Meier survival analysis of post-transplant graft survival according to the number of transplants. Log-Rank = 13.737, $P = 0.001$.

transplantation and repeat transplant, patients who were transplanted between day 8-30 had the worse 1-year post transplant survival followed by those transplanted within the first 7 d. Patients who were transplanted > 30 d had significantly improved 1-year post-LRT survival (Log-Rank test: 6.952, $P = 0.031$). Table 4 summarises prognostic variables and indications for LRT according to time interval between transplants. Age, MELD at transplantation and the presence of comorbidity were not significantly different between the groups. Majority of patients who had LRT within 7 d of index transplant had early graft dysfunction. Majority of patients who had LRT 8-30 d of index transplant had vascular complications.

We performed Cox proportional hazard analysis to identify factors associated with post-transplant patient

and graft survival in retransplanted patients. CCI (OR = 2.048, 95%CI: 1.294-3.241, $P = 0.002$), the presence of any comorbidity (HR = 1.920, 95%CI: 1.092-3.373, $P = 0.023$) and requirement for RRT (HR = 1.890, 95%CI: 1.044-3.424, $P = 0.036$) were associated with post-LRT patient survival on univariate analysis. Liver prognostic models (MELD, UKELD), donor or graft variables were not associated with patient survival in retransplanted patients. With regards to graft survival, only vasopressor support prior to LRT was associated with increased graft loss on univariate analysis (HR = 1.974, 95%CI: 1.033-3.744, $P = 0.04$).

Table 3 summarises variables associated with 1-year post-LRT patient and graft survival on Cox proportional hazard analysis. Only the presence of encephalopathy at LRT, Hb level at LRT and ABO

Table 4 Comparison of prognostic variables according to time interval of liver retransplantation

Time between transplants (d)	0-7 (n = 19)	8-30 (n = 16)	> 30 (n = 86)	P value
Age	54 (18-67)	44 (20-63)	43 (19-70)	0.086
Transplant MELD	22 (10-40)	17 (8-36)	17 (6-31)	0.104
CCI ≥ 1 , n (%)	10 (71)	11 (61)	44 (49)	0.095
Indication, n (%)				
Early graft dysfunction	14 (74)	2 (13)	2 (2)	< 0.001
Graft rejection	0 (0)	1 (6)	30 (35)	< 0.001
Vascular	5 (26)	13 (81)	23 (27)	< 0.001
Disease recurrence	0 (0)	0 (0)	24 (28)	0.001
Other indications	0 (0)	0 (0)	7 (8)	0.106

CCI: Charlson comorbidity index; MELD: Model for end stage liver disease.

mismatch were chosen as fixed variables in the model to avoid cross interaction between variables of similar clinical significance. The CCI, RI, pre-LRT mechanical ventilation, requirement for renal replacement therapy, vasopressor support and listing MELD ≥ 18 were independently associated with 1-year patient survival. Similar findings were found for graft survival except for mechanical ventilation which was not associated with outcome.

Graft quality

Median donor age was 44 years (10-76), 55 (45.5%) of donors were males. Donor - recipient gender mismatch was seen in 45 cases (37.2%). Donor ethnicity was Caucasian in 117 (96.7%). Donor cause of death was trauma related in 20 donors (16.5%). Median donor height was 170 cm (147-196), median donor weight was 70 kg (28-110) and BMI was 24 kg/m² (16-34). Only 4 patients received split organs and 1 patient received a graft donated after cardiac death (DCD). Blood group mismatch was seen in 17 cases (14%). Median cold ischemia time was 10.55 h (0.92-19.53) and median DRI was 1.511 (1.0-2.8). There were 24 patients (20.2%) who received marginal grafts (DRI > 1.8). The DRI, or components of DRI in isolation, and DRI > 1.8 were not associated with 12-mo or long-term post-transplant patient or graft survival on Cox proportional hazard analysis.

DISCUSSION

The CCI was originally developed and validated as a tool to predict hospital outcome in general medical patients^[20]. Composed of medical conditions with varying assigned weights, versions of CCI were found to predict outcomes in multiple clinical settings^[21-26]. In this study, we reported on 150 episodes of assessment for LRT from a single centre. We demonstrated that comorbidity as defined by CCI is common (56%) in patients assessed for LRT, and higher than that reported for PLT (40%)^[14]. This high prevalence of comorbidity is mainly attributed to the high prevalence of renal impairment (44%) in this cohort. It is difficult to estimate the rate of renal dysfunction in LRT patients

from previously published studies^[3,4,12,18]. RI was seen in 33% of candidates listed for PLT according to the data of the SRTR^[7].

Renal dysfunction is a well recognised complication in patients with ESLD, critical illness and in PLT^[27-30]. Renal impairment is known to have detrimental impact on survival of patients with ESLD^[31,32]. Therefore, the increased prevalence of RI in our cohort can be explained by the fact that patients listed for LRT have more severe liver dysfunction, reflected by higher MELD scores compared to PLT patients and also by the large proportion of patients who were transplanted from ICU (33%) reflecting the severity of their illness. Furthermore, standard immunosuppression agents with Calcineurin inhibitors such as Ciclosporin or Tacrolimus which is routinely used following liver transplantation to prevent rejection are known to cause or at least contribute to renal impairment following liver transplantation^[33]. Other comorbidities, apart from DM, were rare which may be explained by the relatively young median age of patients listed for LRT compared to PLT. The younger age of LRT patients compared to PLT is consistent with previous reports^[18,34].

This is the first study to demonstrate the impact of comorbidity on WL mortality in LRT patients. The presence of any comorbidity defined by the CCI was independently associated with a greater than 5 times the risk of death on the wait list. Furthermore, this study has shown that the presence of any comorbidity was associated with twice the risk of post-LRT patient death. Similarly, comorbidity was associated with a three-fold increased risk of patient death and two fold increased risk of graft loss within 12 mo post-LRT. The only study to date which investigated the effect of comorbidity on post liver transplant outcome showed that the presence of any comorbidity was associated with 21% increase in patient death following PLT^[14]. Comorbidity was also found to predict post-transplant outcome in patients who received renal and allogeneic stem cell transplantation^[35-38].

We have demonstrated in this study that the median MELD score for patients assessed for LRT was significantly higher compared to PLT patients. We have also shown that the increase in MELD among

LRT candidates was attributable to the high median bilirubin and creatinine levels but not to an increase in INR which is consistent with UNOS data (Table 1)^[34]. We have also shown that the already established models to assess the severity of hepatic impairment (MELD and UKELD) were independently associated with WL mortality. Furthermore, MELD score at a cut-off as low as 18 was associated with WL mortality which was increased by more than 4 fold. This suggests that patients listed for LRT with MELD score ≥ 18 may benefit from prioritization on WL and earlier transplantation to improve LRT outcome.

Our data showed increased WL mortality in LRT patients with MELD score of 18 or higher. In a report from The University of Nebraska, Watt *et al.*^[39] showed that MELD score was predictive of WL mortality in 63 patients listed for a second transplant. WL mortality was also shown to increase with increasing MELD scores, especially at the lower range of MELD^[34]. None of the other previously reported studies examined the performance of MELD in predicting WL mortality in LRT patients. Instead, these reports focused on factors predictive of post-LRT outcomes^[2,3,5,11,18,40,41]. Surprisingly, WL mortality was lower for LRT patients (11% vs 24%, $P < 0.001$), discordant to previous reports^[34]. This can be explained by the fact that patients listed for LRT had significantly shorter median waiting time (16 d vs 100 d, $P < 0.001$) which may indicate an informal prioritization mechanism for patients listed for LRT in our hospital. Our report also suggests that UKELD score retains its predictive capacity of WL mortality in patients listed for LRT with a 12% rise in WL mortality with every point increase in the UKELD score. Another important finding of the current study is that recipient age > 60 years was independently associated with death on the WL in LRT patients, consistent with previous studies that identified advanced recipient age as a risk factor for WL mortality in patients listed for PLT^[28,42,43].

We have shown that 1-, 3- and 5-year patient and graft survival were inferior in patients who underwent retransplantation, consistent with previously published reports^[5,13]. This inferior post-transplant survival in our cohort is mainly attributed to the poor post-LRT survival in patients who received ≥ 3 grafts. Patients who had a second graft had slightly lower patient survival compared to PLT. Although these findings contrast with the outcome of patients who underwent retransplantation 1984-2001 at The University of California Los Angeles, improved survival of patients who had a second transplant in our cohort may be explained by both a different era of transplantation, advances made in immunosuppression and local patient selection processes^[13]. Our findings also suggest that a second liver transplant may represent an acceptable use of donated organs in selected patients. However, if we take into consideration the rule of 50% survival benefit at 5 years post-transplant, according to our findings a third or subsequent grafts may not represent

an appropriate use of donated organs, except in rare instances^[6].

Published reports suggested that the time interval between PLT and LRT has an influence on post-transplant outcome. Reports from 2 transplant programs indicated that LRT 4-30 d or 8-30 d following first transplant carries a worse post-transplant survival^[11,13,40]. Our data showed inferior survival in patients who were transplanted within 30 d from previous liver transplantation, irrespective of whether LRT occurred in the first 7 d or between 8-30 d. In our cohort, the most common indication for LRT within the first 7 d following a previous transplant was early graft dysfunction whilst vascular complications (thrombotic and non-thrombotic graft infarction) were the primary indication in patients who had LRT 8-30 d following a previous transplant. This increased post-LRT mortality in patients who receive early LRT may be explained by severity of illness, intense immunosuppression, hence increased risk of infections^[2,44]. Our findings are consistent with those of Rosen *et al.*^[18] who reported significantly inferior long term survival in patients who had LRT for PNF and vascular complications. In both United States and the United Kingdom, in recognition of the severity of illness and the high mortality associated with PNF and early HAT without LRT, an urgent priority for LRT is given^[45,46].

Regarding post-LRT survival, we demonstrated that the CCI, RI, MELD score ≥ 18 and requirement for organ support were independent factors associated with 1-year post-LRT patient and graft survival consistent with the reported literature in which MELD, or individual components of MELD, were associated with post-LRT outcome^[2,3,9,10,12,40,41]. Similarly, requirement for mechanical ventilation and renal replacement therapy were found to negatively impact on post-LRT outcome in agreement with the reported literature^[2,5,12,40]. Interestingly, we identified pre-LRT vasopressor support as the only factor associated with long term graft outcome. Vasopressor use was also an independent factor associated with 12 mo post-transplant patient and graft survival. This finding has never been reported in previous studies. The requirement for vasopressors may therefore reflect the severity of recipient illness with hemodynamic instability and it may indirectly suggest the negative impact of graft ischemia on patient and graft survival.

Despite our detailed analysis of donor and graft variables, we found no association between graft quality and post-LRT outcomes. This is likely to reflect our local donor-recipient matching practices demonstrated by the limited use of marginal grafts in this cohort and a low median donor age of 44 years which is well within the confines of non-extended criteria donor parameters. Few studies analyzed the impact of graft and donor factors on post-LRT survival. Whilst Pfitzmann *et al.*^[5] found no correlation between graft survival and donor variables, others identified donor age, ethnicity and warm ischemia time as factors

independently associated with inferior outcome^[5,10,40].

Limitations of this study were that it represents a single centre experience; therefore, applicability of the findings on other cohorts may be limited. Secondly, data on immunosuppression were not included in our analysis, although standard immunosuppression was used in all cases except for patients with eGFR < 50 mL/min, a renal sparing regimen of low dose Tacrolimus and interleukin-2 (IL-2) blocker and prednisolone was used preferentially. Indeed, the choice of immunosuppression not only can influence post-transplant outcomes in patients underwent PLT, it can influence the rate of complications related to immunosuppression such as RI which we found as an important factor associated with inferior patient and graft survival^[33,47,48]. Thirdly, we used a version of the CCI tested in liver transplant cohort^[14]. Therefore, the impact of other comorbidities on post-transplant survival such as inflammatory bowel disease, peptic ulcer disease, valvular heart disease or obesity, which were found to affect patient survival, remains unknown given they were not incorporated in the model^[20,49]. Lastly, although the definitions of individual comorbidities were consistent with previous reports, clinical applicability of these definitions maybe limited.

In conclusion, our data indicates that the presence of comorbidity in liver retransplant candidates increases mortality on the WL and following LRT. The severity of recipient liver disease was associated with WL mortality. MELD score was able to discriminate between survival and death whilst on the WL at a lower cut-off value of 18 which suggests that patients undergoing LRT should be transplanted at lower MELD scores. Post-transplant mortality progressively increased according to the number of transplanted grafts; however, the greatest adverse impact was seen after transplanting ≥ 3 grafts with only 40% 5-year survival seen in this group. Graft and donor variables were not found to influence patient or graft survival in this study which may reflect centre-related donor-recipient matching.

COMMENTS

Background

The prevalence and impact of comorbidities on waiting list (WL) and post-transplant survival in patients undergoing liver retransplantation (LRT) is not known. This study evaluates the impact of comorbidity on the above parameters.

Research frontiers

Model for end-stage liver disease (MELD) score > 25, recipient age, creatinine level, bilirubin level, indication for retransplantation, the urgency for LRT, coma episodes, haemoglobin level and the number of fresh frozen plasma units transfused were identified as factors associated with reduced post-LRT survival in a number of studies.

Innovations and breakthroughs

Comorbidity in liver retransplant patients increases mortality on the WL and following LRT. MELD score of ≥ 18 was associated with increased risk of

death on WL and within 12 mo following retransplantation. Post-transplant mortality progressively increased according to the number of transplanted grafts.

Applications

Patients undergoing LRT should be transplanted at lower MELD scores. Assessment of comorbidity in LRT candidates can provide important prognostic information. A third or subsequent grafts may not represent an appropriate use of donated organs, except in rare instances.

Terminology

ALD: Alcohol-related liver disease; CCI: Charlson comorbidity index; CI: Confidence interval; CIT: Cold ischemia time; DBD: Donation after brain death; DCD: Donation after cardiac death; DM: Diabetes mellitus; DRI: Donor risk index; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus infection; ICU: Intensive care unit; IL-2: Interleukin-2; INR: International normalized ratio; LRT: Liver retransplantation; MELD: Model for end-stage liver disease; Na: Sodium; NHS: National Health Services; OR: Odds ratio; PLT: Primary liver transplantation; RI: Renal impairment; SSTR: Scientific Registry of Transplant Recipients; UCLA: University of California Los Angeles; UKELD: United Kingdom End-stage Liver Disease; UNOS: United Network of Organ Sharing; WL: Waiting list.

Peer-review

Very well written paper.

REFERENCES

- Ghobrial RM**, Farmer DG, Baquerizo A, Colquhoun S, Rosen HR, Yersiz H, Markmann JF, Drazan KE, Holt C, Imagawa D, Goldstein LI, Martin P, Busuttil RW. Orthotopic liver transplantation for hepatitis C: outcome, effect of immunosuppression, and causes of retransplantation during an 8-year single-center experience. *Ann Surg* 1999; **229**: 824-831; discussion 831-833 [PMID: 10363896]
- Markmann JF**, Markowitz JS, Yersiz H, Morrissey M, Farmer DG, Farmer DA, Goss J, Ghobrial R, McDiarmid SV, Stribling R, Martin P, Goldstein LI, Seu P, Shackleton C, Busuttil RW. Long-term survival after retransplantation of the liver. *Ann Surg* 1997; **226**: 408-418; discussion 418-420 [PMID: 9351709 DOI: 10.1097/0000658-199710000-00002]
- Rosen HR**, Madden JP, Martin P. A model to predict survival following liver retransplantation. *Hepatology* 1999; **29**: 365-370 [PMID: 9918911 DOI: 10.1002/hep.510290221]
- Ghobrial RM**. Retransplantation for recurrent hepatitis C. *Liver Transpl* 2002; **8**: S38-S43 [PMID: 12362296 DOI: 10.1053/jlts.2002.35861]
- Pfützmann R**, Benschmidt B, Langrehr JM, Schumacher G, Neuhaus R, Neuhaus P. Trends and experiences in liver retransplantation over 15 years. *Liver Transpl* 2007; **13**: 248-257 [PMID: 17205553 DOI: 10.1002/lt.20904]
- Neuberger J**, Gimson A, Davies M, Akyol M, O'Grady J, Burroughs A, Hudson M. Selection of patients for liver transplantation and allocation of donated livers in the UK. *Gut* 2008; **57**: 252-257 [PMID: 17895356 DOI: 10.1136/gut.2007.131730]
- Thuluvath PJ**, Guidinger MK, Fung JJ, Johnson LB, Rayhill SC, Pelletier SJ. Liver transplantation in the United States, 1999-2008. *Am J Transplant* 2010; **10**: 1003-1019 [PMID: 20420649 DOI: 10.1111/j.1600-6143.2010.03037.x]
- Biggins SW**. Futility and rationing in liver retransplantation: when and how can we say no? *J Hepatol* 2012; **56**: 1404-1411 [PMID: 22314427 DOI: 10.1016/j.jhep.2011.11.027]
- Watt KD**, Lyden ER, McCashland TM. Poor survival after liver retransplantation: is hepatitis C to blame? *Liver Transpl* 2003; **9**: 1019-1024 [PMID: 14526394 DOI: 10.1053/jlts.2003.50206]
- Ghabril M**, Dickson R, Wiesner R. Improving outcomes of liver retransplantation: an analysis of trends and the impact of Hepatitis C infection. *Am J Transplant* 2008; **8**: 404-411 [PMID: 18211509 DOI: 10.1111/j.1600-6143.2007.02082.x]

- 11 **Powelson JA**, Cosimi AB, Lewis WD, Rohrer RJ, Freeman RB, Vacanti JP, Jonas M, Lorber MI, Marks WH, Bradley J. Hepatic retransplantation in New England--a regional experience and survival model. *Transplantation* 1993; **55**: 802-806 [PMID: 8475555 DOI: 10.1097/00007890-199304000-00023]
- 12 **Doyle HR**, Morelli F, McMichael J, Doria C, Aldrighetti L, Starzl TE, Marino IR. Hepatic Retransplantation--an analysis of risk factors associated with outcome. *Transplantation* 1996; **61**: 1499-1505 [PMID: 8633379 DOI: 10.1097/00007890-199605270-00016]
- 13 **Busuttil RW**, Farmer DG, Yersiz H, Hiatt JR, McDiarmid SV, Goldstein LI, Saab S, Han S, Durazo F, Weaver M, Cao C, Chen T, Lipshutz GS, Holt C, Gordon S, Gornbein J, Amersi F, Ghobrial RM. Analysis of long-term outcomes of 3200 liver transplantations over two decades: a single-center experience. *Ann Surg* 2005; **241**: 905-916; discussion 916-918 [PMID: 15912040]
- 14 **Volk ML**, Hernandez JC, Lok AS, Marrero JA. Modified Charlson comorbidity index for predicting survival after liver transplantation. *Liver Transpl* 2007; **13**: 1515-1520 [PMID: 17969207 DOI: 10.1002/lt.21172]
- 15 **Wiesner R**, Edwards E, Freeman R, Harper A, Kim R, Kamath P, Kremers W, Lake J, Howard T, Merion RM, Wolfe RA, Krom R. Model for end-stage liver disease (MELD) and allocation of donor livers. *Gastroenterology* 2003; **124**: 91-96 [PMID: 12512033 DOI: 10.1053/gast.2003.50016]
- 16 **Barber K**, Madden S, Allen J, Collett D, Neuberger J, Gimson A. Elective liver transplant list mortality: development of a United Kingdom end-stage liver disease score. *Transplantation* 2011; **92**: 469-476 [PMID: 21775931 DOI: 10.1097/TP.0b013e318225db4d]
- 17 **Feng S**, Goodrich NP, Bragg-Gresham JL, Dykstra DM, Punch JD, DeRoy MA, Greenstein SM, Merion RM. Characteristics associated with liver graft failure: the concept of a donor risk index. *Am J Transplant* 2006; **6**: 783-790 [PMID: 16539636 DOI: 10.1111/j.1600-6143.2006.01242.x]
- 18 **Rosen HR**, Prieto M, Casanovas-Taltavull T, Cuervas-Mons V, Guckelberger O, Muesan P, Strong RW, Bechstein WO, O'grady J, Zaman A, Chan B, Berenguer J, Williams R, Heaton N, Neuhaus P. Validation and refinement of survival models for liver retransplantation. *Hepatology* 2003; **38**: 460-469 [PMID: 12883491 DOI: 10.1053/jhep.2003.50328]
- 19 **Edwards E**, Harper A. Does MELD work for relisted candidates? *Liver Transpl* 2004; **10**: S10-S16 [PMID: 15382287 DOI: 10.1002/lt.20271]
- 20 **Charlson ME**, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; **40**: 373-383 [PMID: 3558716 DOI: 10.1016/0021-9681(87)90171-8]
- 21 **Fried L**, Bernardini J, Piraino B. Charlson comorbidity index as a predictor of outcomes in incident peritoneal dialysis patients. *Am J Kidney Dis* 2001; **37**: 337-342 [PMID: 11157375 DOI: 10.1053/ajkd.2001.21300]
- 22 **Beddhu S**, Bruns FJ, Saul M, Seddon P, Zeidel ML. A simple comorbidity scale predicts clinical outcomes and costs in dialysis patients. *Am J Med* 2000; **108**: 609-613 [PMID: 10856407 DOI: 10.1016/S0002-9343(00)00371-5]
- 23 **Wang CY**, Lin YS, Tzao C, Lee HC, Huang MH, Hsu WH, Hsu HS. Comparison of Charlson comorbidity index and Kaplan-Feinstein index in patients with stage I lung cancer after surgical resection. *Eur J Cardiothorac Surg* 2007; **32**: 877-881 [PMID: 17920921]
- 24 **Christensen S**, Johansen MB, Christiansen CF, Jensen R, Lemeshow S. Comparison of Charlson comorbidity index with SAPS and APACHE scores for prediction of mortality following intensive care. *Clin Epidemiol* 2011; **3**: 203-211 [PMID: 21750629 DOI: 10.2147/CLEP.S20247]
- 25 **Thompson HJ**, Rivara FP, Nathens A, Wang J, Jurkovich GJ, Mackenzie EJ. Development and validation of the mortality risk for trauma comorbidity index. *Ann Surg* 2010; **252**: 370-375 [PMID: 20622665 DOI: 10.1097/SLA.0b013e3181df03d6]
- 26 **Hines RB**, Chatla C, Bumpers HL, Waterbor JW, McGwin G, Funkhouser E, Coffey CS, Posey J, Manne U. Predictive capacity of three comorbidity indices in estimating mortality after surgery for colon cancer. *J Clin Oncol* 2009; **27**: 4339-4345 [PMID: 19652054 DOI: 10.1200/JCO.2009.22.4758]
- 27 **Malinchoc M**, Kamath PS, Gordon FD, Peine CJ, Rank J, ter Borg PC. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. *Hepatology* 2000; **31**: 864-871 [PMID: 10733541 DOI: 10.1053/he.2000.5852]
- 28 **Luca A**, Angermayr B, Bertolini G, Koenig F, Vizzini G, Ploner M, Peck-Radosavljevic M, Gridelli B, Bosch J. An integrated MELD model including serum sodium and age improves the prediction of early mortality in patients with cirrhosis. *Liver Transpl* 2007; **13**: 1174-1180 [PMID: 17663415 DOI: 10.1002/lt.21197]
- 29 **Silvester W**, Bellomo R, Cole L. Epidemiology, management, and outcome of severe acute renal failure of critical illness in Australia. *Crit Care Med* 2001; **29**: 1910-1915 [PMID: 11588450 DOI: 10.1097/00003246-200110000-00010]
- 30 **de Mendonça A**, Vincent JL, Suter PM, Moreno R, Dearden NM, Antonelli M, Takala J, Sprung C, Cantraine F. Acute renal failure in the ICU: risk factors and outcome evaluated by the SOFA score. *Intensive Care Med* 2000; **26**: 915-921 [PMID: 10990106 DOI: 10.1007/s001340051281]
- 31 **Fernández-Esparrach G**, Sánchez-Fueyo A, Ginès P, Uriz J, Quintó L, Ventura PJ, Cárdenas A, Guevara M, Sort P, Jiménez W, Bataller R, Arroyo V, Rodés J. A prognostic model for predicting survival in cirrhosis with ascites. *J Hepatol* 2001; **34**: 46-52 [PMID: 11211907 DOI: 10.1016/S0168-8278(00)00011-8]
- 32 **Cooper GS**, Bellamy P, Dawson NV, Desbiens N, Fulkerson WJ, Goldman L, Quinn LM, Speroff T, Landefeld CS. A prognostic model for patients with end-stage liver disease. *Gastroenterology* 1997; **113**: 1278-1288 [PMID: 9322523 DOI: 10.1053/gast.1997.v113.pm9322523]
- 33 **Lucey MR**, Abdelmalek MF, Gagliardi R, Granger D, Holt C, Kam I, Klintmalm G, Langnas A, Shetty K, Tzakis A, Woodle ES. A comparison of tacrolimus and cyclosporine in liver transplantation: effects on renal function and cardiovascular risk status. *Am J Transplant* 2005; **5**: 1111-1119 [PMID: 15816894 DOI: 10.1111/j.1600-6143.2005.00808.x]
- 34 **Kim HJ**, Larson JJ, Lim YS, Kim WR, Pedersen RA, Therneau TM, Rosen CB. Impact of MELD on waitlist outcome of retransplant candidates. *Am J Transplant* 2010; **10**: 2652-2657 [PMID: 21070603 DOI: 10.1111/j.1600-6143.2010.03315.x]
- 35 **Sorrór ML**, Maris MB, Storer B, Sandmaier BM, Diaconescu R, Flowers C, Maloney DG, Storb R. Comparing morbidity and mortality of HLA-matched unrelated donor hematopoietic cell transplantation after nonmyeloablative and myeloablative conditioning: influence of pretransplantation comorbidities. *Blood* 2004; **104**: 961-968 [PMID: 15113759 DOI: 10.1182/blood-2004-02-0545]
- 36 **Sorrór ML**, Maris MB, Storb R, Baron F, Sandmaier BM, Maloney DG, Storer B. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. *Blood* 2005; **106**: 2912-2919 [PMID: 15994282 DOI: 10.1182/blood-2005-05-2004]
- 37 **Jassal SV**, Schaubel DE, Fenton SS. Baseline comorbidity in kidney transplant recipients: a comparison of comorbidity indices. *Am J Kidney Dis* 2005; **46**: 136-142 [PMID: 15983967 DOI: 10.1053/j.ajkd.2005.03.006]
- 38 **Diaconescu R**, Flowers CR, Storer B, Sorror ML, Maris MB, Maloney DG, Sandmaier BM, Storb R. Morbidity and mortality with nonmyeloablative compared with myeloablative conditioning before hematopoietic cell transplantation from HLA-matched related donors. *Blood* 2004; **104**: 1550-1558 [PMID: 15150081 DOI: 10.1182/blood-2004-03-0804]
- 39 **Watt KD**, Menke T, Lyden E, McCashland TM. Mortality while awaiting liver retransplantation: predictability of MELD scores. *Transplant Proc* 2005; **37**: 2172-2173 [PMID: 15964370 DOI: 10.1016/j.transproceed.2005.03.004]
- 40 **Hong JC**, Kaldas FM, Kositamongkol P, Petrowsky H, Farmer DG, Markovic D, Hiatt JR, Busuttil RW. Predictive index for long-

- term survival after retransplantation of the liver in adult recipients: analysis of a 26-year experience in a single center. *Ann Surg* 2011; **254**: 444-448; discussion 444-448 [PMID: 21817890 DOI: 10.1097/SLA.0b013e31822c5878]
- 41 **Yao FY**, Saab S, Bass NM, Hirose R, Ly D, Terrault N, Lazar AA, Bacchetti P, Ascher NL, Roberts JP. Prediction of survival after liver retransplantation for late graft failure based on preoperative prognostic scores. *Hepatology* 2004; **39**: 230-238 [PMID: 14752842 DOI: 10.1002/hep.20005]
 - 42 **Ripoll C**, Bañares R, Rincón D, Catalina MV, Lo Iacono O, Salcedo M, Clemente G, Núñez O, Matilla A, Molinero LM. Influence of hepatic venous pressure gradient on the prediction of survival of patients with cirrhosis in the MELD Era. *Hepatology* 2005; **42**: 793-801 [PMID: 16175621 DOI: 10.1002/hep.20871]
 - 43 **Dickson ER**, Grambsch PM, Fleming TR, Fisher LD, Langworthy A. Prognosis in primary biliary cirrhosis: model for decision making. *Hepatology* 1989; **10**: 1-7 [PMID: 2737595 DOI: 10.1002/hep.1840100102]
 - 44 **Marudanayagam R**, Shanmugam V, Sandhu B, Gunson BK, Mirza DF, Mayer D, Buckels J, Bramhall SR. Liver retransplantation in adults: a single-centre, 25-year experience. *HPB (Oxford)* 2010; **12**: 217-224 [PMID: 20590890 DOI: 10.1111/j.1477-2574.2010.00162.x]
 - 45 **OPTN**. Organ distribution: allocation of livers. [Accessed 02/02/2011]. Available from: URL: http://optn.transplants.hrsa.gov/policies-andbylaws2/policies/pdfs/policy_8pdf
 - 46 **NHS OD**. NHS Blood and Transplant Liver Advisory Group. Protocols and guidelines for adults undergoing deceased donor liver transplantation in the UK. 4.1.1 Super-urgent liver transplantation, 2012: NHS Blood and Transplant Liver Advisory Group. Protocols and guidelines for adults undergoing deceased donor liver transplantation in the UK. 4.1.1 Super-urgent liver transplantation. Accessed 24/09/2012. Available from: URL: http://www.organdonation.nhs.uk/ukt/about_transplants/organ_allocation/liver/liver_organ_sharing_principles/liver_organ_sharing_principles.asp#b1
 - 47 **O'Grady JG**, Burroughs A, Hardy P, Elbourne D, Truesdale A. Tacrolimus versus microemulsified ciclosporin in liver transplantation: the TMC randomised controlled trial. *Lancet* 2002; **360**: 1119-1125 [PMID: 12387959 DOI: 10.1016/S0140-6736(02)11196-2]
 - 48 **Wiesner RH**. A long-term comparison of tacrolimus (FK506) versus cyclosporine in liver transplantation: a report of the United States FK506 Study Group. *Transplantation* 1998; **66**: 493-499 [PMID: 9734494 DOI: 10.1097/00007890-199808270-00014]
 - 49 **Martins M**, Blais R. Evaluation of comorbidity indices for inpatient mortality prediction models. *J Clin Epidemiol* 2006; **59**: 665-669 [PMID: 16765268 DOI: 10.1016/j.jclinepi.2005.11.017]

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Prospective Study

Bacterial infections post-living-donor liver transplantation in Egyptian hepatitis C virus-cirrhotic patients: A single-center study

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Abstract

AIM

To determine risk factors, causative organisms and

antimicrobial resistance of bacterial infections following living-donor liver transplantation (LDLT) in cirrhotic patients.

METHODS

This prospective study included 45 patients with hepatitis C virus-related end-stage liver disease who underwent LDLT at Ain Shams Center for Organ Transplant, Cairo, Egypt from January 2014 to November 2015. Patients were followed-up for the first 3 mo after LDLT for detection of bacterial infections. All patients were examined for the possible risk factors suggestive of acquiring infection pre-, intra- and post-operatively. Positive cultures based on clinical suspicion and patterns of antimicrobial resistance were identified.

RESULTS

Thirty-three patients (73.3%) suffered from bacterial infections; 21 of them had a single infection episode, and 12 had repeated infection episodes. Bile was the most common site for both single and repeated episodes of infection (28.6% and 27.8%, respectively). The most common isolated organisms were gram-negative bacteria. *Acinetobacter baumannii* was the most common organism isolated from both single and repeated infection episodes (19% and 33.3%, respectively), followed by *Escherichia coli* for repeated infections (11.1%), and *Pseudomonas aeruginosa* for single infections (19%). Levofloxacin showed high sensitivity against repeated infection episodes ($P = 0.03$). *Klebsiella*, *Acinetobacter* and *Pseudomonas* were multi-drug resistant (MDR). Pre-transplant hepatocellular carcinoma (HCC) and duration of drain insertion (in days) were independent risk factors for the occurrence of repeated infection episodes ($P = 0.024$).

CONCLUSION

MDR gram-negative bacterial infections are common post-LDLT. Pre-transplant HCC and duration of drain insertion were independent risk factors for the occurrence of repeated infection episodes.

Key words: Living-donor liver transplantation; Bacterial infection; Multi-drug resistance; Hepatitis C virus; Liver cirrhosis

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Core tip: We evaluated 45 patients with hepatitis C virus-related end-stage liver disease for the occurrence of bacterial infections during the first 3 mo post-living-donor liver transplantation. Thirty-three patients (73.3%) suffered from bacterial infections; 21 of them had a single infection episode, and 12 had repeated infection episodes. Bile was the most common site for both single and repeated episodes of infection (28.6% and 27.8%, respectively). Multi-drug resistant gram-negative bacteria, especially *Klebsiella*, *Acinetobacter* and *Pseudomonas*, were the most commonly isolated bacteria. Pre-transplant hepatocellular carcinoma

and duration of drain insertion were independent risk factors for occurrence of repeated infection episodes.

Montasser MF, Abdelkader NA, Abdelhakam SM, Dabbous H, Montasser IF, Massoud YM, Abdelmoaty W, Saleh SA, Bahaa M, Said H, El-Meteini M. Bacterial infections post-living-donor liver transplantation in Egyptian hepatitis C virus-cirrhotic patients: A single-center study. *World J Hepatol* 2017; 9(20): 896-904 Available from: URL: <http://www.wjgnet.com/1948-5182/full/v9/i20/896.htm> DOI: <http://dx.doi.org/10.4254/wjh.v9.i20.896>

INTRODUCTION

Infection following living-donor liver transplantation (LDLT) is a serious problem with a high mortality rate reaching 50%. Many factors were associated with high risks of acquiring infection following LDLT, including the difficulty of surgery, the poor patient's condition, and the immunosuppressive drugs^[1].

Nearly 80% of recipients develop one infection episode during the first year, predominantly during the first three months post-transplant. Bacterial infections account for 50%-75% of infections post-LDLT and commonly occur in the first month post-transplant^[2].

Patients may become infected with antimicrobial-resistant bacteria, especially methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus faecalis*, *Clostridium difficile*, and gram-negative bacteria^[3]. Currently, multidrug-resistant (MDR) organisms are the most common cause of nosocomial infections in liver transplant recipients^[1].

Multiple organism infection is common as well as concurrent infections caused by different infectious agents^[4]. Infections are usually difficult to diagnose because the usual manifestations of infection, such as fever and leukocytosis, may be absent and because of the need to exclude an acute rejection episode^[5].

The aim of the present study was to determine risk factors, causative organisms and antimicrobial resistance patterns of bacterial infections following LDLT in Egyptian cirrhotic patients.

MATERIALS AND METHODS

Forty-five adult patients with hepatitis C virus (HCV)-related end-stage liver disease (ESLD) who were eligible for and underwent LDLT at Ain Shams Center for Organ Transplant, Cairo, Egypt, during the period from January 2014 to November 2015, were included in the current prospective study. They were followed-up for the first 3 mo post-LDLT for detection of bacterial infections.

Patients with other etiologies for ESLD (hepatitis B virus, primary biliary cirrhosis, and others) and patients with pre-operative infections, infections within 48 h after transplantation or early post-operative death

were excluded.

Each patient provided an informed written consent prior to enrollment. The study protocol was accepted by the Research Ethical Committee of the Faculty of Medicine-Ain Shams University. This was in accordance to the ethical guidelines of the 1975 Declaration of Helsinki.

Immunosuppressive drugs

Immediately following liver transplantation (LT), we used triple-therapy of immunosuppressive drugs which was comprised of a steroid, a calcineurin inhibitor: Cyclosporine or tacrolimus, and mycophenolate mofetil. In patients with renal dysfunction, immunosuppression with monoclonal antibodies to T-cells was used. In patients with hepatocellular carcinoma (HCC), tacrolimus monotherapy was used to decrease the incidence of HCC recurrence.

Antimicrobial prophylaxis

Piperacillin/tazobactam 4.5 mg/d was used post-operatively for 5 d. A polymerase chain reaction (PCR) assay for cytomegalovirus (CMV) was done every two weeks until patient's discharge. Ganciclovir for prevention of CMV disease was used if the PCR assay was positive.

Checked parameters

All patients were checked for the following parameters: (1) pre-operatively: Demographic data, other co-morbidities, presence of HCC, any bridging techniques, Child and MELD scores, CBC with differential cell count, liver profile, C-reactive protein, serum ferritin, documented or suspected SBP and third generation cephalosporin administration, renal impairment, and positive cultures; (2) intra-operatively: Total operative period, cold and warm ischemia time, amount of transfused blood or blood products and type of biliary anastomosis; and (3) post-operatively: Intensive care unit stay, ventilator duration, duration of central venous line and catheter insertion, duration of abdominal drain placement, dialysis post-transplant and immunosuppressive drugs.

Case identification

Post-operative infection was defined as any positive culture, based on clinical suspicion, within 3 mo following LDLT, according to the Centers for Disease Control and Prevention's definition of a nosocomial infection and as described in liver transplant recipients^[6,7]. The diagnosis of wound infection was established by the presence of redness/induration and the presence of pus on exploration and/or positive wound culture. The diagnosis of urinary tract infection was based upon the following criteria: The patient has at least one of the following symptoms or signs with no other identified cause: fever ($> 38^{\circ}\text{C}$), dysuria, frequency, urgency, suprapubic or costovertebral angle pain or tenderness, as well

as a positive urine culture, that is, $\geq 10^5$ CFU/mL of urine with no more than 2 species of microorganisms. The diagnosis of pneumonia was based upon the presence of pulmonary infiltrates together with clinical symptoms indicating lower respiratory tract infection, the identification of a relevant etiologic microorganism, and the absence of another possible diagnosis during the follow-up. Bloodstream infection was diagnosed when microorganisms were isolated from one blood culture. Ascitic fluid cultures were performed for all patients with manifestations of bacterial peritonitis or who were suspected of having bacterial peritonitis. Samples were collected before the start of any antimicrobial treatment. Bile samples were withdrawn for those suspected of having a biliary tract infection. In cases of suspected sepsis-induced cholestasis, cultures from blood, the biliary tube, abdominal drains, urine, and sputum were collected, and culture based-treatment was started accordingly.

The term multidrug-resistant (MDR) was used to refer to pathogens resistant to three or more classes of the following antibiotics: extended-spectrum penicillins, 3rd generation cephalosporins, quinolones, carbapenems, and aminoglycosides^[8].

Recruited patients were divided into two groups. Group 1 included patients who had a single episode of post-operative bacterial infection, and Group 2 included those patients who had more than one episode of a bacterial infection.

Statistical analysis

Statistical analyses were performed using IBM® SPSS® Statistics version 22 (IBM® Corp., Armonk, NY, United States). Continuous numerical variables were shown as the mean and standard deviation, and differences between groups were compared using the unpaired *t* test. Discrete numerical variables were shown as the median and interquartile range, and the Mann-Whitney test was used to compare intergroup differences. Categorical data were shown as ratios or as the number and percentage, and differences between groups were compared using Pearson's χ^2 test or Fisher's exact test. Variables shown to be significantly associated with the occurrence of repeated infection episodes by univariate analysis were entered in multivariate binary logistic regression analysis to identify independent predictors of this outcome. Time-to-event analysis was done using the Kaplan-Meier method, and the log-rank test was used to compare individual Kaplan-Meier curves. A *P*-value < 0.05 was considered significant.

The statistical methods for this study were performed by Sameh M. Hakim, Diploma of Medical Biostatistics, Faculty of Medicine of Ain Shams University, Cairo, Egypt.

RESULTS

The present study enrolled forty-five adult patients

Table 1 Comparison between patients who developed post-living-donor liver transplantation single episode and those who developed repeated episodes of infection regarding pre-operative parameters *n* (%)

	Single episode of infection (<i>n</i> = 21)	Repeated episodes of infection (<i>n</i> = 12)	<i>P</i> value
Recipient's age (yr, mean ± SD)	51.2 ± 8.3	52.08 ± 8.7	0.767
Donor's age (yr, mean ± SD)	26.9 ± 6.3	32.3 ± 6.1	0.021
Recipient's gender (male/female)	19/2	12/0	0.523
Donor's gender (male/female)	19/2	10/2	0.610
Hepatocellular carcinoma	6 (28.6)	8 (66.7)	0.033
History of bridging procedures ¹	4 (19.0)	6 (50.0)	0.114
History of SBP	10 (47.6)	1 (8.3)	0.052
History of paracentesis	11 (52.4)	4 (33.3)	0.290
Diabetes mellitus	8 (38.1)	5 (41.7)	1.000
Child-Pugh class (B/C)	10/11	5/7	0.741
MELD score (median, interquartile range)	14 (12-16)	16 (15-18)	0.136
Thrombocytopenia ²	20 (95.2)	12 (100.0)	1.000
Leucopenia ³	9 (42.9)	5 (41.7)	0.947
Renal impairment	2 (9.5)	1 (8.3)	1.000
High serum ferritin ⁴	13 (61.9)	5 (41.7)	0.261
High C-reactive protein ⁵	14 (66.7)	11 (91.7)	0.206

¹Bridging procedures included: Radiofrequency ablation, trans-arterial chemo-embolization and micro-wave ablation; ²Thrombocytopenia: Platelets less than 150000/mm³; ³Leucopenia: WBCs less than 4000/mm³; ⁴High serum ferritin: More than 333 ng; ⁵High C-reactive protein: More than 0.5 mg/L. SBP: Spontaneous bacterial peritonitis.

with HCV-related ESLD, and each patient was followed-up for 3 mo post-LDLT for the occurrence of bacterial infections. Thirty-three patients (73.3%) suffered from bacterial infections post-transplant and fulfilled the inclusion criteria. They were further subdivided into two groups. Group 1 included 21 patients who developed a single episode of infection (19 males and 2 females), and Group 2 included 12 patients (all of them were males) who developed recurrent episodes of infection (total number of attacks = 36) throughout the follow-up period.

Table 1 shows the comparison between patients who developed a single episode of infection post-LDLT and those who developed repeated episodes of infection regarding pre-operative parameters. The presence of pre-transplant hepatocellular carcinoma (HCC) showed a statistically significant increased risk of developing repeated episodes of infection post-LDLT (*P* = 0.033).

There was no significant difference between patients who developed a single episode and those who developed repeated episodes of infection regarding the operative details (*P* > 0.05) (Table 2).

Table 3 shows that the duration of drain insertion revealed a statistically significant increased risk for the development of repeated episodes of infection (*P* = 0.002).

Table 4 shows that bile was found to be the most common site for both single and repeated episodes of infection (28.6% and 27.8%, respectively), followed by the bloodstream for repeated infection episodes (22.2%) and drains for a single infection episode (23.8%).

The most common isolated organisms were gram-negative bacteria for both single and repeated episodes of infections. *Acinetobacter baumannii* was found

solely to be the most common organism isolated from both single and repeated infection episodes (19% and 33.3%, respectively), followed by *Escherichia coli* (*E. coli*) for repeated infections (11.1%), and *Pseudomonas aeruginosa* for a single infection (19%). Additionally, *Acinetobacter baumannii* was found in combination with other organisms in three cultures.

Table 5 shows the antimicrobial sensitivity pattern in patients who suffered from single vs repeated episodes of infection. The sensitivity of levofloxacin was found to be statistically significant against repeated episodes of infection (*P* = 0.03). Repeated episodes of infection showed 100% resistance to penicillins. Single episodes of infection were 100% resistant to ciprofloxacin and co-trimoxazole. Both single and repeated episodes of infections were 100% resistant to cefotaxime and aztreonam.

Regarding the pattern of resistance of isolated organisms to the major antibiotic groups, most of the isolated gram-negative organisms were found to be resistant to several groups of antibiotics; especially *Klebsiella* species, *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, all of which were proven to be MDR.

The detailed antibiotic-resistance pattern was as follows: For *Klebsiella* species, 100% of the isolates showed resistance to each of the quinolones and aminoglycosides, 87.5% showed resistance to cephalosporins, 80% to carbapenems, and 25% showed resistance to piperacillin-tazobactam. For *Acinetobacter baumannii*, 100% of the isolates showed resistance to aminoglycosides, 60% to carbapenems, 46.5% to quinolones, 42% to cephalosporins, and 33.3% showed resistance to piperacillin-tazobactam. For *Pseudomonas aeruginosa*, 100% of the isolates showed resistance to quinolones, and 83.3% showed

Table 2 Comparison between patients who developed single episode and those who developed repeated episodes of infection regarding operative details

	Single episode of infection (<i>n</i> = 21)	Repeated episodes of infection (<i>n</i> = 12)	<i>P</i> value
CIT (min), mean ± SD	43.6 ± 17.3	50.8 ± 17.7	0.259
WIT (min), mean ± SD	45.7 ± 13.4	50.8 ± 12.4	0.288
Recipient's operative time (h), mean ± SD	10.3 ± 1.1	10.5 ± 1.5	0.704
Packed red cell transfusion (U), (median, interquartile range)	2 (2-4)	3 (2-6)	0.493

CIT: Cold ischemia time; WIT: Warm ischemia time.

Table 3 Length of intensive care unit stay, length of exposure to invasive procedures, and time to occurrence of infection in patients who suffered from single *vs* repeated episodes of infection

	Single episode of infection (<i>n</i> = 21)	Repeated episodes of infection (<i>n</i> = 12)	<i>P</i> value
Length of ICU stay (d)	6 (5-7)	7 (5-7)	0.969
Days on mechanical ventilator	1 (1-1)	1 (1-1)	0.176
Days with CVC	6 (5-7)	6 (5-7)	0.770
Days with urinary catheter	6 (5-7)	7 (6-8)	0.467
Days with drains	17 (15-20)	25 (21-30)	0.002
Time-to-infection (d)	14 (12-17)	9 (6-19)	0.189

Data are presented as median (interquartile range). ICU: Intensive care unit; CVC: Central venous catheter.

Table 4 Site of infection and implicated organisms in patients who suffered from single *vs* repeated episodes of infection *n* (%)

	Single episode (<i>n</i> = 21)	Repeated episodes (<i>n</i> = 36) ¹	<i>P</i> value
Site of organism isolation			0.896
Bile	6 (28.6)	10 (27.8)	
Wound	1 (4.8)	2 (5.6)	
Sputum	3 (14.3)	7 (19.4)	
Drains	5 (23.8)	7 (19.4)	
Blood	3 (14.3)	8 (22.2)	
Urine	2 (9.5)	2 (5.6)	
Ascitic fluid	1 (4.8)	0 (0.0)	
Organism isolated			0.456
<i>Coagulase (-) Staph. aureus</i>	3 (14.3)	1 (2.8)	
<i>Staph. aureus</i>	0 (0.0)	1 (2.8)	
MRSA	3 (14.3)	1 (2.8)	
<i>E. coli</i>	2 (9.5)	4 (11.1)	
<i>Klebsiella species</i>	2 (9.5)	3 (8.3)	
<i>Pseudomonas aeruginosa</i>	4 (19.0)	3 (8.3)	
<i>Acinetobacter baumannii</i>	4 (19.0)	12 (33.3)	
<i>Proteus</i>	0 (0.0)	2 (5.6)	
<i>Enterobacteriaceae</i>	1 (4.8)	1 (2.8)	
<i>Enterococci</i>	1 (4.8)	2 (5.6)	
<i>Bacillus species</i>	0 (0.0)	2 (5.6)	
<i>Pseudomonas + Acinetobacter</i>	1 (4.8)	0 (0.0)	
<i>Pseudomonas + Klebsiella</i>	0 (0.0)	2 (5.6)	
<i>Acinetobacter + Klebsiella</i>	0 (0.0)	1 (2.8)	
<i>Acinetobacter + coagulase (-) Staph. aureus</i>	0 (0.0)	1 (2.8)	

¹Represents the total number of attacks occurred among the 12 patients who developed repeated episodes of infections. MRSA: Methicillin-resistant *Staphylococcus aureus*.

resistance to cephalosporins. Meanwhile, 100% of them were sensitive to aminoglycosides, piperacillin-tazobactam and carbapenems. For *E. coli*, 70% of the isolates showed resistance to cephalosporins,

50% to quinolones, and 25% showed resistance to aminoglycosides. Moreover, 100% of them were sensitive to piperacillin-tazobactam and carbapenems.

Table 6 and Figure 1 show that the two variables identified by multivariate analysis as independent risk factors for the occurrence of repeated episodes of infection were HCC and the duration of drain insertion (in days) (*P* = 0.024 and odds ratio = 25.44 and 1.38, respectively).

The median time-to-infection was 14 d in the single infection episode group and 8.5 d in the repeated infection episodes group, with no significant difference observed between groups (*P* = 0.647) (Table 7 and Figure 2).

DISCUSSION

Infectious complications have become the most common sources of mortality and morbidity following LT. Multiple organism infection is common. The occurrence of infection following LT is due to the dysfunction of the patient's defensive mechanisms, as a result of liver cirrhosis and the use of immunosuppressant drugs^[4].

The current study included 45 patients with HCV-related ESLD who were eligible for and underwent LDLT at Ain Shams Center for Organ Transplant, Cairo, Egypt during the period from January 2014 to November 2015. They were followed-up for the first 3 mo post-LDLT for the detection of bacterial infections.

In the current study, 73.3% of included patients developed a nosocomial bacterial infection in the first 3 mo post-LDLT. This finding is in agreement with previous reports, which denoted a high incidence of bacterial infections post-LDLT ranging from 50% to 75%^[1,2].

Table 5 Antimicrobial sensitivity in patients who suffered from single *vs* repeated episodes of infection *n* (%)

Antimicrobial		All episodes of infection (<i>n</i> = 57)	Single episode of infection (<i>n</i> = 21)	Repeated episodes of infection (<i>n</i> = 36)	<i>P</i> value
Levofloxacin	S	11 (52.4)	2 (22.2)	9 (75.0)	0.030
	R	10 (47.6)	7 (77.8)	3 (25.0)	
Ciprofloxacin	S	5 (38.5)	0 (0.0)	5 (45.5)	0.487
	R	8 (61.5)	2 (100.0)	6 (54.5)	
Co-trimoxazole	S	1 (7.1)	0 (0.0)	1 (10.0)	1.000
	R	13 (92.9)	4 (100.0)	9 (90.0)	
Penicillin	S	1 (11.1)	1 (14.3)	0 (0.0)	1.000
	R	8 (88.9)	6 (85.7)	2 (100.0)	
Doxycycline	S	14 (77.8)	5 (100.0)	9 (69.2)	0.278
	R	4 (22.2)	0 (0.0)	4 (30.8)	
Vancomycin	S	8 (88.9)	4 (100.0)	4 (80.0)	1.000
	R	1 (11.1)	0 (0.0)	1 (20.0)	
Piperacillin-tazobactam	S	8 (72.7)	3 (75.0)	5 (71.4)	1.000
	R	3 (27.3)	1 (25.0)	2 (28.6)	
Aminoglycosides	S	9 (75.0)	1 (50.0)	8 (80.0)	0.455
	R	3 (25.0)	1 (50.0)	2 (20.0)	
Imipenem	S	20 (69.0)	8 (88.9)	12 (60.0)	0.201
	R	9 (31.0)	1 (11.1)	8 (40.0)	
Ceftriaxone	S	7 (38.9)	1 (16.7)	6 (50.0)	0.316
	R	11 (61.1)	5 (83.3)	6 (50.0)	
Cefotaxime	R	8 (100.0)	7 (100.0)	1 (100.0)	-
Aztreonam	R	6 (100.0)	1 (100.0)	5 (100.0)	-

S: Sensitive; R: Resistant.

Table 6 Multivariate binary logistic regression model for prediction of the occurrence of repeated episodes of infection

	Regression coefficient	SE	Odds ratio	95%CI	<i>P</i> value
Donor's age (yr)	0.05	0.08	1.05	0.90-1.23	0.552
Hepatocellular carcinoma (HCC = 1, no HCC = 0)	3.24	1.43	25.44	1.53-422.21	0.024
Duration of drain insertion (d)	0.32	0.14	1.38	1.04-1.83	0.024
Constant	-10.28				
Model diagnostics					
-2 Log Likelihood test			<i>P</i> value, < 0.001		
Hosmer and Lemeshow test			<i>P</i> value, 0.369		
Correct classification rate			87.88%		
ROC curve analysis					
AUC		0.935 (95%CI: 0.791-0.991; <i>P</i> value < 0.0001)			
Sensitivity, %		91.7 (95%CI: 61.5-99.8)			
Specificity, %		81.0 (95%CI: 58.1-94.6)			
PPV, %		73.3 (95%CI: 43.8-92.7)			
NPV, %		94.4 (95%CI: 72.7-99.9)			

HCC: Hepatocellular carcinoma; AUC: Area under ROC curve; ROC: Receiver-operating characteristic; PPV: Positive predictive value; NPV: Negative predictive value.

In the current study, the presence of pre-transplant HCC was an independent risk factor for the occurrence of repeated episodes of bacterial infection in the recipients during the early post-transplant period. HCC patients are more susceptible to infection due to poor long-term nutrition, poor physical condition and weak immune system^[1].

In the present study, the duration of time for abdominal drain placement was considered an independent risk factor for the development of repeated episodes of bacterial infection as confirmed by the multivariate binary logistic regression model. Patients with prolonged drain insertion time had an increased risk of developing recurrent episodes of infection compared to

patients who had less drain insertion time.

Results in our study revealed that the major sites of bacterial infections in patients who experienced a single infection episode were as follows: Bile (28.6%), followed by the drains (23.8%), sputum (14.3%), bloodstream infections (14.3%), urine (9.5%) and lastly wound and ascitic fluid infection (4.8% each). These results were in accordance with another Egyptian multicenter study performed by Mukhtar *et al*^[11]. In contrast, Kim *et al*^[9] and Iida *et al*^[10] revealed that the most dominant bacterial infection was bacteremia, which was catheter-related. El-Araby *et al*^[11] showed that the main sites of infection were the chest (24.4%), followed by the bile duct or cholangitis (17.1%), and

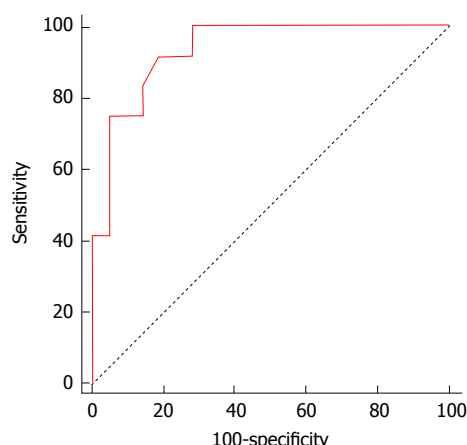


Figure 1 Receiver-operating characteristic curve derived from the multivariate binary logistic regression model for prediction of the occurrence of repeated episodes of infection. AUC = 0.935 (95%CI: 79.1%-99.1%; $P < 0.0001$); sensitivity: 91.7% (95%CI: 61.5%-99.8%); specificity: 81.0% (95%CI: 58.1%-94.6%); PPV: 73.3% (95%CI: 43.8%-92.7%); NPV: 94.4% (95%CI: 72.7%-99.9%). AUC: Area under ROC curve; PPV: Positive predictive value; NPV: Negative predictive value.

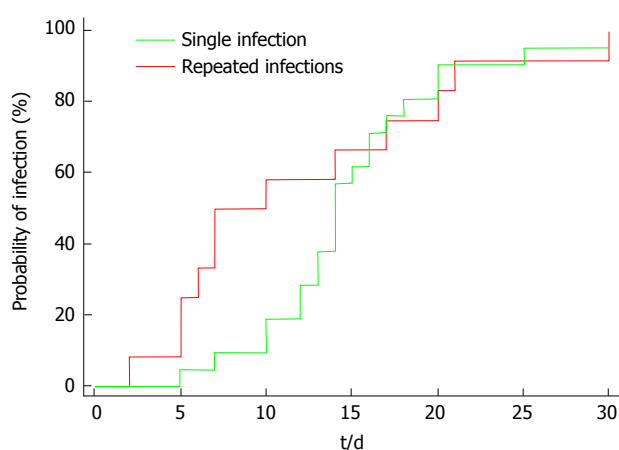


Figure 2 Kaplan-Meier curves for the time-to-infection in patients who suffered from single and repeated episodes of infection. HR = 1.16 (95%CI: 56%-92.4%; $P = 0.647$).

lastly the bloodstream (12.2%). However, Kawecki *et al.*^[12] revealed that the urinary tract was the main site of infection after LDLT. The discrepancies between the major sites of post-transplant infection between the different centers are most likely related to the variability of the hygienic measures, infection control programs, as well as the peri-, intra- and post-operative disparities.

In the current study, the most common isolated organisms were the gram-negative bacteria for both single and repeated episodes of infections, and these results were consistent with El-Araby *et al.*^[11] and Linares *et al.*^[13]. Shi *et al.*^[14] reported the same results and explained that the prevalence of gram-negative bacteria may be because these bacteria are inhabitants of the digestive tract. In the current study, *Acinetobacter baumannii* and *Pseudomonas aeruginosa* were found to be the most common organisms in the

Table 7 Results of the Kaplan-Meier analysis for time to infection in patients who suffered from single and repeated infection episodes

	Single infection episode ($n = 21$)	Repeated infection episodes ($n = 12$)
Median time to infection (d)	14 (95%CI: 13-16)	8.5 (95%CI: 6-17)
Hazard ratio	1.16 (95%CI: 56-2.40)	
Log-rank test	P value = 0.647	

single infection episode group (19% each), followed by methicillin resistant *Staphylococcus aureus* (MRSA) and coagulase-negative *Staphylococcus aureus* (14.3% each), and *Klebsiella* species and *E. coli* (9.5% each). These results were in accordance with Zhong *et al.*^[15]. However, Sganga *et al.*^[5] and Iida *et al.*^[10] concluded that *Pseudomonas aeruginosa* was the most common isolated organism.

At present, MDR organisms are the most common causes of nosocomial infections in post-LDLT patients. Zhong *et al.*^[15] found that MDR gram-negative bacilli were isolated in 56% of patients with gram-negative infection, which was in accordance with Shi *et al.*^[14], who stated that the three most common pathogens of MDR gram-negative bacilli were *Acinetobacter baumannii*, *E. coli* and *Klebsiella* species. This finding is not fully consistent with a previous report by Pappas *et al.*^[16] who found that the four most common MDR gram-negative bacilli were *E. coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. The difference in the findings between the studies was related to differences in patients' underlying diseases and nosocomial infections.

Our results are consistent to some extent with that of Mukhtar *et al.*^[1] in their retrospective multicenter Egyptian study on bacterial infections post-LDLT. The authors reported that *Pseudomonas aeruginosa* was the most commonly isolated species (26%), followed by *Klebsiella* (19%), *E. coli* (16%), *Acinetobacter baumannii* (8%), and MRSA (7.7%). In their study, 75% of the gram-negative bacteria were MDR, including 90% of *Acinetobacter baumannii* isolates, 76% of *Pseudomonas aeruginosa* isolates, 57% of *Klebsiella* species isolates, and 53% of *E. coli* isolates.

Our study revealed that most of the gram-negative organisms were found to be resistant to several groups of antibiotics, especially *Klebsiella* species, *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, which proved to be MDR. In the study of Zhong *et al.*^[15], *Acinetobacter baumannii* displayed resistance to all antibiotic groups, including β -lactams, quinolones, and aminoglycosides and even showed high resistance to carbapenems, including 100% resistance to meropenem and imipenem. *E. coli* was found to be sensitive to aminoglycosides, carbapenems and piperacillin-tazobactam but showed a pattern of resistance to cephalosporins. Among all the antibiotics used in the current cohort, levofloxacin was found to be of

statistical significance regarding its sensitivity in the treatment of repeated episodes of infection.

It is worth mentioning that all infection episodes in our study occurred in the first month post-operative and by applying Kaplan-Meier analysis for time-to-infection. The median time-to-infection was 14 d in the single infection episode group and 8.5 d in the repeated infection episodes group. Similarly, previous studies have reported that the majority of bacterial infections occurred during the first month following LT^[1,17].

In conclusion, MDR gram-negative bacterial infections are common post-LDLT. Pre-transplant HCC and duration of drain insertion are independent risk factors for the occurrence of repeated infection episodes.

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COMMENTS

Background

Bacterial infections are common following living-donor liver transplantation (LDLT), especially multiple-organism infections. The occurrence of infection following liver transplantation is due to the dysfunction of the patient's defensive mechanisms, as a result of liver cirrhosis and the use of immunosuppressant drugs.

Research frontiers

The authors assessed 45 patients with hepatitis C virus-related end-stage liver disease for the occurrence of bacterial infections during the first 3 mo post-LDLT. Thirty-three patients (73.3%) suffered from bacterial infections; 21 patients experienced a single episode of infection, and 12 patients experienced repeated episodes of infection. Bile was the most common site for both single and repeated episodes of infection (28.6% and 27.8%, respectively). Multi-drug resistant (MDR) gram-negative bacteria, especially *Klebsiella*, *Acinetobacter* and *Pseudomonas*, were the most commonly isolated bacteria. Pre-transplant hepatocellular carcinoma and duration of drain insertion were independent risk factors for the occurrence of repeated infection episodes.

Innovations and breakthroughs

This study is a single-center Egyptian study that addresses risk factors, causative organisms and antimicrobial resistance of bacterial infections following LDLT in cirrhotic patients.

Applications

The findings in this study may help in determining the proper antimicrobial prophylaxis for cirrhotic patients pre-LDLT.

Terminology

MDR was used to refer to pathogens resistant to three or more classes of the following antibiotics: Extended-spectrum penicillins, 3rd generation cephalosporins, quinolones, carbapenems, and aminoglycosides.

Peer-review

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REFERENCES

1 Mukhtar A, Abdelaal A, Hussein M, Dabous H, Fawzy I, Obayah

- G, Hasanin A, Adel N, Ghaith D, Bahaa M, Abdelaal A, Fathy M, El Meteini M. Infection complications and pattern of bacterial resistance in living-donor liver transplantation: a multicenter epidemiologic study in Egypt. *Transplant Proc* 2014; **46**: 1444-1447 [PMID: 24935311 DOI: 10.1016/j.transproceed.2014.02.022]
- 2 Saner FH, Olde Damink SW, Pavlakovic G, van den Broek MA, Rath PM, Sotiropoulos GC, Radtke A, Canbay A, Paul A, Nadalin S, Malagó M, Broelsch CE. Pulmonary and blood stream infections in adult living donor and cadaveric liver transplant patients. *Transplantation* 2008; **85**: 1564-1568 [PMID: 18551060 DOI: 10.1097/TP.0b013e31816f61a6]
- 3 del Pozo JL. Update and actual trends on bacterial infections following liver transplantation. *World J Gastroenterol* 2008; **14**: 4977-4983 [PMID: 18763277 DOI: 10.3748/wjg.14.4977]
- 4 Fagioli S, Colli A, Bruno R, Burra P, Craxi A, Gaeta GB, Grossi P, Mondelli MU, Puoti M, Sagnelli E, Stefani S, Toniutto P. Management of infections in cirrhotic patients: report of a consensus conference. *Dig Liver Dis* 2014; **46**: 204-212 [PMID: 24021271 DOI: 10.1016/j.dld.2013.07.015]
- 5 Sganga G, Bianco G, Fiori B, Nure E, Spanu T, Lirosi MC, Frongillo F, Agnes S. Surveillance of bacterial and fungal infections in the postoperative period following liver transplantation: a series from 2005-2011. *Transplant Proc* 2013; **45**: 2718-2721 [PMID: 24034031 DOI: 10.1016/j.transproceed.2013.08.010]
- 6 Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections, 1988. *Am J Infect Control* 1988; **16**: 128-140 [PMID: 2841893]
- 7 CDC definitions for nosocomial infections, 1988. *Am Rev Respir Dis* 1989; **139**: 1058-1059 [PMID: 2539031 DOI: 10.1164/ajrccm/139.4.1058]
- 8 Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, Harbarth S, Hindler JF, Kahlmeter G, Olsson-Liljequist B, Paterson DL, Rice LB, Stelling J, Struelens MJ, Vatopoulos A, Weber JT, Monnet DL. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clin Microbiol Infect* 2012; **18**: 268-281 [PMID: 21793988 DOI: 10.1111/j.1469-0691.2011.03570.x]
- 9 Kim SI, Kim YJ, Jun YH, Wie SH, Kim YR, Choi JY, Yoon SK, Moon IS, Kim DG, Lee MD, Kang MW. Epidemiology and risk factors for bacteremia in 144 consecutive living-donor liver transplant recipients. *Yonsei Med J* 2009; **50**: 112-121 [PMID: 19259357 DOI: 10.3349/ymj.2009.50.1.112]
- 10 Iida T, Kaido T, Yagi S, Yoshizawa A, Hata K, Mizumoto M, Mori A, Ogura Y, Oike F, Uemoto S. Posttransplant bacteremia in adult living donor liver transplant recipients. *Liver Transpl* 2010; **16**: 1379-1385 [PMID: 21117247 DOI: 10.1002/lt.22165]
- 11 El-Araby H, Ghoneim EM, Abd Elaziz AM, Ibrahim TM. Early infections after Living Donor Liver Transplantation in Egyptian Children (Single center experience). *EJMM* 2010; **19**: 67-75. Available from: URL: <https://www.yumpu.com/en/document/view/41683533/amal-a-wafy-md-kamal-m-hanna-md-ayman-salem-md-9>
- 12 Kawecki D, Pacholczyk M, Łagiewska B, Adadyński L, Lisik W, Sawicka-Grzelak A, Durlak M, Paczek L, Chmura A, Mlynarczyk G, Rowinski W, Luczak M. Urinary tract infections in the early posttransplant period after liver transplantation: etiologic agents and their susceptibility. *Transplant Proc* 2011; **43**: 3052-3054 [PMID: 21996222 DOI: 10.1016/j.transproceed.2011.09.003]
- 13 Linares L, Garcia-Gomez JF, Cervera C, Almela M, Sanclemente G, Cofán F, Ricart MJ, Navasa M, Moreno A. Early bacteremia after solid organ transplantation. *Transplant Proc* 2009; **41**: 2262-2264 [PMID: 19715892 DOI: 10.1016/j.transproceed.2009.06.079]
- 14 Shi SH, Kong HS, Xu J, Zhang WJ, Jia CK, Wang WL, Shen Y, Zhang M, Zheng SS. Multidrug resistant gram-negative bacilli as predominant bacteremic pathogens in liver transplant recipients. *Transpl Infect Dis* 2009; **11**: 405-412 [PMID: 19638006]
- 15 Zhong L, Men TY, Li H, Peng ZH, Gu Y, Ding X, Xing TH, Fan JW. Multidrug-resistant gram-negative bacterial infections after liver transplantation-spectrum and risk factors. *J Infect* 2012; **64**: 299-310 [PMID: 22198738 DOI: 10.1016/j.jinf.2011.12.005]
- 16 Pappas PG, Kauffman CA, Andes D, Benjamin DK, Calandra TF,

Edwards JE, Filler SG, Fisher JF, Kullberg BJ, Ostrosky-Zeichner L, Reboli AC, Rex JH, Walsh TJ, Sobel JD. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2009; **48**:

503-535 [PMID: 19191635 DOI: 10.1093/cid/civ933]

- 17 **Romero FA**, Razonable RR. Infections in liver transplant recipients. *World J Hepatol* 2011; **3**: 83-92 [PMID: 21603030 DOI: 10.4254/wjh.v3.i4.83]

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Changing landscape of hepatitis C virus-positive donors

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antiviral therapies, there has been a dramatic increase in the use of the hepatitis C virus (HCV)-positive livers in HCV-positive recipients. In the majority of studies, HCV positivity was defined as a donor testing HCV Ab positive. In 2015, all Organ Procurement Organizations were mandated to perform and report HCV Nucleic Acid Amplification Testing (NAT) results on all deceased and living donors. Studies are not yet available on how organs are being utilized based on NAT status and whether NAT status affects recipient outcomes. Further studies are needed to maximize the use of these organs.

Key words: Hepatitis C organ utilization; Hepatitis C virus aviremic; Liver transplantation; Hepatitis C positive recipients

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Core tip: For many years hepatitis C virus (HCV) positive livers have been used with caution in carefully selected mostly HCV-positive patients. With the introduction of the new highly effective antiviral therapies discard rate of HCV-positive livers, although improved, continues to be high. On August 10, 2015, the United Network for Organ Sharing mandated all Organ Procurement Organizations to perform and report HCV Nucleic Acid Amplification Testing (NAT) results on all deceased and living donors. We believe further research in the outcome of viremic and aviremic HCV livers is needed so that the utilization of these organs can be maximized in HCV NAT + and potentially HCV NAT - recipients.

Kling CE, Limaye AP, Sibulesky L. Changing landscape of hepatitis C virus-positive donors. *World J Hepatol* 2017; 9(20): 905-906 Available from: URL: <http://www.wjgnet.com/1948-5182/full/v9/i20/905.htm> DOI: <http://dx.doi.org/10.4254/wjh.v9.i20.905>

Abstract

With the introduction of the new highly effective

TO THE EDITOR

In the face of liver graft shortage, increasing numbers

of extended criteria or marginal grafts are being used. Such grafts include those from donors after circulatory death, older donors, livers with steatosis, and livers from donors infected with hepatitis C. For many years, hepatitis C (HCV) positive livers have been used with caution in carefully selected mostly HCV positive patients.

In the recent study Bowring *et al.*^[1] noted that with the introduction of the new highly effective antiviral therapies, there has been a dramatic increase, from 6.9% to 16.9%, in the use of the HCV-positive livers in HCV-positive recipients. The authors demonstrated that the allograft survival in HCV-positive recipients was similar for patients who received an HCV-positive liver and those who received an HCV-negative liver. Despite a better use of these organs, the reluctance to utilize these livers continues, demonstrated by the 1.7 times higher discard rate when compared to non-infected liver allografts^[1].

In the majority of studies, HCV positivity is defined as a donor testing HCV Ab positive. However, there is variability among HCV Ab positive donors - some donors are actively viremic and hence are HCV Ab positive and RNA positive by Nucleic Acid Amplification Testing (NAT), while others are Ab positive but aviremic and NAT negative. Approximately 10%-25% of people will spontaneously clear the virus without treatment^[2,3] and thus would be Ab positive NAT negative. Other donors have cleared the virus with treatment. Sustained virologic response, defined as aviremia 24 wk after completion of antiviral therapy for chronic HCV infection, would also result in Ab positive NAT negative serostatus, and relapse and thus transmission of infection is expected to be minimal.

On August 10, 2015, the United Network for Organ

Sharing mandated all Organ Procurement Organizations perform and report HCV NAT results on all deceased and living donors^[4]. As a result, transplant centers must specify whether candidates who are listed as accepting livers from HCV Ab positive donors are willing to accept organs from NAT positive and/or NAT negative donors. Studies are not yet available on how organs are being utilized based on NAT status and whether NAT status affects recipient outcomes, but given the difference in viremic status between the two populations, there likely is a difference.

As a result of these changes in donor testing and recipient listing, and in the era of new DAA therapies, we believe further research in the outcome of viremic and aviremic HCV livers is needed so that the utilization of these organs can be maximized in HCV NAT + and potentially HCV NAT-recipients.

REFERENCES

- 1 **Bowring MG**, Kucirka LM, Massie AB, Luo X, Cameron A, Sulkowski M, Rakestraw K, Gurakar A, Kuo I, Segev DL, Durand CM. Changes in Utilization and Discard of Hepatitis C-Infected Donor Livers in the Recent Era. *Am J Transplant* 2017; **17**: 519-527 [PMID: 27456927 DOI: 10.1111/ajt.13976]
- 2 **Villano SA**, Vlahov D, Nelson KE, Cohn S, Thomas DL. Persistence of viremia and the importance of long-term follow-up after acute hepatitis C infection. *Hepatology* 1999; **29**: 908-914 [PMID: 10051497 DOI: 10.1002/hep.510290311]
- 3 **Micallef JM**, Kaldor JM, Dore GJ. Spontaneous viral clearance following acute hepatitis C infection: a systematic review of longitudinal studies. *J Viral Hepat* 2006; **13**: 34-41 [PMID: 16364080 DOI: 10.1111/j.1365-2893.2005.00651.x]
- 4 **UNet System Notice**. Upcoming Waitlist and DonorNet changes will reflect policy changes regarding infectious diseases screening [Internet]. UNOS System Notices-General Notice. 2017 [cited 16 March 2017]. Available from: URL: <https://portal.unos.org/ViewSystemNotice.aspx?id=3074>

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