Clinical endpoints in liver transplantation according to value based care

Due to the nature and the complexity of the topics treated and the substantial lack of focused evidence, with particular reference to direct comparisons between different endpoints, the analysis has not been developed starting from PICO questions.
More general research questions have been formulated to produce a literature search, to select relevant evidence and to draft “good clinical practice recommendations” according to the GRADE definition.

Research questions

1. Which is the best single measure to evaluate the liver transplantation process as a whole from the VBC perspective?
   a. Gain in life years (whether QALY adjusted or not)
   b. Reduction in life years lost (whether QALY adjusted or not)

2. When gain in life years or reduction in years lost are not available/calculable which is the best measure to describe the transplant process from a VBM perspective?

   a. ITT survival
   b. Posttransplant survival
   c. Graft survival
   d. Others*

3. What is the most appropriate time frame to assess liver transplant outcomes from a VBM perspective?
   a. 5 years
   b. 10 years
   c. 20 years
   d. Others*

4. In liver transplant recipients which is the best tool to adjust for quality of life in life gain of liver transplantation?

5. Which are the unmet needs in defining the critical PROMs and PREMs to be included in liver transplant “core” evaluation and clinical trial design?

6. In a setting with optimal potential candidate referral and listing process, which is the best measure to evaluate the quality of waiting list management in a VBHM perspective?
   a. waiting list dropout because of death/deterioration
   b. waiting list mortality
   c. others*

7. Which is the best metric to describe the quality of early postoperative course?

8. Which is the best metrics to describe the quality of late posttransplant course?

Metrics of liver transplantation as a process

QUESTION 1: Which is the best single measure to evaluate liver transplantation process as a whole from the VBC perspective?
- Gain in life years (whether QALY adjusted or not)
- Reduction in life years lost (whether QALY adjusted or not)
- Others

Coordinator Umberto Cillo

INTRODUCTION

Both intent to treat (from patient listing) gain in life years (whether QALY adjusted or not) and intent to treat reduction in life years lost (whether QALY adjusted or not) are adequate metrics to measure liver transplantation process as a whole since they capture factors impacting the waitlist phase, donor availability and donor-recipient matching, the intraoperative phase and the posttransplant course at various endpoints. These two metrics have been diffusely used in measuring liver transplantation results. Gain in life expectancy is the most adopted metrics in cost effectiveness analysis. The best QALY adjustment has still to be determined and validated.

Search strategy (systemic search) used to query the literature
Resources: Medline, Embase and the Transplant Library

1. (life years gained or life-years gained or LYG or life years saved or life-years saved or life years lost or life-years lost or LYL or years of potential life lost or YPLL or potential years of life lost or PYLL).mp.
2. ((life years adj5 gained) or (life-years adj5 gained)).mp.
3. ((life years adj5 lost) or (life-years adj5 lost)).mp.
4. or/1-3
5. liver transplantation/
6. (liver transplant or liver transplantation).ti,ab.
7. 5 or 6
8. 4 and 7
9. limit 8 to yr="1990 - 2022"
10. remove duplicates from 9

The time period in which the published literature has been reviewed
1990-2022
Used exclusion criteria
- Any language other than English
- Studies published <1990 (search date: 06/09/2022)
- Paediatric patients

The number of references found (after removal of duplicates)
The search identified 89 potentially relevant references.
The final number of papers included/meeting the PICO criteria (including type of study)
9
Received support from the Centre for Evidence in Transplantation (CET) in drafting the search query
• Yes

PUBLICATION	STUDY DESIGN	RISK OF BIAS	QUALITY	IMPORTANCE	RECOMMENDATION
Barber, K., et al. (2007). "Life expectancy of adult liver allograft recipients in the UK." Gut 56(2): 279-282.	RETROSPECTIVE	not serious	moderate	important but not critical	strong for
Bonsel, G. J., et al. (1990). "Use of prognostic models for assessment of value of liver transplantation in primary biliary cirrhosis." Lancet 335(8688):	RETROSPECTIVE	serious	low	important but not critical	weak for
Cadier, B., et al. (2017). "Early detection and curative treatment of hepatocellular carcinoma: A cost-effectiveness analysis in France and in the United States." Hepatology 65(4): 1237-1248.	RETROSPECTIVE	serious	low	important but not critical	weak for
Dageforde, L. A., et al. (2013). "Is liver transplantation using organs donated after cardiac death cost-effective or does it decrease waitlist death by increasing recipient death?" HPB 15(3): 182-189.	RETROSPECTIVE	serious	low	important but not critical	weak for

Filali Bouami, S., et al. (2018). "Prognostic factors for long-term survival after adult liver transplantation." Langenbecks Archives of Surgery 403(4): 495-508.	RETROSPECTIVE	serious	moderate	important but not critical	weak for
Jackson, W. E., et al. (2022). "Survival Benefit of Living-Donor Liver Transplant." JAMA Surgery 03: 03.	RETROSPECTIVE	not serious	moderate	important but not critical	strong for
Lee, B. P., et al. (2019). "Model to Calculate Harms and Benefits of Early vs Delayed Liver Transplantation for Patients With Alcohol-Associated Hepatitis." Gastroenterology 157(2): 472-480.e475.	RETROSPECTIVE	serious	low	not critical	weak for
Luo, X., et al. (2018). "MELD as a metric for survival benefit of liver transplantation." American Journal of Transplantation 18(5): 1231-1237.	RETROSPECTIVE	not serious	moderate	important but not critical	strong for

Merion, R. M., et al. (2004). "Predicted lifetimes for adult and pediatric split liver versus adult whole liver transplant recipients." American Journal of Transplantation 4(11): 1792-1797.	RETROSPECTIVE	not serious	moderate	important but not critical	weak for
Goudsmit, B., et al. (2022). "Survival benefit from liver transplantation for patients with and without hepatocellular carcinoma." Journal of Hepatology 77(Supplement 1): S798.	RETROSPECTIVE	not serious	moderate	important but not critical	strong for

QUESTION 1 STATEMENT PROPOSAL A

From the patient perspective, intent to treat (from patient listing) gain in life years (better in quality adjusted – see below), seems to be the best metrics to describe the transplant process as a whole, since it reflects all the phases of liver transplant from patient listing to the long term postoperative course. It also provides an estimated measurement of the advantage of liver transplantation on alternative therapies. Such a perspective may be extremely relevant for the patient in the decision process before the transplant.

Level of evidence low
Level of recommendation strong

QUESTION 1 STATEMENT PROPOSAL B

From the point of view of transplant stakeholders, gain in life years, preferably quality adjusted, represents the most adopted metrics to describe the cost-effectiveness of liver transplantation as a process. Life years lost provide further information on long term results, potentially integrating the understanding on liver transplantation as a process

Level of evidence moderate
Level of recommendation strong

UNMET NEED

More accurate gain life years predictions are needed through prospective intent to treat studies focused on the comparison between liver transplant and the natural history of the diseases or alternative therapies potentially available

References

The studies below meet the criteria for inclusion or were selected as they may be of interest.

Barber, K., et al. (2007). "Life expectancy of adult liver allograft recipients in the UK." Gut 56(2): 279-282. http://dx.doi.org/10.1136/gut.2006.093195

Bonsel, G. J., et al. (1990). "Use of prognostic models for assessment of value of liver transplantation in primary biliary cirrhosis." Lancet 335(8688): 493-497. https://doi.org/10.1016/0140-6736(90)90734-M

Cadier, B., et al. (2017). "Early detection and curative treatment of hepatocellular carcinoma: A cost-effectiveness analysis in France and in the United States." Hepatology 65(4): 1237-1248. https://dx.doi.org/10.1002/hep.28961

Dageforde, L. A., et al. (2013). "Is liver transplantation using organs donated after cardiac death cost-effective or does it decrease waitlist death by increasing recipient death?" HPB 15(3): 182-189. https://dx.doi.org/10.1111/j.1477-2574.2012.00524.x

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Lee, B. P., et al. (2019). "Model to Calculate Harms and Benefits of Early vs Delayed Liver Transplantation for Patients With Alcohol-Associated Hepatitis." Gastroenterology 157(2): 472-480.e475. https://dx.doi.org/10.1053/j.gastro.2019.04.012

Luo, X., et al. (2018). "MELD as a metric for survival benefit of liver transplantation." American Journal of Transplantation 18(5): 1231-1237. https://dx.doi.org/10.1111/ajt.14660

Merion, R. M., et al. (2004). "Predicted lifetimes for adult and pediatric split liver versus adult whole liver transplant recipients." American Journal of Transplantation 4(11): 1792-1797. https://doi.org/10.1111/j.1600-6143.2004.00594.x

Congress abstract

Goudsmit, B., et al. (2022). "Survival benefit from liver transplantation for patients with and without hepatocellular carcinoma." Journal of Hepatology 77(Supplement 1): S798. https://dx.doi.org/10.1016/S0168-8278%2822%2901902-X

Alternative metrics to describe liver transplantation as a process

QUESTION 2: When estimates of gain in life years or reduction in years lost are not available/calculable, which is the best measure to describe the transplant process from a VBC perspective?

Coordinator: Marco Carbone

"*...human survival is so uncertain that even the best statistical analysis cannot provide single-number predictions of real use for individual patients*" (R Henderson, N Keiding)

"*From a patient perspective, mortality matters either before or after transplantation*" (Kwong AJ)

INTRODUCTION

The transplant community agrees that survival alone is a limited measure for outcome after LT, thus there is a need to look for multiple, complementary metrics that enable the benchmarking across centres/countries to assess their processes, measure their current performance, and enhance decision-making by providing evidence on the effectiveness, benefits, and disadvantages of different approaches to LT.

Patients and their families need to be aware of the outcomes after any procedure so that they can make suitably informed decisions about undergoing transplantation. Furthermore, comparisons of center performance may affect the decision to refer patients to one center rather than another. Clinicians also need evidence that their outcomes are acceptable and, should outcomes fall below acceptable levels, need early warning so that any problems can be identified quickly and corrected.

ESOT should coordinate a group of clinicians, patients and other interested parties to develop and validate a national/international registry/ies to collect and monitor prospective data on a selected sets of variables and potential endpoints, using a standardization of variable definitions and terms.

Developing a culture of quality improvement means setting goals, measuring processes and outcomes, developing action plans based on results, and assessing the impact of change. The final aim should not be to meet or beat established benchmarks, but rather to develop a system that continually redefines them toward yielding optimal patient care.

In the consensus conference of VBM in LT in Prague, we aim to gather all stakeholders to develop a core outcome set that are useful, informative and take into account the patient's perspective. Critical components of this work are the uniformity of the definitions and the prospective design of parameters collection.

From a patient perspective, mortality matters either before or after transplantation. The survival from the point at which a patient is listed for transplant, can be of interest to both clinicians, patients and regulators.

Undue emphasis on outcomes after transplantation means that transplant figures will be better if the offer is declined for an ill recipient and the death occurs on the waiting list rather than after transplantation. This can be overcome, at least in part, if we also compare outcomes from the date of listing rather than transplantation. This approach will be valid when there is a common point of listing. Thus for some centres, the outcomes of patients after transplantation are better than average, but when survival on the transplant list is assessed, patients in that center have a much worse survival rate in comparison with the national average. An explanation for such a scenario could be that center X had a higher rate of refusing offered organs that were subsequently used in other centers.

This should be risk-adjusted for known risk factors including age, gender, ethnicity, blood group, serum creatinine, serum bilirubin, serum sodium, INR, primary disease. Reports of survival from LT and survival from listing are regularly issued per centre to allow benchmarking.
In the work of Kwong AJ et al. using SRTR data, higher rates of ITT mortality were correlated with increased WL mortality, increased post-LT mortality, lower volume centers, and lower transplant rate ratio. The transplant center was an independent predictor of ITT survival even after adjustment for age, sex, MELD, and sociodemographic variables. Center variation for ITT survival was larger compared with post-LT survival.
ITT survival analyses should take into account that, even with a common point of listing, not all patients will be listed at a similar time with respect to their risk of death and that death, whether before or after transplantation, may be due to factors unrelated to the disease or its treatment (eg. road traffic accident);
The combination of ITT survival and post-LT 1-year survival may also improve the ability of providers to use the best case–worst case framework for communication about high-stakes surgical decisions.

QUESTION 2 STATEMENT PROPOSAL

From patients and regulators perspective, outcomes from the point of listing (ITT survival) offer a complementary method to assess liver transplant processes taking into account multiple phases, i.e. patient selection, waiting list dynamics, allocation and acceptance of organs, and transplant outcome, as reported in the field of HCC.

Level of evidence moderate
Level of recommendation strong

References

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A methodological review of clinical outcomes reported in liver transplantation trials. R Brustia, A Dechartres, O Scatton. HPB, June 2020, 833-844
http://odt.nhs.uk/pdf/patient_survival_from_time_of_listing_for_transplant.pdf
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Kwong AJ, et al. Center Variation in Intention-to-Treat Survival Among Patients Listed for Liver Transplant.Liver Transpl. 2020.
Clavien 2018 Defining Benchmarks in Liver Transplantation: A Multicenter Outcome Analysis Determining Best Achievable Results. Ann Surg. 2018 Mar;267(3):419-425.
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Endpoint time horizon

Question 3: What is the most appropriate time frame to describe liver transplant outcomes from a VBC perspective?

Coordinator Marco Carbone

INTRODUCTION

One issue is at what stage of survival is assessed: whether 1, 5, 10 or 20 years – they measure different things and have different risk factors. Donor factors, for example, are less important at 20 years than 1 year. Also, different healthcare professionals are responsible at different times.

- Because short-term survival exceeds 90% for most transplant indications, this has poor discrimination for center performance, and has become more an expectation than a metric of performance. Also, a system focused on short term outcomes (e.g. within 3 years) may lead centers to avoid higher risk recipients, a situation that undervalues the survival benefit of transplant. A system focused on long term outcomes may incentivise centers to follow patients for longer periods, when managing the side effects of immunosuppression is key to continued patient health, with potential long-term sequelae of immunosuppression including an increased risk for malignancy, cardiovascular disease, and renal failure. Also, long term outcomes will account for what matters most to patients, i.e. decreased physical functioning, impaired mental health, and inability to return to work experienced by recipients.

A counter-argument to use long term follow up is that patients may choose not to be followed at the center where they underwent transplant, because that centers should not be held accountable for outcomes of patients for whom they are no longer providing primary care.

QUESTION 3 STATEMENT PROPOSAL

When describing liver transplantation as a process the timeframe of comparison should be more than 5 years and ideally 10 years to balance urgency and utility

Level of evidence low

Level of recommendation strong.

Quality of life metrics

QUESTION 4: In liver transplant recipients, which is the best tool to adjust for quality of life in life gain of liver transplantation?

Coordinator James Neuberger

INTRODUCTION

'The purpose of a doctor or any human, in general, should not be to simply delay the death of the patient, but to increase the person's quality of life'. Patch Adams

The World Health Organisation (WHO) defines Quality of Life (QoL) as an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a broad ranging concept affected in a complex way by the person's physical health, psychological state, level of independence, social relationships, personal beliefs and their relationship to salient features of their environment'. The WHO defines six domains, four of which relate to health (physical health, psychological health, level of independence and social relationships) and two broader domains (environmental and personal values and beliefs). These are all complex areas and both definition and quantitation are challenges. The health-related quality of life measures are a subset of patient reported outcome measures. The term health-related quality of life (HRQoL) is described as: "a term referring to the health aspects of quality of life, generally considered to reflect the impact of disease and treatment on disability and daily functioning; it has also been considered to reflect the impact of perceived health on an individual's ability to live a fulfilling life. However, more specifically HRQoL is a measure of the value assigned to duration of life as modified by impairments, functional states, perceptions and opportunities, as influenced by disease, injury, treatment and policy" (Mayo)

As ever when giving numerical values to concepts such as quality of life, it is important to remember that 'It is often much worse to have good measurement of the wrong thing - especially when, as is so often the case, the wrong thing will in fact be used as an indicator of the right thing - than to have poor measurement of the right thing.' (John Tukey).

There is often a mismatch between the clinician's assessment of the patient's quality of life and the patient's own assessment and nowadays health-related quality of life is now usually assessed using patient questionnaires. These questionnaires, often called instruments, are usually completed by the patient and aim not only to provide a descriptive profile of the patient's state of health but also to give a numerical score to the state(s) of health.

Instruments used should meet the criteria below: they should

- Be relevant and acceptable to both patients and the general population
- Use simple language
- Be culturally relevant and in language the patient understands
- Be simple and use as few questions as practicable
- Be easy to complete in a relatively short period of time
- Be validated in the population under evaluation
- Be reliable and consistent when used by patients
- Be consistent and not have measures reported in different domains
- Be able to identify changes in health
- Be generalisable and transferable
- Avoid ceiling and floor measures

Such instruments can be used in a variety of contexts including in clinical trials, in observational studies, in population health surveys and in routine outcome measurement. In the context of liver transplantation, these instruments can be used at different timepoints for the same patient, such as before and at varying times after transplant or for comparing quality of life in different cohorts of patients and in different countries. They can be used to compare, for example, the impact on quality of life of different treatment options, say in the management of patients with liver cell cancer.
Some instruments are generic whereas others are disease or process-specific and so include disease related symptoms, therapy induced side effects, and even the financial impact of medical conditions.
Commonly used generic instruments include
CDC HRQOL–14 "Healthy Days Measure":
A questionnaire with four base questions and ten optional questions used by the Center for Disease Control and Prevention (CDC). CDC uses a set of questions called the “Healthy Days Measures.” The four base questions include the following:

Would you say that in general your health is excellent, very good, good, fair or poor?

Now thinking about your physical health, which includes physical illness and injury, how many days during the past 30 days was your physical health not good?

Now thinking about your mental health, which includes stress, depression, and problems with emotions, how many days during the past 30 days was your mental health not good?

During the past 30 days, approximately how many days did poor physical or mental health keep you from doing your usual activities, such as self-care, work, or recreation

There are 10 additional questions about health-related quality of life which ask about recent pain, depression, anxiety, sleeplessness, vitality, and the cause, duration, and severity of a current activity limitation an individual may have in their life. (https://www.cdc.gov/hrqol/hrqol14_measure.htm).
Short-Form Health Survey (SF-36, SF-12, SF-8):
The SF-36 was developed by the RAND Corporation and has 36 items grouped in eight dimensions: vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, mental health. Scores are derived for each scale or aggregated into a Mental Component Summary(MCS) and a Physical Component Summary (https://www.rand.org/health-care/surveys_tools/mos/36-item-short-form.html). There is a charge for the use of the SF software.

EQ-5D or Euroquol 5
This is a simple quality of life questionnaire (https://euroqol.org). The EQ-5D essentially consists of two pages: the EQ-5D descriptive system and the EQ-5D visual analogue scale. The EQ-5D descriptive system comprises five dimensions: mobility, self-care, usual activities, pain and discomfort, and anxiety and depression. The number of levels in these dimensions differ in the EQ-5D-3L (three levels) and the EQ-5D-5L (five levels). The EQ-5D-Y has the same five dimensions, but they are worded more appropriately for young people. The instrument is available in several different languages. In EQ-5D-3L, the five dimensions each have three response levels of severity and patients choose the statement in each dimension that best describes their health status on the day they are surveyed. Responses are coded as 1, 2, or 3, according to the level of severity so the patient will generate a 5-digit number, ranging from 11111 (having no problems in any of the dimensions) to 33333 (having extreme problems in all the dimensions) that describes their HRQoL. In EQ-5D-5L, the same five dimensions are used with some minor modifications but the patient has to choose one of 5 levels. The EQ-5D-Y version is designed for children and adolescents; it is based on 3L but with some modification of language.
WHO Quality of Life (WHO-QOL)

The WHOQOL-100 assesses individuals' perceptions of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a 100-question assessment that currently exists in directly comparable forms in 29 language versions and yields a multi-dimensional profile of scores across domains and sub-domains (facets) of quality of life. An abbreviated 26 item assessment has been developed. The WHOQOL-100 assesses an individual's perceptions of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It was developed collaboratively in some 15 cultural settings over several years and has now been field tested in 37 field centres. It is a 100-question assessment that currently exists in directly comparable forms in 29 language versions. It yields a multi-dimensional profile of scores across domains and sub-domains (facets) of quality of life. More recently, the WHOQOL-BREF, an abbreviated 26 item assessment has been developed (WHOQOL-BREF). (https://www.who.int/publications/i/item/WHO-HIS-HSI-Rev.2012.03)

Disease and condition specific instruments

There are many disease and condition specific instruments that have been proposed and these are designed and validated for patients with specific condition, such as cancer renal disease and so on, and these are discussed below.

Use of HRQoL instruments in practice

There are many quality-of-life measures used in publications, some of which are health-related (HRQoL). A recent review identified 151 general and disease specific instruments: the most commonly used generic instruments for adults included Short Form-36 (SF-36), EQ 5D, EORTC QLQ C-30, WHOQOL-BREF, and SF-12. (Haraldstad).

QoL Outcomes in transplantation

However, assessing QoL is more complex than in many other interventions: for procedures such as, for instance, cholecystectomy, there is a single intervention that will (usually at least) lead to a single outcome. In contrast, assessment of liver transplantation starts from when a patient reaches a stage when transplantation becomes a therapeutic option, through assessment, listing, awaiting transplantation, the transplant and the post-transplant follow-up which will usually be lifelong. Although there are few published data, clinical experience confirms that those areas of concern and importance vary considerably depending on the stage of the patient's journey, so that, for example, concerns over the risks of donated organs are much less post-transplant. Furthermore, it is important to distinguish between those areas of importance to the patient relating to their care in general (such as being treated with respect and being listened to) and those relating to the transplant (such as side-effects of immunosuppressive drugs). Strazzabosco and colleagues have identified some of the approaches to developing value-based outcome measures in liver transplantation (Strazzabsco).

In solid organ transplantation, most studies report outcomes in terms of patient, transplant or graft survival, often censored at relatively short intervals after transplantation (such as 10 years). Patient survival is simply the duration of survival of the patient from the time of transplant, graft survival is length of survival of the graft from the time of transplant to graft failure and transplant survival is survival of the patient censored at the time of death with a functioning graft (that is death is not due to graft failure). Other studies evaluate process-driven measures, such as time in intensive care use, blood use or development of complications. It must be stressed that HRQoL measures and outcome measures are complementary and not alternatives.

Parizi and colleagues undertook a scoping review of the literature to provide an overview of all instruments that have been used to assess health-related quality of life (HRQoL) after solid organ transplantation and to provide a list of health items they include to support future studies on the development of a new-generation HRQoL instrument. 1218 of 8013 distinct publications were reviewed. Among the instruments applied, 53 measured generic, 51 organ-specific, 271 domain-specific, and 43 transplant-specific HRQoL. A total of 78 distinct health items grouped into 16 sub-domains were identified and depicted graphically. Most publications did not report a logical rationale for the choice of specific HRQoL instrument. The most commonly used types of instruments were generic health instruments, followed by domain-specific instruments. The top transplant specific instruments were

End-Stage Renal Disease Symptom Checklist-Transplantation Module (ESRD-SCLTM)
Kidney Transplant Questionnaire (KTQ)
Modified Transplant Symptom Occurrence and Symptom Distress Scale (MTSOSD)
Transplant Effects Questionnaire (TxEQ)
Heart Transplant Symptom Checklist

In a recent review of heart transplantation, Mahmoudi and colleagues identified 102 articles which used 115 different patient reported outcome measures. These were categorized as generic HR-QoL instruments (n = 19), domain-specific instruments (n = 71), heart disease-specific instruments (n = 9), and heart transplant-specific instruments (n = 16). They covered different dimensions of HR-QoL and of immunosuppressive-drug experience, with diverse numbers of items, types of scales, and psychometric properties. They concluded that despite the abundance of instruments, outcome measures for heart transplantation can be improved to meet other patient expectations such as by including important issues such as coping strategies, employment, social support, sexual relationships, spirituality, and beliefs), while paying attention to ease of use, reliability, validity, and the contribution of new technologies.

In the ATTOM study (Gibbons), assessing PROMs amongst renal transplant recipients, the authors used a series of measures including EuroQoL, Visual Analogue Scale, Renal-Dependent Quality of Life score, Renal Treatment Satisfaction Questionnaire change version; Well Being Questionnaire (WBQ-12). From the qualitative interviews, three themes emerged: the positive impact of transplantation, the impact of expectations on the ability to cope post-transplant, and the feelings towards donors. The same group reported similar conclusions in patients undergoing simultaneous kidney and pancreas (SPK) transplantation (Gibbons) with the authors concluding that unrealistic expectations of SPKT caused some disappointment and measuring condition-specific outcome measures over time will help in demonstrating the benefits and limitations of SPKT.

Instruments used for HRQoL in liver transplantation

A review in 2009 by Jay and colleagues identified 128 relevant articles using more than 50 different QOL instruments in liver transplantation. Most used generic health status instruments (such as SF-36, HADS and the Beck Depression Inventory (BDI). Only 16% included targeted, disease-specific instruments such as NIDDK Quality of Life questionnaire, the Liver Disease Quality of Life questionnaire, and the Chronic Liver Disease questionnaire although these instruments have been designed to assess QOL in patients with chronic liver disease rather than patients after liver transplantation. Cristin undertook a systematic review demonstrated more publications on liver transplantation since the review of Jay. SF-36 was the most widely used instrument (54 of 128 studies) across populations allowing for normative comparisons. Of the disease-specific, instruments developed to address the symptoms associated with liver disease. the most commonly used tools were the National Institute of Diabetes and Digestive and Kidney Diseases [NIDDK] Transplantation Quality of Life Questionnaire, Liver Disease Quality of Life Questionnaire [LDQOL], and Chronic Liver Disease Questionnaire [CLDQ]) assess QOL in chronic liver disease and not specifically in the posttransplant population. The computer adaptive tests, Patient-Reported Outcomes Measurement Information System (PROMIS), use both generic and disease-specific components. These are validated in the CLD population; Cristin and colleagues suggested these may be the future of posttransplant population assessment as well. They noted the absence of uniformity in study designs and the wide variety of instruments have limited the widespread utility of HRQOL outcomes for decision making and long-term follow-up.

Quality of life studies in patients with liver diseases have used a variety of instruments (see for example Buchanan-Hughes, Choo, Le, Stine Isa, Jacoby, Younossi) but their relevance to patients after liver transplantation is uncertain.

What is the best instrument for measuring quality of life after liver transplantation?

Review of the literature identifies several themes: there are many instruments available for assessing QoL: the generic ones most commonly used are SF36 and the Euroquol instruments. It should be noted that these are not specific for liver transplant recipients. There are several liver-disease specific instruments, but these apply primarily to specific diseases. There are a few instruments designed to assess quality of life post-transplant.

In selecting the most appropriate instrument to measure quality of life, it is important to consider the issues being addressed and whether the instrument selected is designed for that purpose and validated for the population in question.

When considering QoL outcomes after liver transplantation, it is clearly desirable for researchers to use a common instrument (provided the instrument meets the needs of the research). Ideally, the selected instrument would be applicable to patients before and after transplant to evaluate the impact of transplantation on the quality of life and allow comparison of transplantation with other interventions (such as the various modalities for treatment of hepatocellular cell carcinoma, colonic liver metastases or transplantation for pruritus or intractable ascites). Indeed, the European Network for Health Technology Assessment recommended to always include a generic HRQoL instrument in clinical trials to cover a wide range of possible future uses of the HRQoL data (Table). We propose the EQ-5D is used in preference as this is applicable in all phases of transplantation and is explicitly linked with health utility for cost-effectiveness analyses.

QUESTION 4 STATEMENT PROPOSAL

Given the relative lack of accepted, validated instruments for measuring quality of life after liver transplantation specifically, the following recommendations are suggested:

1.Researchers should be encouraged to use one of the generic instruments available to measure quality of life in patients with liver disease and after transplantation

2.It is recommended that the EQ-5D (see appendix) instrument should be used in preference since it applies to all phases of transplantation

Level of evidence moderate
Level of recommendation strong

UNMET NEED

Research should be dedicated to develop quality of life tools specifically addressing the different phases of liver transplantation

References

TABLE
From the recommendations from the European Network for Health Technology Assessment Guideline @Endpoints used for Relative Effectiveness Assessment: 2015 : https://www.eunethta.eu/wp-content/uploads/2018/01/Endpoints-used-for-Relative-Effectiveness-Assessment-Health-related-quality-of-life-and-utility-measures_Amended-JA1-Guideline_Final-Nov-2015.pdf

1. HRQoL instruments used in the context of Relative Effectiveness Assessment (REA) should be valid for the purpose the REA intends to serve.
2. A general recommendation applicable to all types of REA irrespective of their particular purpose, is to require the inclusion of a disease- or population specific and a generic HRQoL measure for most adequately capturing the impact of a disease on daily life.
3. If there is a need for the calculation of QALYs, a utility measure (Time Trade-Off or Standard Gamble) or generic HRQoL instrument associated with a reference set of utility values (generic utility instrument) is recommended.
3. REA performed for informing resource allocation decisions across indications should primarily be based on HRQoL data obtained with a generic HRQoL instrument, encompassing all HRQoL dimensions in which improvements are considered important by the general public.
4. REA performed for informing resource allocation decisions within indications can be based on validated comprehensive disease-specific HRQoL data, as comparability across indications is in this case less important. Nevertheless, the consideration of generic HRQoL data remains useful for reasons of coherence in the valuation of health benefits, and in consequence, transparency of the decision-making process.
5. REA performed for the purpose of informing health care professionals and patients could be based on disease-specific HRQoL instruments. They can be considered as complementary to generic instruments in REA performed for policy purposes. Disease-specific HRQoL instruments may be useful for more in-depth assessment of the generic HRQoL dimensions affected by an intervention. It should be borne in mind that the burden imposed on respondents increases with the number of questionnaires used.
6. HRQoL benefits of interventions should be demonstrated by means of repeated measurements in both the intervention and the control group.
7. Single item scores for HRQoL alone are considered insufficient to demonstrate relative effectiveness because they are subject to bias and often too crude to detect changes in health. Single item scores are scores derived from one single question asking to value current overall health on a specific scale.
8. Mapping of disease-specific or generic instruments to preference-based instruments to obtain utility values is generally not recommended for REA. Authorities should encourage researchers to always include a preferencebased instrument in their clinical trial protocol in order to avoid the need for mapping.
9. Documentation of the validity, reliability, responsiveness and acceptability of the HRQoL instruments used in REA should be provided, taking into account the applied mode of administration and possible cultural and/or language adaptations.
10. Evaluation of HRQoL by “proxy judges” is not recommended
11. Transparent reporting within due time of the results of all HRQoL measurements is recommended. If not (yet) published, it is required to make these results accessible for HTA bodies to allow critical appraisal.
12. When changes in survival and HRQoL are combined in one outcome measure such as the QALY, separate reporting of changes in survival and HRQoL and a description of the methods to combine the measurements should be requested to allow for separate consideration of both endpoints.

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Patient reported measures in liver transplantation

QUESTION 5 Which are the unmet needs in defining the critical PROMs and PREMs to be included in liver transplant "core" evaluation and clinical trial design?

Coordinator Ian Rowe

INTRODUCTION
Patient reported measures

There is general acceptance that the involvement of patients in coproducing research and in decision-making about their health and care is of critical importance. In the evaluation of outcomes in liver transplantation, patient reported measures likely add value through focusing on measuring what matters to patients. There is utility to these measures in both the clinical trial setting and in routine care where the reporting of health-related quality of life across relevant health domains can support communication between patients and healthcare professionals.

Broadly, there are two types of patient reported measures: patient reported outcome measures (PROMs) and patient reported experience measures (PREMS). PROMs measure individual's perception of their own outcomes in the broadest sense whereas PREMs measure perceptions on services and the experiences of care. A useful taxonomy is provided by Benson(Benson 2020) and this provides a framework to understand the differences between outcomes and experiences of care.

Figure 1. Taxonomy of patient reported outcome and experience measures.

Challenges in the use of patient reported measures in liver transplantation

Lack of standardised tools for assessment
There are two existing systematic reviews of health-related quality of life after liver transplantation(Jay et al. 2009; Yang et al. 2014). Each of these identified multiple PROMs tools or instruments to assess outcomes in patients after liver transplantation and there was substantial heterogeneity between the tools used and the populations being studied. These systematic reviews also both identify a lack of data associating factors available at the time of transplantation, including information regarding the donor, with subsequent health related quality of life. This is a clear evidence gap that needs to be addressed.

Lack of longitudinal quality of life data
The nature of liver transplantation, taking patients from the time of waiting list registration to long-term post-transplant survival strengthens the need for longitudinal health related quality of life data. Studies done to date, and included in the above systematic reviews are most often done in a cross-sectional analysis with little attention to the timing post-transplant.

Recognition of the different phases in the transplant journey demands consideration of the types of PROMs tools or instruments that should be included, and whether these should change with the different phases. In general, the inclusion of generic questionnaires to measure health related quality of life is appropriate at all stages whereas tools that focus largely on the symptoms and complications of end-stage liver disease may be less relevant in long-term post-transplant survivors. Understanding which tools or instruments to use, and when, is lacking and should be the focus of further research.

Lack of patient involvement in the coproduction of patient reported measures

In studies to date in liver transplantation alone there has been little public patient involvement in the health related quality of life tools or instruments that have been chosen or developed. It is critical that, where outcomes described by patients are being assessed, that these measures are co-produced with patients in order that the measure is truly important to the patient. Recent work from Shahabeddin Parizi and co-workers(Shahabeddin Parizi et al. 2020) in a group including all solid organ transplant recipients has shown that co-production in transplant recipients is feasible and that a tool applicable to all patients has been developed as a result.

Proposal of a way forward

A core outcome set of PROMs should be co-produced with public and patient involvement, according to the phase of the transplant journey, that is relevant to both clinical trials and routine healthcare. A general framework for this development includes the following.

- PROMs should include information from across the relevant health domains, physical, social, and mental
- Tools included in the core outcome set should include generic measures of health related quality of life (e.g. EQ-5D), disease specific tools (e.g. Liver Disease QoL questionnaire),and patient perspective measures that include measures of illness perceptions and patient empowerment (e.g. the Brief Illness Perception Questionnaire and the Patient Empowerment Scale).
- Inclusion of PREMs should be considered, primarily for use in routine care, to improve the patient experience of liver transplantation with the aim of improving overall outcomes.

PREMISE

Patient reported measures of experiences and outcomes add value in the evaluation of liver transplantation through a focus on what matters to patients. The appropriate tools to measure outcomes and experiences in liver transplantation have not been fully defined.

QUESTION 5 STATEMENT PROPOSAL

A core outcome set of PROMs, including generic measures of health related quality of life, should be co-produced with public and patient involvement, according to the phase of the transplant journey, that is relevant to both clinical trials and routine healthcare.

Level of evidence Low
Level of recommendation strong

UNMET NEED

ESOT should encourage primary research to co-design patient reported outcome and experience measures applicable to all phases of the liver transplant journey (pre-transplant, early, and late post-transplant) is required to assess aspects of care for individuals on the transplant waiting list and living after liver transplantation. Consideration should be given to inclusion of disease specific patient reported measures where appropriate.

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Measures to evaluate quality of waitlist management

QUESTION 6: In a setting with optimal potential candidate referral and listing process, which is the best measure to evaluate the quality of waiting list management in a VBC perspective?
waiting list dropout because of death/deterioration
waiting list mortality
others*

Coordinator Mario Strazzabosco

INTRODUCTION
Here we will not discuss the issue of access, as we will be focusing on the topics concerning list management. However, we cannot avoid considering that several papers have shown that there are important inequalities of access to transplant. Inequalities have also been reported in waitlist mortality with evidence of gender, racial and socioeconomic disparities.

QUESTION 6 STATEMENT PROPOSAL A
In discussing the principles of waiting list management in Liver Transplantation it is FUNDAMENTAL to underscore the importance of
-Inclusion
-diversity
-Equity

Level of evidence high
Level of recommendation strong

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The Value-Based Care model requires us to consider the patient perspective, the clinical outcomes and the costs. First we need to consider the patient perspective. Patients may spend considerable time in the waiting list (often after a lengthy and difficult candidacy evaluation). Therefore the quality of life while on the list must be measured and managed and be an important component of the evaluation.

Five themes emerged as patient priorities while on the list needing to be measured and analyzed :

1.Managing expectations: most patients feel overwhelmed and want a clear description of the path ahead and how to navigate the process, relationship with their insurance, being respectful of the time involved in the care, which can be substantial.

2.Providing education: most listed patients remarked that misinformation of lack of information was a major determinant of anxiety in the waiting list. Information should be complete, transparent and updated. Information about “extended donor criteria” also appeared unsatisfactory.

3.Responding to patient needs: patients value highly responsive providers who deliver timely, personalized care able to compensate for eventual inefficiencies of the system.

4.Executing the plan of care efficiently: for example, optimizing the follow through once a plan has been decided, avoid delays, respect the patient time, avoid further financial burden to the patient.

5.Maintaining effective interdisciplinary communication and coordination of care. All patents emphasized the need to feel that the different care providers across different departments be informed and up to date on the patient care. Coordination of care is seen as an extremely sensitive issue.

QUESTION 6 STATEMENT PROPOSAL B

Patient reported experiences including managing expectations, providing appropriate education, responding to patient needs, efficient care, and maintaining communication should be assessed while patients are waiting for liver transplantation.

Level of evidence very low
Level of recommendation strong

UNMET NEED:

Patient reported experience measures should be co-developed specifically to cover the pre-transplant period to enable evaluation and improvement of waiting list outcomes beyond mortality.

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The OPTN Board of Directors has recently published a briefing paper on how to enhance performance monitoring systems.
Ideally, a center should list every year a number of patient that equals the removal of patients (for improvement, deterioration, death). From the VBM point of view, a transplant center should be evaluated by how efficiently and equitably provides for the listed patients and fulfills the commitment stipulated at the time of listing, rather than by how many transplant performed per year. Germane to these concepts would be the adoption of an intention to treat analysis when evaluating the transplantation results.

In this regard, it seems interesting to higlight some of the metrics provided for 2021 by the Mayo Clinic Transplant Center in Rochester, MN, USA:

Size of the transplant list at the beginning (79) and at the end of the year (84)
Patient transplanted 124 (included living-related)
Addition to the list 164
Removal 162 (of which 124 due to transplant, 8 due to improvements, 10 to death/deterioration, and the rest due to miscellaneous causes).

Transplantation rates: 134 per 100 person years of waiting list
Pre-transplant mortality: 10, 4 per 100 person years of waiting list.

QUESTION 6 STATEMENT PROPOSAL C

1. Wait list events including mortality, removal for deterioration, removal for improvement, temporary removal and removal for transplant should be recorded. These events should be subsequently processed in a competing risk analysis taking into consideration the center case mix adjusted at the moment of listing and measuring the ability of the Center to accept higher risk patients.
2. Further insights in quality assessment of wait-list management are given by transplant probability at 1 year and overall dropout rate for death or removal for deterioration.
3. Offer acceptance practices. Based on offers that a Centre declines, while another Centre accepts and transplant

   Level of evidence low
   Level of recommendation strong

Literature search
Resources: Medline, Embase and the Transplant Library
Exclusion criteria:

- Any language other than English
- Studies published <1990 (search date: 06/09/2022)
- Paediatric patients
- Congress abstracts

1. (liver transplant or liver transplantation).ti,ab.
2. liver transplantation/
3. 1 or 2
4. ((wait$ list$ or waitlist$ or listing) adj4 (management or therapy or care or treat$)).ti,ab.
5. 3 and 4
6. remove duplicates from 5
7. limit 6 to yr="1990 - 2022"

The search identified 272 potentially relevant references.

The studies below meet the criteria for inclusion or were selected as they may be of interest. Studies are listed according to studies reporting: 1) waitlist dropout because of deterioration; 2) waitlist mortality; 3) both deterioration and mortality; 4) waitlist morbidity; 5) time spent on waiting list; 6) cost-effectiveness

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1. Waitlist dropout because of deterioration (n=19 studies)

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Metrics of early postoperative course

Question 7: Which are the best metrics to describe the quality of early postoperative course?

Coordinator Wojtek Polak

INTRODUCTION

The early postoperative course has a substantial impact on the final outcome of liver transplantation (LT). However, the evidence is lacking what is the best metrics to measure/describe the quality of early postoperative course after LT. Brustia et al. found several types of outcomes used in published and on-going clinical trials describing the early postoperative course. They can be divided into:

1. Mortality (survival):
- short term mortality (in-hospital mortality or 90-days mortality)
- intermediate mortality – 1 year mortality
2. Morbidity (complications);
- Perioperative morbidity (?) – blood loss/blood transfusions, surgical/radiological interventions, SSI, readmission to the ICU Clavien-Dindo complications >grade3?
- Technical complications (biliary/vascular complications)
- Medical complications (neurological, pulmonary, cardiovascular, gastrointestinal, renal, infectious)
- Readmissions rate
- early retransplantations (90-days)
3. Recovery outcomes:
- Length of the stay in the ICU
- Length of the stay in the hospital

Brustia R, Dechartres A, Scatton O. A methodological review of clinical outcomes reported in liver transplantation trials. HPB (Oxford). 2020 Jun;22(6):833-844.

Background: Liver Transplantation (LT) is a life-saving treatment for end-stage liver disease, for which various outcomes are measured in randomized clinical trials (RCT). The aim of this methodological review is to evaluate and classify outcomes reported in RCT in LT.

Methods: PubMed and ClinicalTrials.gov were searched in July 2018 for published and ongoing RCTs on LT in the last 5 years. Studies were eligible if focusing on first LT in adult patients, with interventions during the perioperative period. Data extracted concerned LT characteristics, type of intervention, methodological characteristics and outcomes assessed.

Results: Of 2685 references, 55 were included with a median of 78 (40-120) patients for published trials and planned to include 117 (55-218) patients for ongoing trials. Morbidity was the most frequently used as primary outcome in 37 published (67%) and 13 ongoing trials (54%). We identified 10 different definitions for graft dysfunction, 9 for recovery outcomes and 12 different time-points for mortality. For published trials, among the 397 outcomes specified in the method section, results were reported for 283 (71%).

Conclusion: Outcomes reported in LT trials are very heterogeneous. A consensus approach to develop a core outcome set (COS) should be considered allowing for comparisons of results across trials.

QUESTION 7 STATEMENT PROPOSAL A

There are no single metrics available describing the quality of early postoperative course after liver transplantation. Ninety days survival is one of the most informative but it is suggested to adopt a few simple and comprehensive set of metrics that are easy to obtain, which will describe the early postoperative course after liver transplantation as follows:

- 90-days mortality
- 1 year mortality
-90-days retransplantation rate
-Length of the stay in the ICU
-Length of the stay in the hospital
-Readmissions rate
-Surgical/radiological re-interventions rate
-Clavien DIndo and CCI classifications rate
-Vascular and biliary complications rate (definitions?)
-Infectious complications rate
-Failure to rescue rate

Metrics of late postoperative course

Question 8: Which is the best metrics to describe the quality of late posttransplant course?

Coordinated by: Marco Carbone

QUESTION 8 STATEMENT A

There are no single metrics available describing the quality of long term course after liver transplantation. it is suggested to adopt a few simple and comprehensive set of metrics that are easy to obtain, which will describe the early postoperative course after liver transplantation as follows:

- 5-year risk-adjusted patient & graft survival rates from listing for adult elective first liver registrations
-10-year risk-adjusted patient & graft survival rates from listing for adult elective first liver registrations
- rate of chronic rejection
- recurrence of initial disease (autoimmune)
- recurrence of initial disease (viral)
- rate of chronic renal dysfunction
- rate of de novo metabolic syndrome (e.g. blood hypertension and dyslipidemia)
- rate of de novo T2DM (NODAT)
- rate of cardiovascular events
- rate of HCC (or other malignancies) recurrence
- de novo malignancies(divided in: non-melanoma skin, PTLD, head and neck, lung, colorectal)

Graft survival reflects the overall rate of success of the LT journey. It assumes that all deaths are associated with the transplantation. The assumption that death with functioning graft equates to graft failure, leads to a lower estimate of graft survival than death-censored graft survival. Therefore the method used should be specified. Graft failure rates are more meaningful from a payer perspective considering the burden of an expensive procedure and the high-demand vs low offer and the concept of utility/futility. Patient's survival can be more meaningful to patients.

Notes:
- quality of life is not covered in this set statement;
- An important consideration for the introduction of quality metrics (quality card for transplant centers), particularly in the public domain, is the potential for unintended consequences. The intended benefits of evaluating the quality of programs should be balanced by the way these data can alter practice, that may not be consistent with best practices;
- Finally, it should be highlighted that the costs associated for the development of such program are not insignificant in terms of human resources and healthcare fundings; however, if the program has a good impact, the benefit in quality of care provided to patients and the subsequent cost savings from prevention of complications, and readmissions, are posed to increase overall value.

APPENDIX

Question 1 Literature search

The studies below meet the criteria for inclusion or were selected as they may be of interest.

Barber, K., et al. (2007). "Life expectancy of adult liver allograft recipients in the UK." Gut 56(2): 279-282. http://dx.doi.org/10.1136/gut.2006.093195

BACKGROUND: Liver transplantation is a very successful therapy for those with end stage disease. Although there are numerous data on patient and graft survival after liver transplantation, life expectancy and possible loss of life (compared with a normal matched population) in those who survive remains unknown.
AIMS: To assess the life expectancy and life years lost of adult liver allograft recipients, compared with an age and sex matched UK population to provide patients with more information and to improve the use of a scarce resource.
METHODS: Using the National Transplant Database held by UK Transplant, on over 3600 adult liver allograft recipients transplanted between 1985 and 2003, we analysed survival of all adults who survived more than six months after transplantation and compared survival after transplantation with national age and sex matched controls to assess life years lost.
RESULTS: Estimated median survival time of the analysis cohort of 2702 adult liver allograft recipients was 22.2 years (95% confidence interval 19.3-25.6), with an estimated loss of seven life years compared with an age and sex matched population.
CONCLUSIONS: Overall, female recipients have a longer life expectancy and lose fewer life years than male recipients. While younger recipients have a longer life expectancy, they also lose more life years. Those transplanted for cancer, hepatitis C virus infection, and alcoholic liver disease had the greatest loss of life years.

Bonsel, G. J., et al. (1990). "Use of prognostic models for assessment of value of liver transplantation in primary biliary cirrhosis." Lancet 335(8688): 493-497. https://doi.org/10.1016/0140-6736(90)90734-M

To examine the effectiveness of liver transplantation (LTx) for the treatment of primary biliary cirrhosis (PBC) the actual survival of 30 PBC patients who received liver grafts was compared with predictions of what survival would have been without transplantation. Three models, based on Cox' regression analysis, were used. Two models were derived from survival of PBC patients in drug trials and the third from cirrhotic patients who did not receive transplants. Observed and expected survival were compared for a follow-up time of 7 years. After 1 year the difference in favour of LTx was small, but after 5 years survival with LTx exceeded all predicted survival probabilities without LTx. After 3 years every year of follow-up added about 0.3 years to expected survival gain per transplanted patient, resulting in 1.5 to 2.3 life-years gained at 7 years' follow-up, depending on the model used. The benefit was greatest for patients in Child-Pugh classes B and C. The consistency between the three models in their predictions supports the validity of the use of predictive models in the indirect assessment of LTx.

Cadier, B., et al. (2017). "Early detection and curative treatment of hepatocellular carcinoma: A cost-effectiveness analysis in France and in the United States." Hepatology 65(4): 1237-1248. https://dx.doi.org/10.1002/hep.28961

Hepatocellular carcinoma (HCC) is the leading cause of death in patients with cirrhosis. Patients outside clinical trials seldom benefit from evidence-based monitoring. The objective of this study was to estimate the cost-effectiveness of complying with HCC screening guidelines. The economic evaluation compared surveillance of patients with cirrhosis as recommended by the guidelines ("gold-standard monitoring") to "real-life monitoring" from the health care system perspective. A Markov model described the history of the disease and treatment course including current first-line curative treatment: liver resection, radiofrequency ablation (RFA), and liver transplantation. Transition probabilities were derived mainly from two French cohorts, CIRVIR and CHANGH. Costs were computed using French and U.S. tariffs. Effectiveness was measured in life years gained (LYG). An incremental cost-effectiveness ratio (ICER) was calculated for a 10-year horizon and tested with one-way and probabilistic sensitivity analyses. The cost difference between the two groups was $648 ($87,476 in the gold-standard monitoring group vs. $86,829 in the real-life monitoring group) in France and $11,965 ($93,795 vs. $81,829) in the United States. Survival increased by 0.37 years (7.18 vs. 6.81 years). The ICER was $1,754 per LYG in France and $32,415 per LYG in the United States. The health gain resulted from earlier diagnosis and access to first-line curative treatments, among which RFA provided the best value for money.
CONCLUSION: Our results indicate that gold-standard monitoring for patients with cirrhosis is cost-effective, attributed to a higher probability of benefiting from a curative treatment and so a higher survival probability. (Hepatology 2017;65:1237-1248).

Dageforde, L. A., et al. (2013). "Is liver transplantation using organs donated after cardiac death cost-effective or does it decrease waitlist death by increasing recipient death?" HPB 15(3): 182-189. https://dx.doi.org/10.1111/j.1477-2574.2012.00524.x

OBJECTIVES: The aim of this study was to evaluate the cost-effectiveness in liver transplantation (LT) of utilizing organs donated after cardiac death (DCD) compared with organs donated after brain death (DBD).
METHODS: A Markov-based decision analytic model was created to compare two LT waitlist strategies distinguished by organ type: (i) DBD organs only, and (ii) DBD and DCD organs. The model simulated outcomes for patients over 10 years with annual cycles through one of four health states: survival; ischaemic cholangiopathy; retransplantation, and death. Baseline values and ranges were determined from an extensive literature review. Sensitivity analyses tested model strength and parameter variability.
RESULTS: Overall survival is decreased, and biliary complications and retransplantation are increased in recipients of DCD livers. Recipients of DBD livers gained 5.6 quality-adjusted life years (QALYs) at a cost of US$69 000/QALY, whereas recipients on the DBD + DCD LT waitlist gained 6.0 QALYs at a cost of US$61 000/QALY. The DBD + DCD organ strategy was superior to the DBD organ-only strategy.
CONCLUSIONS: The extension of life and quality of life provided by DCD LT to patients on the waiting list who might otherwise not receive a liver transplant makes the continued use of DCD livers cost-effective.

Filali Bouami, S., et al. (2018). "Prognostic factors for long-term survival after adult liver transplantation." Langenbecks Archives of Surgery 403(4): 495-508. https://dx.doi.org/10.1007/s00423-018-1670-5

PURPOSE: Prognostic factors for survival >= 15 years and life years lost after liver transplantation are largely unknown.
METHODS: One thousand six hundred thirty primary adult liver transplants between 1983 and 2014 were analyzed. Risk factors for survival were identified with multivariable Cox regression and subsequently tested for their relevance as prognostic factors for observed 15-year survival using multivariable logistic regression and c statistics. The difference of life expectancy between a matched national reference population and survival in patients with post-transplant survival >= 15 years was calculated.

RESULTS: Survival of >= 15 years was observed in 361 patients (22%). Sixty-nine adults died after more than 15 years losing a median of 15 years of life expectancy. One of those patients lived longer while 292 patients still have the chance to survive longer than their normal life expectancy. The indication primary sclerosing cholangitis (PSC) and later eras of transplantation were identified as significant independent protective factors while recipient age > 36.8 years, graft loss due to initial non-function or thrombosis, the indications hepatocellular carcinoma (HCC), hepatitis-C-virus-related cirrhosis (HCV-cirrhosis) and all other indications, donor age > 53 years, the number of surgical complications, and operative durations > 4.5 h were identified as significant independent risk factors limiting survival. All of these factors except the duration of operation had also a significant independent influence on observed 15-year survival (AUROC = 0.739).
CONCLUSIONS: Recipients can exceptionally live longer than their normal life expectancy. Older recipients and patients with the indications HCC, HCV-cirrhosis, or other indications except PSC, should be transplanted with younger donor organs.

Jackson, W. E., et al. (2022). "Survival Benefit of Living-Donor Liver Transplant." JAMA Surgery 03: 03. https://dx.doi.org/10.1001/jamasurg.2022.3327

Importance: Despite the acceptance of living-donor liver transplant (LDLT) as a lifesaving procedure for end-stage liver disease, it remains underused in the United States. Quantification of lifetime survival benefit and the Model for End-stage Liver Disease incorporating sodium levels (MELD-Na) score range at which benefit outweighs risk in LDLT is necessary to demonstrate its safety and effectiveness.
Objective: To assess the survival benefit, life-years saved, and the MELD-Na score at which that survival benefit was obtained for individuals who received an LDLT compared with that for individuals who remained on the wait list.
Design, Setting, and Participants: This case-control study was a retrospective, secondary analysis of the Scientific Registry of Transplant Recipients database of 119275 US liver transplant candidates and recipients from January 1, 2012, to September 2, 2021. Liver transplant candidates aged 18 years or older who were assigned to the wait list (N = 116455) or received LDLT (N = 2820) were included. Patients listed for retransplant or multiorgan transplant and those with prior kidney or liver transplants were excluded.
Exposures: Living-donor liver transplant vs remaining on the wait list.
Main Outcomes and Measures: The primary outcome of this study was life-years saved from receiving an LDLT. Secondary outcomes included 1-year relative mortality and risk, time to equal risk, time to equal survival, and the MELD-Na score at which that survival benefit was obtained for individuals who received an LDLT compared with that for individuals who remained on the wait list. MELD-Na score ranges from 6 to 40 and is well correlated with short-term survival. Higher MELD-Na scores (>20) are associated with an increased risk of death.
Results: The mean (SD) age of the 119275 study participants was 55.1 (11.2) years, 63% were male, 0.9% were American Indian or Alaska Native, 4.3% were Asian, 8.2% were Black or African American, 15.8% were Hispanic or Latino, 0.2% were Native Hawaiian or Other Pacific Islander, and 70.2% were White. Mortality risk and survival models confirmed a significant survival benefit for patients receiving an LDLT who had a MELD-Na score of 11 or higher (adjusted hazard ratio, 0.64 [95% CI, 0.47-0.88]; P = .006). Living-donor liver transplant recipients gained an additional 13 to 17 life-years compared with patients who never received an LDLT.
Conclusions and Relevance: An LDLT is associated with a substantial survival benefit to patients with end-stage liver disease even at MELD-Na scores as low as 11. The findings of this study suggest that the life-years gained are comparable to or greater than those conferred by any other lifesaving procedure or by a deceased-donor liver transplant. This study's findings challenge current perceptions regarding when LDLT survival benefit occurs.

Jena, A. B., et al. (2019). "How Does Treating Chronic Hepatitis C Affect Individuals in Need of Organ Transplants in the United Kingdom?" Value in Health 22(6): 669-676. https://dx.doi.org/10.1016/j.jval.2018.09.2923

Objectives: To estimate the impact of cures for chronic hepatitis C (CHC) infection on organ donation in the United Kingdom. Curing CHC infection reduces the need for liver transplants and enables cured individuals to donate organs of all types. Method(s): We adapted a double-queuing model of organ allocation to estimate the effects of CHC infection cures on liver, lung, heart, and kidney transplants in the United Kingdom. We assumed that cured individuals would donate organs at similar rates as the general population and no longer require liver transplants because of CHC infection. We estimated how curing CHC infection influences waitlist lengths for each organ and the annual net present value to society on the basis of quality-adjusted life-years gained through additional transplants under opt-in and opt-out organ donation policies. Result(s): Curing CHC generates the most value for patients on the liver waitlist, because it increases the number of transplantable livers and reduces the need for transplants. Under the current opt-in policy, liver waitlist length falls by 24%, generating 34.3 million of annual net present value. Growth in the number of uninfected lungs, hearts, and kidneys generates an additional 19.2 million annually, with 18.7 million from kidneys. Implementing the opt-out policy, liver waitlist length would decrease by 75%, implying that treating CHC eliminates one-third of the excess liver waitlist due to an opt-in policy. Conclusion(s): Treating CHC has large positive spillovers to uninfected individuals by reducing the need for liver transplants and allowing cured individuals to donate organs. These spillovers have not been included in traditional value assessments of CHC treatment. Copyright © 2019 ISPOR-The Professional Society for Health Economics and Outcomes Research

Lee, B. P., et al. (2019). "Model to Calculate Harms and Benefits of Early vs Delayed Liver Transplantation for Patients With Alcohol-Associated Hepatitis." Gastroenterology 157(2): 472-480.e475. https://dx.doi.org/10.1053/j.gastro.2019.04.012

BACKGROUND & AIMS: Early liver transplantation (without requiring a minimum period of sobriety) for severe alcohol-associated hepatitis (AH) is controversial: many centers delay eligibility until a specific period of sobriety (such as 6 months) has been achieved. To inform ongoing debate and policy, we modeled long-term outcomes of early vs delayed liver transplantation for patients with AH.

METHODS: We developed a mathematical model to simulate early vs delayed liver transplantation for patients with severe AH and different amounts of alcohol use after transplantation: abstinence, slip (alcohol use followed by sobriety), or sustained use. Mortality of patients before transplantation was determined by joint-effect model (based on Model for End-Stage Liver Disease [MELD] and Lille scores). We estimated life expectancies of patients receiving early vs delayed transplantation (6-month wait before placement on the waitlist) and life years lost attributable to alcohol use after receiving the liver transplant.

RESULTS: Patients offered early liver transplantation were estimated to have an average life expectancy of 6.55 life years, compared with an average life expectancy of 1.46 life years for patients offered delayed liver transplantation (4.49-fold increase). The net increase in life expectancy from offering early transplantation was highest for patients with Lille scores of 0.50-0.82 and MELD scores of 32 or more. Patients who were offered early transplantation and had no alcohol use afterward were predicted to survive 10.85 years compared with 3.62 years for patients with sustained alcohol use after transplantation (7.23 life years lost). Compared with delayed transplantation, early liver transplantation increased survival times in all simulated scenarios and combinations of Lille and MELD scores.

CONCLUSIONS: In a modeling study of assumed carefully selected patients with AH, early vs delayed liver transplantation (6 months of abstinence from alcohol before transplantation) increased survival times of patients, regardless of estimated risk of sustained alcohol use after transplantation. These findings support early liver transplantation for patients with severe AH. The net increase in life expectancy was maintained in all simulated extreme scenarios but should be confirmed in prospective studies. Sustained alcohol use after transplantation significantly reduced but did not eliminate the benefits of early transplantation. Strategies are needed to prevent and treat posttransplantation use of alcohol.

Luo, X., et al. (2018). "MELD as a metric for survival benefit of liver transplantation." American Journal of Transplantation 18(5): 1231-1237. https://dx.doi.org/10.1111/ajt.14660

Currently, there is debate among the liver transplant community regarding the most appropriate mechanism for organ allocation: urgency-based (MELD) versus utility-based (survival benefit). We hypothesize that MELD and survival benefit are closely associated, and therefore, our current MELD-based allocation already reflects utility-based allocation. We used generalized gamma parametric models to quantify survival benefit of LT across MELD categories among 74 196 adult liver-only active candidates between 2006 and 2016 in the United States. We calculated time ratios (TR) of relative life expectancy with transplantation versus without and calculated expected life years gained after LT. LT extended life expectancy (TR > 1) for patients with MELD > 10. The highest MELD was associated with the longest relative life expectancy (TR = _{1.05} 1.20_{1.37} for MELD 11-15, _{2.29} 2.49_{2.70} for MELD 16-20, _{5.30} 5.72_{6.16} for MELD 21-25, _{15.12} 16.35_{17.67} for MELD 26-30; _{39.26} 43.21_{47.55} for MELD 31-34; _{120.04} 128.25_{137.02} for MELD 35-40). As a result, candidates with the highest MELD gained the most life years after LT: 0.2, 1.5, 3.5, 5.8, 6.9, 7.2 years for MELD 11-15, 16-20, 21-25, 26-30, 31-34, 35-40, respectively. Therefore, prioritizing candidates by MELD remains a simple, effective strategy for prioritizing candidates with a higher transplant survival benefit over those with lower survival benefit.

Merion, R. M., et al. (2004). "Predicted lifetimes for adult and pediatric split liver versus adult whole liver transplant recipients." American Journal of Transplantation 4(11): 1792-1797. https://doi.org/10.1111/j.1600-6143.2004.00594.x

Split liver transplantation allows 2 recipients to receive transplants from one organ. Comparisons of predicted lifetimes for two alternatives (split liver for an adult and pediatric recipient vs. whole liver for an adult recipient) can help guide the use of donor livers. We analyzed mortality risk for 48,888 waitlisted candidates, 907 split and 21,913 whole deceased donor liver transplant recipients between January 1, 1995 and February 26, 2002. Cox regression models for pediatric and adult patients assessed average relative wait list and post-transplant death risks, for split liver recipients. Life years gained compared with remaining on the waiting list over a 2-year period were calculated. Seventy-six splits (152 recipients) and 24 re-transplants resulted from every 100 livers (13.1% [adult] and 18.0% [pediatric] 2-year re-transplant rates, respectively). Whole livers used for 93 adults also utilized 100 livers (re-transplant rate 7.0%). Eleven extra life years and 59 incremental recipients accrued from each 100 livers used for split compared with whole organ transplants. Split liver transplantation could provide enough organs to satisfy the entire current demand for pediatric donor livers in the United States, provide more aggregate years of life than whole organ transplants and result in larger numbers of recipients.

Congress abstract

Goudsmit, B., et al. (2022). "Survival benefit from liver transplantation for patients with and without hepatocellular carcinoma." Journal of Hepatology 77(Supplement 1): S798. https://dx.doi.org/10.1016/S0168-8278%2822%2901902-X

Background and aims: In the US, inequal liver transplantation (LT) access exists between patients with and without hepatocellular carcinoma (HCC). Survival benefit considers survival without and with LT and could equalize LT access.We calculated and compared LT survival benefit scores for patients with (out) HCC, based on longitudinal data in a recent US cohort. Method(s): Adult LT candidates with (out) HCC between 2010 and 2019 were included. Waitlist survival over time was contrasted to posttransplant survival, to estimate 5-year survival benefit from the moment of LT. Waitlist survival was modeled with bias-corrected time-dependent Cox regression and posttransplant survival was estimated through Cox proportional hazards regression. Result(s): Mean HCC survival without LT was always lower than non- HCC waitlist survival. Below MELD (-Na) 30, HCC patients gained more life-years from LT than non-HCC patients at the same MELD (-Na) score. Only non-HCC patients belowMELD (-Na) 9 had negative benefit. Most HCC patients were transplanted below MELD (-Na) 14 and most non-HCC patients above MELD (-Na) 26. Liver function. (MELD (-Na), albumin) was the main predictor of 5-year benefit. Therefore, during five years, most HCC patients gained 0.12 to 1.96 years from LT, whereas most non-HCC patients gained 2.48 to 3.45 years. Conclusion(s): On an individual level, transplanting patients with HCC resulted in survival benefit. However, on a population level, benefit was indirectly wasted, as non-HCC patients were likely to gain more survival due to decreased liver function. Based on these data, we now provide an online calculator to estimate 5-year survival benefit given specific patient characteristics. Survival benefit scores could serve to equalize LT access.

Question 3 literature research

McGregor, L. M., et al. (2010). "Considering adult living donor liver transplantation: a qualitative study of patients and their potential donors." Psychology & Health 25(6): 751-766. https://dx.doi.org/10.1007/s10620-020-06779-1

In April 2006, the Scottish Liver Transplant Unit became the first NHS transplant unit in the UK to offer adult Living Donor Liver Transplantation (LDLT). However, within the first 21 months of its availability, no patients on the transplant waiting list had pursued this treatment option. A qualitative interview study was devised to elicit the views of patients and their families with regards to LDLT. Interviews were conducted with 21 patients and 20 potential donors. The main reason why recipients did not pursue LDLT was their perception of risk to their donor. The anticipated feelings of guilt if the donor was harmed resulted in LDLT being rejected. However, despite this, many recipients would possibly consider LDLT as a 'last option'. For donors, considering becoming a donor was an automatic response, driven by their need to help their loved one to survive. However, consideration of the effects of donating upon their own immediate family often superseded their wish to donate. Whilst donors need to be given time to consider the implications of LDLT upon their own lives, it is essential that recipients understand that LDLT cannot be a last option, in order to allow them to reconsider their options realistically.

Shen, N. T., et al. (2020). "Patient Perspectives of High-Quality Care on the Liver Transplant Waiting List: A Qualitative Study." Liver Transplantation 26(2): 238-246. https://dx.doi.org/10.1002/lt.25645

The prevalence of advanced liver disease and listing for liver transplantation is increasing. Prior assessments of quality of care neither incorporate nor emphasize the patient perspective on quality of care, which may impact clinical outcomes. Our aim was to identify patients' perceptions on what constitutes high quality of care, comparing the findings to existing frameworks and assessments to determine if a patient-derived tool assessing quality of care could facilitate efforts to improve health care. We conducted semistructured interviews of patients wait-listed for liver transplantation, asking patients to describe the quality of their health care with a specific focus on how coordination, communication, office visits, hospitalizations, and cost affect their perceptions of the quality of their care. Data collection conducted concurrently with analyses determined emerging themes and saturation. Themes were mapped to an existing quality-of-care conceptual framework. Qualitative analysis revealed thematic saturation after 15 interviews, and an additional 15 interviews were analyzed that confirmed thematic saturation, maximizing the strength of the results. The 30 patients had a median age of 56 years (range, 32-72 years) and included 15 (50%) men. Although patients believed they received a high quality of care, which was substantiated on current existing measures, a qualitative analysis suggested that patient priorities emphasized 5 themes not currently assessed: managing expectations, providing education, responding to patient needs, executing the care plan efficiently, and utilizing interdisciplinary communication and coordination of care. In conclusion, transplant candidates perceived 5 themes that constitute quality of care, and existing quality-of-care measures do not assess these domains, suggesting a role for creating a patient-derived quality-of-care tool to improve health care and clinical outcomes.

Vijeratnam, S. S., et al. (2021). "Palliative Care for Patients with End-Stage Liver Disease on the Liver Transplant Waiting List: An International Systematic Review." Digestive Diseases and Sciences 66(12): 4072-4089. https://dx.doi.org/10.1007/s10620-020-06779-1

People with end-stage liver disease on the liver transplant waiting list have high symptom burden, which can successfully be addressed by specialist palliative care. Potential tensions with the perceived curative nature of liver transplant make delivering specialist palliative care challenging. This systematic review seeks to establish what is known on the impact of specialist palliative care for patients on liver transplant waiting lists, healthcare professionals' perspectives of providing specialist palliative care for this population, and uptake of advance care planning (ACP). Medline, Embase, and CINAHL were searched to May 5, 2020. Qualitative and quantitative findings were grouped together according to main relevant themes. Eight studies of mixed quality and mainly quantitative, were identified. Findings suggest early palliative care intervention improve patients' symptoms and prompt ACP conversations, but patients on the waiting list receive limited palliative care input. Liver physicians' lack of clarity on referral criteria and liver transplant patients' concerns of being abandoned, were reasons for reluctance to refer to specialist palliative care. They felt referral to specialist palliative care is appropriate only for patients receiving hospice or end of life care. Uptake and understanding of ACP and goals of care designation by patients is poor. This review found evidence of benefit of specialist palliative care for patients on liver transplant waiting lists, but found in a limited understanding of their role. Evidence is limited to studies from North America. Future research is needed to understand better how palliative care could be provided into this clinical environment.

Question 6 literature search

2. Waitlist dropout because of deterioration (n=19 studies)

Aloia, T. A., et al. (2007). "A decision analysis model identifies the interval of efficacy for Transarterial Chemoembolization (TACE) in cirrhotic patients with hepatocellular carcinoma awaiting liver transplantation." Journal of Gastrointestinal Surgery 11(10): 1328-1332. https://dx.doi.org/10.1007/s11605-007-0211-2

For liver transplant candidates with hepatocellular carcinoma (HCC), the ability of neoadjuvant transarterial chemoembolization (TACE) to improve outcomes remains unproven. The objective of our study was to determine if there was a specific time interval where neoadjuvant TACE would decrease the number of HCC patients removed from the pretransplant waitlist. A decision model was developed to simulate a randomized trial of neoadjuvant treatment with TACE vs. no TACE in 600 virtual patients with HCC and cirrhosis. Transition probabilities for TACE morbidity (1+/-1%), TACE response rates (30+/-20%), and disease progression (7+/-7% per month) were assigned by systematic review of the literature (18 reports). Sensitivity analyses were performed to determine time thresholds where TACE would decrease the number of delisted patients. TACE treatment had statistical benefit at waitlist time breakpoints of 4 and 9 months (P<0.05). When waitlist times were less than 4 months, waitlist attrition was similar (20% vs. 34%, P=0.08). When waitlist times exceed 9 months, waitlist dropout rates re-equilibrated (33% vs. 46%, P=0.06). Review of the current literature determined that only those studies reporting on patients with waitlist times between 4 and 9 months found a benefit to neoadjuvant TACE. This analysis indicates that the benefit of neoadjuvant TACE may be limited to those patients transplanted from 4 to 9 months from first TACE. These data may help transplant programs to tailor TACE treatments based on predicted waitlist times to achieve optimal resource utilization and improved organ allocation efficiency. © 2007 The Society for Surgery of the Alimentary Tract.

Aravinthan, A. D., et al. (2017). "Liver Transplantation is a Preferable Alternative to Palliative Therapy for Selected Patients with Advanced Hepatocellular Carcinoma." Annals of Surgical Oncology 24(7): 1843-1851. https://dx.doi.org/10.1245/s10434-017-5789-3

BACKGROUND: Patients with hepatocellular carcinoma (HCC) beyond the traditional criteria (advanced HCC) are typically offered palliation, which is associated with a 3-year survival rate lower than 30%. This study aimed to describe the outcomes for a subset of patients with advanced HCC who satisfied the Extended Toronto Criteria (ETC) and were listed for liver transplantation (LT).
METHODS: All patients listed in the Toronto liver transplantation program with HCC beyond both the Milan and University of California, San Francisco criteria were included in this study. Data were extracted from the prospectively collected electronic database. All radiologic images were reviewed by two independent radiologists. The primary end point was patient survival.
RESULTS: Between January 1999 and August 2014, 96 patients with advanced HCC were listed for LT, and 62 (65%) of these patients received bridging therapy while on the waiting list. Bridging therapy led to a significant reduction in tumor progression (p = 0.02) and tumor burden (p < 0.001). The majority of those listed underwent LT (n = 69, 72%). Both tumor progression on waiting list (hazard ratio [HR] 4.973; range1.599-15.464; p = 0.006) and peak alpha-fetoprotein (AFP) at 400 ng/ml or higher (HR, 4.604; range 1.660-12.768; p = 0.003) were independently associated with waiting list dropout. Post-LT HCC recurrence occurred in 35% of the patients (n = 24). Among those with HCC recurrence, survival was significantly better for those who received curative treatment (p = 0.004). The overall actuarial survival rates from the listing were 76% at 1 year, 56% at 3 years, and 47% at 5 years, and the corresponding rates from LT were 93, 71, and 66%.
CONCLUSION: Liver transplantation provides significantly better survival rates than palliation for patients with selected advanced HCC.

Ashoori, N., et al. (2012). "Multimodality treatment for early-stage hepatocellular carcinoma: A bridging therapy for liver transplantation." Digestion 86(4): 338-348. https://dx.doi.org/10.1159/000342813

Purpose: To evaluate the efficiency of a multimodality approach consisting of transcatheter arterial chemoembolization (TACE) and radiofrequency ablation (RFA) as bridging therapy for patients with hepatocellular carcinoma (HCC) awaiting orthotopic liver transplantation (OLT) and to evaluate the histopathological response in explant specimens. Material(s) and Method(s): Between April 2001 and November 2011, 36 patients with 50 HCC nodules (1.4-5.0 cm, median 2.8 cm) on the waiting list for liver transplantation were treated by TACE and RFA. The drop-out rate during the follow-up period was recorded. The local efficacy was evaluated by histopathological examination of the explanted livers. Result(s): During a median follow-up time of 29 (4.0-95.3) months the cumulative drop-out rate for the patients on the waiting list was 0, 2.8, 5.5, 11.0, 13.9 and 16.7% at 3, 6, 12, 24, 36 and 48 months, respectively. 16 patients (with 26 HCC lesions) out of 36 (44.4%) were transplanted by the end of study with a median waiting list time of 13.7 (2.5-37.8) months. The histopathological examination of the explanted specimens revealed a complete necrosis in 20 of 26 HCCs (76.9%), whereas 6 (23.1%) nodules showed viable residual tumor tissue. All transplanted patients are alive at a median time of 29.9 months. Imaging correlation showed 100% specificity and 66.7% sensitivity for the depiction of residual or recurrent tumor. Conclusion(s): We conclude that TACE combined with RFA could provide an effective treatment to decrease the drop-out rate from the OLT waiting list for HCC patients. Furthermore, this combination therapy results in high rates of complete tumor necrosis as evaluated in the histopathological analysis of the explanted livers. Further randomized trials are needed to demonstrate if there is a benefit in comparison with a single-treatment approach. © 2012 S. Karger AG, Basel.

Bababekov, Y. J., et al. (2020). "Do social determinants define "Too Sick" to transplant in patients with end-stage liver disease?" Transplantation: 280-284. https://dx.doi.org/10.1097/TP.0000000000002858

Background. Delisting for being "too sick" to be transplanted is subjective. Previous work has demonstrated that the mortality of patients delisted for "too sick" is unexpectedly low. Transplant centers use their best clinical judgment for determining "too sick," but it is unclear how social determinants influence decisions to delist for "too sick." We hypothesized that social determinants and Donor Service Area (DSA) characteristics may be associated with determination of "too sick" to transplant. Methods. Data were obtained from the Scientific Registry of Transplant Recipients for adults listed and removed from the liver transplant waitlist from 2002 to 2017. Patients were included if delisted for "too sick." Our primary outcome was Model for End-Stage Liver Disease (MELD) score at waitlist removal for "too sick." Regression assessed the association between social determinants and MELD at removal for "too sick." Results. We included 5250 delisted for "too sick" at 127 centers, in 53 DSAs, over 16 years. The mean MELD at delisting for "too sick" was 25.8 (SD +/- 11.2). On adjusted analysis, social determinants including age, race, sex, and education predicted the MELD at delisting for "too sick" ($P < 0.05$). Conclusions. There is variation in delisting MELD for "too sick" score across DSA and time. While social determinants at the patient and system level are associated with delisting practices, the interplay of these variables warrants additional research. In addition, center outcome reports should include waitlist removal rate for "too sick" and waitlist death ratios, so waitlist management practice at individual centers can be monitored. Copyright © 2019 Wolters Kluwer Health, Inc. All rights reserved.

Cucchetti, A., et al. (2011). "Priority of candidates with hepatocellular carcinoma awaiting liver transplantation can be reduced after successful bridge therapy." Liver Transpl 17(11): 1344-1354. https://pubmed.ncbi.nlm.nih.gov/21837731/

The allocation rules for patients with hepatocellular carcinoma (HCC) who are awaiting liver transplantation (LT) are a difficult issue and are continually evolving. To reduce tumor progression or down-stage advanced disease, most transplant centers have adopted the practice of treating HCC candidates with resection or locoregional therapies. This study was designed to assess the effectiveness of bridge therapy in preventing removal from the waiting list for death/sickness severity or tumor progression beyond the Milan criteria and in determining posttransplant outcomes. The removal rates for 315 adult patients with HCC who were listed for LT were analyzed and were correlated to responses to bridge therapy with a competing risk analysis. The 3-, 6-, and 12-month dropout rates were 3.5%, 6.5%, and 19.9%, respectively, and they were significantly affected by the Model for End-Stage Liver Disease score (P = 0.032), the tumor stage at diagnosis (P = 0.041), and the response to bridge therapy (P < 0.001). The stratification of candidates by the tumor stage and the response to bridge therapy showed that patients with T2 tumors who achieved only a partial response or no response to bridge therapy had the highest dropout rates, and they were followed by patients with successfully down-staged T3-T4a tumors (P = 0.037). Patients with T2 tumors who had a complete response and patients with T1 tumors had similar dropout rates (P = 0.964). The response to bridge therapy significantly affected both the recurrence rate of 176 transplant patients (P = 0.017) and the overall intention-to-treat survival rate (P = 0.001). In conclusion, the response to therapy is a potentially effective tool for prioritizing HCC patients for LT as well as select cases with different risks of tumor recurrence after transplantation.

Graziadei, I. W., et al. (2003). "Chemoembolization followed by liver transplantation for hepatocellular carcinoma impedes tumor progression while on the waiting list and leads to excellent outcome." Liver Transpl 9(6): 557-563. https://pubmed.ncbi.nlm.nih.gov/12783395/

Orthotopic liver transplantation (OLT) has been considered the best treatment option for patients with hepatocellular carcinoma (HCC). Because of a steadily increasing waiting time, a noteworthy proportion of patients are excluded from OLT because of tumor progression. A 20% and more dropout rate from the waiting list has recently been reported. In this prospective study, we evaluated the effect of preoperative transarterial chemoembolization (TACE) on preventing tumor progression while on the waiting list in patients meeting current selection criteria (solitary lesion < or = 5 cm, three lesions < or = 3 cm). In addition, we analyzed the outcome of a separate group of patients with advanced-stage HCC outside the selection criteria but with at least 50% tumor reduction after TACE (downstaging) to expand current criteria. Forty-eight patients met the selection criteria and were eligible for this study. Seven patients are still on the waiting list; 41 underwent OLT. None of these patients had to be removed from the list because of tumor progression after a mean waiting time of 178 days (23 patients > or =180 days). The 1-, 2-, and 5-year intention-to-treat survival was 98%, 98%, and 94%. The outcome after OLT was also excellent with 1-, 2-, and 5-year survival rates of 98%, 98%, and 93%. Tumor recurrence occurred only in 1 patient (2.4%). Fifteen patients with advanced-stage HCC were included in this study. Three developed a tumor progression and had to be removed from the list (20% dropout rate). Despite tumor reduction before OLT, these patients had a significantly less favorable outcome in the intention-to-treat analysis as well as in the posttransplantation survival. Tumor recurrence was seen in 30% of patients after OLT. In conclusion, TACE followed by OLT is associated with an excellent outcome in selected patients. Furthermore, TACE is highly efficacious in preventing tumor progression while waiting for OLT. Although TACE reduced tumor preoperatively, it failed to show a beneficial effect on patient survival in advanced-stage HCCs.

Hayashi, P. H., et al. (2004). "Hepatic artery chemoembolization for hepatocellular carcinoma in patients listed for liver transplantation." Am J Transplant 4(5): 782-787. https://pubmed.ncbi.nlm.nih.gov/15084175/

We retrospectively analyzed all listed patients having hepatic artery chemoembolization (HACE) for hepatocellular carcinoma (HCC) stage T2 or less. Outcomes were transplantation, waiting list removal, death, and HCC recurrence. Twenty patients (mean age 55.7 years; 15 males) were identified. Twelve (60%) were transplanted, seven (35%) were removed from the list and one (5%) remains listed. Fourteen (70%) are alive. All 12 transplanted patients are alive (mean 2.94 years); one of seven removed from the list is alive (mean 1.45 years). Survival was significantly higher for those transplanted or listed vs. removed from the list (100% vs. 14.3%, p = 0.0002). No HCC's recurred. Three patients (15%) were removed from the list after prolonged waiting times before MELD. Hepatic artery chemoembolization induced deterioration and removal from the list of one (5%) patient. Survival for those transplanted was excellent(100%), but overall survival was significantly lower (61.3%) at a mean 5.48 years. Hepatic artery chemoembolization for listed patients with <or=euro T2 stage HCC is beneficial, but must be weighed against decreased waiting times and risk of HACE-induced deterioration. This balance is influenced greatly by the MELD system's determination of waiting times for HCC patients.

Khan, A. S., et al. (2020). "Liver transplantation for hepatitis C patients in the era of direct-acting antiviral treatment: A retrospective cohort study." International Journal Of Surgery 75: 84-90. https://dx.doi.org/10.1016/j.ijsu.2020.01.145

Introduction: Direct-acting antivirals (DAA's) have revolutionized hepatitis-C virus (HCV) treatment, however controversy remains regarding timing of treatment in relation to liver-transplant (LT). Method(s): Single-center retrospective study assessing outcomes of listed HCV positive patients in the DAA-era (2014-2017). Patients treated with DAA's before LT (DAA pre-LT) were compared to those who were not treated before LT (No DAA pre-LT) Results: 156 HCV positive patients were listed during study-period; 104 (67%) underwent LT while 52 (33%) were de-listed. Of transplanted patients, 48 (46%) received DAA pre-LT while 56 (54%) were treated post-LT. Both groups were comparable in age, gender, MELD, patient and graft survival and cure-rates (98% in DAA pre-LTvs.95% in No DAA pre-LT; p > 0.05). DAA pre-LT group required higher number of treatments-per-patient to clear virus (1.46vs.1.06; p = 0.0006), spent more time on waitlist (331d.vs150d; p = 0.0040) and were less likely to receive livers from HCV positive donors (6%vs.25%; p = 0.0148). Twenty-nine (56%) of the 52 delisted received DAA. They had lower listing-MELD (12vs.18; p = 0.0033), and were more likely to be delisted for "condition improved" (34%vs.4%; p = 0.0143) compared to the 23 (44%) delisted patients who did not receive DAA's. Conclusion(s): DAA's were equally effective in clearing HCV in listed patients irrespective of timing. DAA pre-LT can disadvantage some patients through increase number of treatments needed and longer waitlist times, but treatment in some listed patients with low-MELD can improve condition and alleviate need for LT. Copyright © 2020 IJS Publishing Group Ltd

Kwong, A. J., et al. (2022). "National Trends and Waitlist Outcomes of Locoregional Therapy Among Liver Transplant Candidates With Hepatocellular Carcinoma in the United States." Clinical Gastroenterology & Hepatology 20(5): 1142-1150.e1144. https://dx.doi.org/10.1016/j.cgh.2021.07.048

BACKGROUND & AIMS: Policy changes in the United States have lengthened overall waiting times for patients with hepatocellular carcinoma (HCC). We investigated temporal trends in utilization of locoregional therapy (LRT) and associated waitlist outcomes among liver transplant (LT) candidates in the United States.
METHODS: Data for primary adult LT candidates listed from 2003 to 2018 who received HCC exception were extracted from the Organ Procurement and Transplantation Network database. Explant histology was examined, and multivariable competing risk analysis was used to evaluate the association between LRT type and waitlist dropout.

RESULTS: There were 31,609 eligible patients with at least 1 approved HCC exception, and 34,610 treatments among 24,145 LT candidates. The proportion with at least 1 LRT recorded increased from 42.3% in 2003 to 92.4% in 2018. Chemoembolization remains the most frequent type, followed by thermal ablation, with a notable increase in radioembolization from 3% in 2013 to 19% in 2018. An increased incidence of LRT was observed among patients with tumor burden beyond Milan criteria, higher alpha-fetoprotein level, and more compensated liver disease. Receipt of any type of LRT was associated with a lower risk of waitlist dropout; there was no significant difference by number of LRTs. In inverse probability of treatment weighting-adjusted analysis, radioembolization or ablation as the first LRT was associated with a reduced risk of waitlist dropout compared with chemoembolization.
CONCLUSIONS: In a large nationwide cohort of LT candidates with HCC, LRT, and in particular radioembolization, increasingly was used to bridge to LT. Patients with greater tumor burden and those with more compensated liver disease received more treatments while awaiting LT. Bridging LRT was associated with a lower risk of waitlist dropout.

Maggs, J. R. L., et al. (2012). "Systematic review: The role of liver transplantation in the management of hepatocellular carcinoma." Alimentary Pharmacology and Therapeutics 35(10): 1113-1134. https://dx.doi.org/10.1111/j.1365-2036.2012.05072.x

Background Hepatocellular carcinoma (HCC) is a major cause of morbidity and mortality worldwide. Liver transplantation offers a potential cure for this otherwise devastating disease. The selection of the most appropriate candidates is paramount in an era of graft shortage. Aim To review systematically the role of liver transplantation in the management of HCC in current clinical practice. Methods An electronic literature search using PUBMED (1980-2010) was performed. Search terms included HCC, hepatoma, liver cancer, and liver transplantation. Results Liver transplantation is a highly successful treatment for HCC, in patients within Milan criteria (MC), defined as a solitary tumour >=50 mm in diameter or >=3 tumours >=30 mm in diameter in the absence of extra-hepatic or vascular spread. Other eligibility criteria for liver transplantation are also used in clinical practice, such as the University of California, San Francisco criteria, with outcomes comparable to MC. Loco-regional therapies have a role in the bridging treatment of HCC by minimising wait-list drop-out secondary to tumour progression. Beyond MC, encouraging results have been demonstrated for patients with down-staged tumours. Post-liver transplantation, there is no evidence to support a specific immunosuppressive regimen. In the context of an insufficient cadaveric donor pool to meet demand, the role of adult living donation may be increasingly important. Conclusions Liver transplantation offers a curative therapy for selected patients with HCC. The optimisation of eligibility criteria is paramount to ensure that maximum benefit is accrued. Although wait-list therapies have been incorporated into clinical practice, additional high quality data are required to support this strategy.

Marelli, L., et al. (2006). "Treatment outcomes for hepatocellular carcinoma using chemoembolization in combination with other therapies." Cancer Treatment Reviews 32(8): 594-606. https://dx.doi.org/10.1016/j.ctrv.2006.08.002

Background: Although transarterial chemoembolization (TACE) improves survival in patients with hepatocellular carcinoma (HCC), it is not known if TACE combined with other treatments is beneficial. Aim(s): To evaluate the evidence for improved outcomes in HCC with a multimodal treatment approach involving TACE. Method(s): PubMed search for all cohort and randomized trials (n = 84) evaluating TACE combined with other therapies; meta-analysis performed where appropriate. Result(s): A meta-analysis involving 4 RCTs showed a significant decrease in mortality favouring combination treatment (TACE plus percutaneous ablation) compared to monotherapy in patients with either small (<3 cm) or large HCC nodules (>3 cm) (OR, 0.534; 95% CI, 0.288-0.990; p = 0.046). TACE combined with local radiotherapy improved survival in patients with tumour thrombosis of the portal vein in 7 non-randomized studies. Two RCTs and 13 non-randomized studies showed that TACE prior to hepatic resection does not improve survival nor tumour recurrence. Conversely, 2 RCTs and 5 comparative studies showed that transarterial injection of chemotherapeutic drugs mixed with lipiodol (TOCE) following hepatectomy confers survival benefit and less tumour recurrence. TACE before liver transplantation is safe and reduces drop-out rate from the waiting list, but there is no current evidence of improvement in subsequent survival or recurrence rate. Conclusion(s): A combined approach involving TACE and percutaneous ablation improves survival. Adjuvant TOCE improves outcome after hepatectomy. TACE is useful to control tumours burden while on the waiting list for OLT. Multimodal treatment seems to be the best way to optimize TACE outcomes in HCC.

Muna-Aguon, P., et al. (2019). "Lymphovascular invasion on explant is associated with presenting tumor characteristics and not direct acting antiviral utilization in hepatitis C candidates undergoing liver transplantation." Clinical & Experimental Hepatology 5(4): 279-284. https://dx.doi.org/10.5114/ceh.2019.88105

AIM OF THE STUDY: Utilization of direct acting antiviral (DAA) therapy in candidates with well-compensated hepatitis C virus (HCV) cirrhosis and hepatocellular carcinoma (HCC) accruing end stage liver disease (MELD) exception points is highly variable among transplant centers based on center location, local organ procurement dynamics, HCV(+) organ availability, and patient preference. The association between DAA utilization prior to transplant and incidence of lymphovascular invasion on explant is unknown.
MATERIAL AND METHODS: Retrospective evaluation from 2013-2017 of patients on a liver transplant (LT) waitlist with HCV-related cirrhosis, MELD-Na < 15, and HCC (within T2/Milan criteria). The cohort was divided into the pre-LT DAA treated group and untreated group with clinical/viral demographics collected. Tumor presenting characteristics, locoregional treatments, wait time to LT, dropout rates and explant pathology were compared.
RESULTS: DAAs were used in 44 patients prior to LT (SVR12 of 37/44 [84%]) and 19 left untreated with LT performed in 81% (51/63) of the waitlisted cohort. No significant differences were found between groups with regards to clinical/viral demographics, local-regional therapy (LRT) sessions, or frequency of lymphovascular invasion on explant. The untreated cohort had a higher rate of dropout (6.3% vs. 3.2%) (p = 0.041). On subgroup analysis of 51 subjects undergoing LT, AFP > 250 ng/ml (p = 0.003) and multifocal HCC (> 1 lesion) (p = 0.006) were associated with lymphovascular invasion on explant while DAA therapy was not (p = 0.578).
CONCLUSIONS: DAA therapy for waitlist active HCV candidates accruing MELD exception points has no deleterious effects on bridging LRT, nor is it associated with increased frequency of lymphovascular invasion on explant. The latter appears driven by tumor related characteristics (AFP and number of lesions) irrespective of DAA utilization prior to LT.

Perricone, G., et al. (2018). "Delisting HCV-infected liver transplant candidates who improved after viral eradication: Outcome 2 years after delisting." Liver International 38(12): 2170-2177. https://dx.doi.org/10.1111/liv.13878

BACKGROUNDS & AIMS: Treating patients with decompensated cirrhosis with direct-acting antiviral (DAA) therapy while on the waiting list for liver transplantation results in substantial improvement of liver function allowing 1 in 4 patients to be removed from the waiting list or delisted, as reported in a previous study promoted by the European Liver and Intestine Transplant Association (ELITA). The aim of this study was to report on clinical outcomes of delisted patients, including mortality risk, hepatocellular carcinoma development and clinical decompensation requiring relisting.
METHODS: One hundred and forty-two HCV-positive patients on the liver transplant waiting list for decompensated cirrhosis, negative for hepatocellular carcinoma, between February 2014 and June 2015 were treated with DAA therapy and were prospectively followed up.
RESULTS: Forty-four patients (30.9%) were delisted following clinical improvement. This percentage was higher than in the original study because of a number of patients being delisted long after starting DAAs. The median Child-Pugh and MELD score of delisted patients was 5.5 and 9 respectively. Four patients were relisted, because of HCC diagnosis in 1 case and 3 patients developed ascites. One further patient died (2.4%) because of rapidly progressing hepatocellular carcinoma twenty-two months after delisting. Of the 70 patients who received a liver graft, 9 died (13%).
CONCLUSIONS: Antiviral therapy allows for a long-term improvement of liver function and the delisting of one-third of treated patients with risk of liver-related complications after delisting being very low.

Pinero, F., et al. (2018). "Results of liver transplantation for hepatocellular carcinoma in a multicenter latin American cohort study." Annals of Hepatology 17(2): 256-267. https://dx.doi.org/10.5604/01.3001.0010.8648

Background and aims. Heterogeneous data has been reported regarding liver transplantation (LT) for hepatocellular carcinoma (HCC) in Latin America. We aimed to describe treatment during waiting list, survival and recurrence of HCC after LT in a multicenter study from Latin America. Material and methods. Patients with HCC diagnosed prior to transplant (cHCC) and incidentally found in the explanted liver (iHCC) were included. Imaging-explanted features were compared in cHCC (non-discordant if pre and post-LT were within Milan, discordant if pre-LT was within and post-LT exceeding Milan). Results. Overall, 435 patients with cHCC and 92 with iHCC were included. At listing, 81% and 91% of cHCC patients were within Milan and San Francisco criteria (UCSF), respectively. Five-year survival and recurrence rates for cHCC within Milan, exceeding Milan/within UCSF and beyond UCSF were 71% and 16%; 66% and 26%; 46% and 55%, respectively. Locoregional treatment prior to LT was performed in 39% of cHCC within Milan, in 53% beyond Milan/within UCSF and in 83% exceeding UCSF ($p < 0.0001$). This treatment difference was not observed according to AFP values (<=100, 44%; 101-1,000, 39%, and > 1,000 ng/mL 64%; $p = 0.12$). Discordant imaging-explanted data was observed in 29% of cHCC, showing lower survival HR 2.02 (CI 1.29; 3.15) and higher recurrence rates HR 2.34 when compared to AFP <100 ng/mL. Serum AFP > 1,000 ng/mL at listing was independently associated with a higher 5-year recurrence rate and a HR of 3.24 when compared to AFP <100 ng/mL. Conclusion. Although overall results are comparable to other regions worldwide, pre-LT treatment not only considering imaging data but also AFP values should be contemplated during the next years.

Pinero, F., et al. (2022). "Performance of pre-transplant criteria in prediction of hepatocellular carcinoma progression and waitlist dropout." Liver International 42(8): 1879-1890. https://dx.doi.org/10.1111/liv.15223

BACKGROUND & AIM: Liver transplantation (LT) selection models for hepatocellular carcinoma (HCC) have not been proposed to predict waitlist dropout because of tumour progression. The aim of this study was to compare the alpha-foetoprotein (AFP) model and other pre-LT models in their prediction of HCC dropout.

METHODS: A multicentre cohort study was conducted in 20 Latin American transplant centres, including 994 listed patients for LT with HCC from 2012 to 2018. Longitudinal tumour characteristics, and patterns of progression were recorded at time of listing, after treatments and at last follow-up over the waitlist period. Competing risk regression models were performed, and model's discrimination was compared estimating Harrell's adapted c-statistics.
RESULTS: HCC dropout rate was significantly higher in patients beyond (24% [95% CI 16-28]) compared to those within Milan criteria (8% [95% IC 5%-12%]; p < .0001), with a SHR of 3.01 [95% CI 2.03-4.47]), adjusted for waiting list time and bridging therapies (c-index 0.63 [95% CI 0.57; 0.69). HCC dropout rates were higher in patients with AFP scores >2 (adjusted SHR of 3.17 [CI 2.13-4.71]), c-index of 0.71 (95% CI 0.65-0.77; p = .09 vs Milan). Similar discrimination power for HCC dropout was observed between the AFP score and the Metroticket 2.0 model. In patients within Milan, an AFP score >2 points discriminated two populations with a higher risk of HCC dropout (SHR 1.68 [95% CI 1.08-2.61]).
CONCLUSIONS: Pre-transplant selection models similarly predicted HCC dropout. However, the AFP model can discriminate a higher risk of dropout among patients within Milan criteria.

Toso, C., et al. (2014). "Validation of a dropout assessment model of candidates with/without hepatocellular carcinoma on a common liver transplant waiting list." Transplant International 27(7): 686-695. https://dx.doi.org/10.1111/tri.12323

The model of end-stage liver disease (MELD) score is often used for liver graft allocation, and patients with hepatocellular carcinoma (HCC) receive exception points (22 in the US). A better model is desirable for patients with HCC as they tend to have a privileged access to transplantation, without taking HCC characteristics into account. A new simpler model designed from a training set of US patients (n = 49 026) was tested on two validation sets (US and UK patient cohorts with, respectively, n = 20 475 and n = 1781). The risk of dropout was between 3.2 and 7.8% at 3 months in patients with HCC, and was captured into a score, including HCC size, HCC number, AFP, and MELD (-37.8 +1.9MELD+5.9 if HCC Nb >= 2 + 5.9 if AFP > 400 + 21.2 if HCC size > 1 cm). This new model could be validated on external US and UK liver candidate cohorts. It provides a dynamic and more accurate assessment of dropout than the use of exception MELD (C-indices of 66.2-73.7% vs. 52.7-56.6%). In addition, the model shows a similar distribution as MELD for patients with non-HCC, and both scores could be used in parallel for the management of waiting-list patients with and without HCC.

Uemura, T., et al. (2019). "Stereotactic Body Radiation Therapy: A New Strategy for Loco-Regional Treatment for Hepatocellular Carcinoma While Awaiting Liver Transplantation." World Journal of Surgery 43(3): 886-893. https://dx.doi.org/10.1007/s00268-018-4829-x

BACKGROUND: Trans-arterial chemoembolization and radiofrequency ablation are commonly used for control of hepatocellular carcinoma (HCC) on liver transplant (LTx) waiting list. Stereotactic body radiation therapy (SBRT) was introduced to our institution for HCC as a bridging or downsizing therapy to LTx. PATIENTS AND METHODS: Twenty-five HCC lesions in 22 patients were treated with SBRT while waiting for LTx from January 2010 to December 2015. Nineteen of these patients received deceased donor LTx. SBRT was defined as 40-50 Gy delivered in 4-6 fractions. Pre- and post-liver transplant outcome were analyzed in addition to the dropout rate and tumor response to SBRT. RESULT(S): Median size of original tumors was 3.2 cm (2.0-8.9), and median size of tumor after SBRT was significantly smaller at 0.9 cm (0-3.2) in the explanted livers (p<0.01). The dropout rate was 9%, and they were only downsized patients outside of Milan criteria. Liver disease did not progress between pre- and post-SBRT except one patient. Twenty-eight percent of treated HCCs showed complete pathologic response, and 22% had extensive partial response with some residual tumor. No HCC recurrence was experienced after LTx. CONCLUSION(S): SBRT is indicated to be safe, effective treatment for HCC on LTx waiting list, and it leads to satisfactory post-liver transplant outcomes.

Yamashiki, N., et al. (2005). "Ablation therapy in containing extension of hepatocellular carcinoma: a simulative analysis of dropout from the waiting list for liver transplantation." Liver Transpl 11(5): 508-514. https://pubmed.ncbi.nlm.nih.gov/15838878/

The dropout from the waiting list for liver transplantation among patients with hepatocellular carcinoma (HCC) is reportedly as high as 12% to 40% per year, mostly due to tumor progression. Considering the scarcity of donor organs, it would be beneficial if we could retain them within the Milan criteria with a bridging therapy. We retrospectively analyzed the prognosis of 288 HCC patients with relatively preserved liver function we treated with ablation therapy between 1997 and 2001, concentrating on whether they subsequently remained in the criteria, and analyzed the risk factors of dropout with Cox proportional hazards model. During a median follow-up period of 39 months (range, 1-86 months), 33 (11%) died without tumor progression, while 85 (30%) dropped out due to tumor progression. The overall dropout rate was 9.0% and 32.8% at 1 and 3 years, respectively, and that due to tumor progression was 6.2% and 23.0%. Cox regression analysis indicated that a high serum level of alpha-fetoprotein or des-gamma-carboxy prothrombin, and a tumor size exceeding 3 cm in diameter affected the dropout due to tumor progression, while low albumin concentration was a risk factor of death independently of tumor progression. In conclusion, local ablation therapy for HCC was effective in containing the tumor progression within the Milan criteria in selected patients.

Zanetto, A., et al. (2017). "Dropout rate from the liver transplant waiting list because of hepatocellular carcinoma progression in hepatitis C virus-infected patients treated with direct-acting antivirals." Liver Transplantation 23(9): 1103-1112. https://dx.doi.org/10.1002/lt.24790

Concerns about an increased hepatocellular carcinoma (HCC) recurrence rate following direct-acting antiviral (DAA) therapy in patients with cirrhosis with a prior complete oncological response have been raised. Data regarding the impact of HCV treatment with DAAs on wait-list dropout rates in patients with active HCC and HCV-related cirrhosis awaiting liver transplantation (LT) are lacking. HCV-HCC patients listed for LT between January 2015 and May 2016 at Padua Liver Transplant Center were considered eligible for the study. After enrollment, patients were divided into 2 groups, depending on whether they underwent DAA treatment while awaiting LT or not. For each patient clinical, serological, and virological data were collected. HCC characteristics were radiologically evaluated at baseline and during follow-up (FU). For transplanted patients, pathological assessment of the explants was performed and recurrence rates were calculated. A total of 23 patients treated with DAAs and 23 controls were enrolled. HCC characteristics at time of LT listing were comparable between the 2 groups. Median FU was 10 and 7 months, respectively, during which 2/23 (8.7%) and 1/23 (4.3%) dropout events due to HCC progression were registered (P = 0.90). No significant differences in terms of radiological progression were highlighted (P = 0.16). A total of 9 out of 23 (39%) patients and 14 out of 23 (61%) controls underwent LT, and histopathological analysis showed no differences in terms of median number and total tumor volume of HCC nodules, tumor differentiation, or microvascular invasion. During post-LT FU, 1/8 (12.5%) DAA-treated patient and 1/12 (8.3%) control patient experienced HCC recurrence (P = 0.60). In conclusion, viral eradication does not seem to be associated with an increased risk of dropout due to neoplastic progression in HCV-HCC patients awaiting LT. Liver Transplantation 23 1103-1112 2017 AASLD. Copyright © 2017 by the American Association for the Study of Liver Diseases.

3. Waitlist mortality (n=5)

Annicchiarico, B. E., et al. (2008). "Treatment of chronic hepatitis C virus infection with pegylated interferon and ribavirin in cirrhotic patients awaiting liver transplantation." Transplantation Proceedings 40(6): 1918-1920. https://dx.doi.org/10.1016/j.transproceed.2008.06.002

Successful treatment of chronic hepatitis C virus (HCV) infection can prevent reinfection after orthotopic liver transplantation (OLT). Pegylated interferon (PEG-IFN) may ameliorate virological response (VR), making the risk-to-benefit ratio of therapy favorable in waiting list patients. From January 2001 to April 2006, we treated 15 HCV cirrhotics with PEG-IFN alpha-2b (1.5 microg/kg/week) and ribavirin (RIBA; >or=10.6 mg/kg/d). Their mean age was 51.5 years. There were 9 men. In 6 cases the genotype was 1b. With Child-Pugh scores >or=9 (range 9-12) and Model for End-Stage Liver Disease (MELD) scores >or=14 (range, 14-22). Adverse events occurred in all subjects: thrombocytopenia (<40,000/microL) in 8; neutropenia (<700/microL) in 10; anemia (Hb <8.5 g/dL) in 1; grade III hepatic encephalopathy in 2; pelvic infection in 1; variceal hemorrhage in 1; and hepatocellular carcinoma (HCC) recurrence in 1. Adverse events caused treatment withdrawal in 6 (40.0%) and RIBA and/or PEG-IFN dose reduction in 10 (66.6%). Early VR (EVR) was obtained in 9 subjects (60.0%), end-of-treatment (EOT) VR in 7 (46.6%), and sustained VR (SVR) in 3 (20.0%). Three subjects--2 nonresponder and 1 breakthrough--were transplanted at 25, 23, and 16 months after the EOT, respectively. Three subjects died at 6, 8, and 15 months after the EOT due to HCC, spontaneous bacterial peritonitis, and liver failure. Nine patients are awaiting OLT. The risk-to-benefit ratio is against PEG-INF and RIBA treatment of severely decompensated cirrhotics infected with genotype 1 awaiting OLT, but therapy is probably beneficial in genotype 2 subjects, due to an expected SVR rate of more than 40%. However, one must carefully consider the high risk for severe adverse events.

Belli, L. S., et al. (2021). "Liver transplantation for patients with acute-on-chronic liver failure (ACLF) in Europe: Results of the ELITA/EF-CLIF collaborative study (ECLIS)." Journal of Hepatology 75(3): 610-622. https://dx.doi.org/10.1016/j.jhep.2021.03.030

Background & Aims: Liver transplantation (LT) has been proposed as an effective salvage therapy even for the sickest patients with acute-on-chronic liver failure (ACLF). This large collaborative study was designed to assess the current clinical practice and outcomes of patients with ACLF who are wait-listed for LT in Europe. Method(s): This was a retrospective study including 308 consecutive patients with ACLF, listed in 20 centres across 8 European countries, from January 2018 to June 2019. Result(s): A total of 2,677 patients received a LT: 1,216 (45.4%) for decompensated cirrhosis. Of these, 234 (19.2%) had ACLF at LT: 58 (4.8%) had ACLF-1, 78 (6.4%) had ACLF-2, and 98 (8.1%) had ACLF-3. Wide variations were observed amongst countries: France and Germany had high rates of ACLF-2/3 (27-41%); Italy, Switzerland, Poland and the Netherlands had medium rates (9-15%); and the United Kingdom and Spain had low rates (3-5%) (p <0.0001). The 1-year probability of survival after LT for patients with ACLF was 81% (95% CI 74-87). Pre-LT arterial lactate levels >4 mmol/L (hazard ratio [HR] 3.14; 95% CI 1.37-7.19), recent infection from multidrug resistant organisms (HR 3.67; 95% CI 1.63-8.28), and renal replacement therapy (HR 2.74; 95% CI 1.37-5.51) were independent predictors of post-LT mortality. During the same period, 74 patients with ACLF died on the waiting list. In an intention-to-treat analysis, 1-year survival of patients with ACLF on the LT waiting list was 73% for ACLF-1 or -2 and 50% for ACLF-3. Conclusion(s): The results reveal wide variations in the listing of patients with ACLF in Europe despite favourable post-LT survival. Risk factors for mortality were identified, enabling a more precise prognostic assessment of patients with ACLF. Lay summary: Acute-on-chronic liver failure (ACLF) is a severe clinical condition for which liver transplantation is an effective therapeutic option. This study has demonstrated that in Europe, referral and access to liver transplantation (LT) for patients with ACLF needs to be harmonised to avoid inequities. Post-LT survival for patients with ACLF was >80% after 1 year and some factors have been identified to help select patients with favourable outcomes. Copyright © 2021 European Association for the Study of the Liver

Brown, C. S., et al. (2021). "Associations among Different Domains of Quality among US Liver Transplant Programs." JAMA Network Open (no pagination). https://dx.doi.org/10.1001/jamanetworkopen.2021.18502

Importance: US liver transplant programs have traditionally been evaluated on 1-year patient and graft survival. However, there is concern that a narrow focus on recipient outcomes may not incentivize programs to improve in other ways that would benefit patients with end-stage liver disease. Objective(s): To determine the correlation among different potential domains of quality for adult liver transplant programs. Design, Setting, and Participant(s): This retrospective cohort study was conducted from 2014 to 2019 among adult liver transplant programs included in the United Network for Organ Sharing and Scientific Registry of Transplant Recipients program-specific reports. Liver transplant programs in the United States completing at least 10 liver transplants per year were included. Data were analyzed from March 2 to August 13, 2020. Main Outcomes and Measures: The potential domains of quality examined included recipient outcomes (1-year graft and patient survival), aggressiveness (ie, marginal graft use, defined as the rate of use of donors with body mass index [calculated as weight in kilograms divided by height in meters squared] greater than 40, age older than 65 years, or deceased by cardiac death), and waiting list management (ie, waiting list mortality). The correlation among measures, aggregated at the center level, was evaluated using linear regression to control for mean Model for End Stage Liver Disease-Sodium score at organ allocation. The extent to which programs were able to achieve high quality across multiple domains was also evaluated. Result(s): Among 114 transplant programs that performed a total of 44554 transplants, the mean (SD) 1-year graft and patient survival was 90.3% (3.0%) with a total range of 75.9% to 96.6%. The mean (SD) waiting list mortality rate was 16.7 (6.1) deaths per 100 person-years, with a total range of 6.3 to 53.0 deaths per 100 person years. The mean (SD) marginal graft use rate was 15.8 (8.8) donors per 100 transplants, with a total range of 0 to 49.3 donors. There was no correlation between 1-year graft and patient survival and waiting list mortality (beta = -0.053; P =.19) or marginal graft use (beta = -0.007; P =.84) after correcting for mean allocation Model for End Stage Liver Disease-Sodium scores. There were 2 transplant programs (1.8%) that performed in the top quartile on all 3 measures, while 4 transplant programs (3.6%) performed in the bottom quartile on all 3 measures. Conclusions and Relevance: This cohort study found that among US liver transplant programs, there were no correlations among 1-year recipient outcomes, measures of program aggressiveness, or waiting list management. These findings suggest that a program's performance in one domain may be independent and unrelated to its performance on others and that the understanding of factors contributing to these domains is incomplete. Copyright © 2021 Wolters Kluwer Medknow Publications. All rights reserved.

Dumortier, J., et al. (2006). "Impact of adult-to-adult living donor liver transplantation on access to transplantation and patients' survival: An 8-year single-center experience." Liver Transplantation 12(12): 1770-1775. https://dx.doi.org/10.1002/lt.20895

While the number of candidates for liver transplantation has increased in the recent years, the pool of cadaveric donor organs has remained constant and the waiting time progressively increases. These facts led us to start a program of adult-to-adult living-donor liver transplantation in 1998. The aim of this study was to compare the outcome of all patients put on the waiting list since 1998. Between January 1, 1998, and January 1, 2005, 505 patients were put on the waiting list in our center, and living donor liver transplantation was considered in 57 cases (11.3%). At the time of evaluation (April 1, 2006), liver transplantation was performed in 377 patients (46 living donor liver transplantations), and 89 patients died on waiting list. On an intention-to-treat basis, the 1-year survival rate from the time of listing was 87.5% in the "living donor" group vs. 76.2% in the "cadaveric donor" group (P < 0.05), whereas the 1-year survival after liver transplantation was similar (92.3% vs. 86.9%). Our living donor liver transplantation program was able to improve the access to liver transplantation by reducing waiting time and the number of deaths on waiting list, despite the fact that these patients were more critically ill (liver failure and/or liver cancer). © 2006 AASLD.

Hogen, R., et al. (2019). "More Than Just Wait Time? Regional Differences in Liver Transplant Outcomes for Hepatocellular Carcinoma." Transplantation 103(4): 747-754. https://dx.doi.org/10.1097/TP.0000000000002248

BACKGROUND: Regional allocation of deceased donor livers has led to variable wait times for hepatocellular carcinoma (HCC) patients on the liver transplant list. The purpose of our study was to evaluate how regional differences in wait time affect outcomes for HCC patients.
METHODS: A retrospective, observational study was performed using the Organ Procurement and Transplantation Network database from February 27, 2002, to September 25, 2015. The cumulative incidences of transplant and waitlist death as well as intention-to-treat and posttransplant survival were evaluated for patients 18 years or older listed for deceased donor liver transplantation with stage II HCC exception points in each United Network for Organ Sharing region. A multivariable analysis of predictive factors for posttransplant survival was performed.
RESULTS: Cumulative incidence of transplant decreased and cumulative incidence of waitlist death increased as regional wait time increased. Intention-to-treat survival decreased with increased regional wait time with long wait time regions 1, 5, and 9 having significantly lower intention-to-treat survival compared with many of the shorter wait time regions ($P < 0.05$). Wait time did not predict posttransplant survival. Significant predictive factors of posttransplant survival included alpha-fetoprotein, size of the largest tumor, number of tumors, age of the recipient, laboratory model for end-stage liver disease, donor risk index, period of transplantation, and region ($P < 0.05$).
CONCLUSIONS: Wait time inequality affects waitlist mortality and intention-to-treat survival but does not affect posttransplant survival. Posttransplant survival is predicted by tumor biology, graft quality, recipient age, underlying liver function, and region. Regional environments of HCC care seem to drive posttransplant survival.

4. Deterioration and waitlist mortality (n=2)

Kulik, L., et al. (2018). "Therapies for patients with hepatocellular carcinoma awaiting liver transplantation: A systematic review and meta-analysis." Hepatology 67(1): 381-400. https://dx.doi.org/10.1002/hep.29485

Patients with hepatocellular carcinoma (HCC) who are listed for liver transplantation (LT) are often treated while on the waiting list with locoregional therapy (LRT), which is aimed at either preventing progression of HCC or reducing the measurable disease burden of HCC in order to receive increased allocation priority. We aimed to synthesize evidence regarding the effectiveness of LRT in the management of patients with HCC who were on the LT waitlist. We conducted a comprehensive search of multiple databases from 1996 to April 25, 2016, for studies that enrolled adults with cirrhosis awaiting LT and treated with bridging or down-staging therapies before LT. Therapies included transcatheter arterial chemoembolization, transarterial radioembolization, ablation, and radiotherapy. We included both comparative and noncomparative studies. There were no randomized controlled trials identified. For adults with T1 HCC and waiting for LT, there were only two nonrandomized comparative studies, both with a high risk of bias, which reported the outcome of interest. In one series, the rate of dropout from all causes at 6 months in T1 HCC patients who underwent LRT was 5.3%, while in the other series of T1 HCC patients who did not receive LRT, the dropout rate at median follow-up of 2.4 years and the progression rate to T2 HCC were 30% and 88%, respectively. For adults with T2 HCC awaiting LT, transplant with any bridging therapy showed a nonsignificant reduction in the risk of waitlist dropout due to progression (relative risk [RR], 0.32; 95% confidence interval [CI], 0.06-1.85; I² = 0%) and of waitlist dropout from all causes (RR, 0.38; 95% CI, 0.060-2.370; I² = 85.7%) compared to no therapy based on three comparative studies. The quality of evidence is very low due to high risk of bias, imprecision, and inconsistency. There were five comparative studies which reported on posttransplant survival rates and 10 comparative studies which reported on posttransplant recurrence, and there was no significant difference seen in either of these endpoints. For adults initially with stage T3 HCC who received LRT, there were three studies reporting on transplant with any down-staging therapy versus no downstaging, and this showed a significant increase in 1-year (two studies, RR, 1.11; 95% CI, 1.01-1.23) and 5-year (1 study, RR, 1.17; 95% CI, 1.03-1.32) post-LT survival rates for patients who received LRT. The quality of evidence is very low due to serious risk of bias and imprecision. Conclusion(s): In patients with HCC listed for LT, the use of LRT is associated with a nonsignificant trend toward improved waitlist and posttransplant outcomes, though there is a high risk of selection bias in the available evidence. (Hepatology 2018;67:381-400). Copyright © 2017 by the American Association for the Study of Liver Diseases.

Trapani, S., et al. (2017). "Hepatitis C Virus Positive Patients on the Waiting List for Liver Transplantation: Turnover and Characteristics of the Population on the Eve of the Therapeutic Revolution With Direct-Acting Antivirals." Transplantation Proceedings 49(4): 658-666. https://dx.doi.org/10.1016/j.transproceed.2017.02.039

Introduction Antivirals direct acting (DAA) for hepatitis C virus (HCV) have brought a revolution in the field of transplantation. It is likely to think that in the future patients on the waiting list for liver transplantation (LT) will no longer be registered for HCV-related cirrhosis but for liver disease from other causes. On the eve of this change, we show a snapshot of the Italian waiting list for LT. Methods From October 1, 2012 to September 30, 2013, we estimated the total number of patients on the liver waiting list as intention to treat (ITT), the number of incident cases, and the delistings, particularly in the HCV positive (HCV+) population. Gender, median age, etiology and prognosis of liver disease, presence of hepatocellular carcinoma (HCC), reason for delisting, mean waiting time for LT, and rate of death on waiting list were evaluated. Results In the time period, there were 517 new patients who were HCV+ (median age, 53 years): 255 (49.3%) mono-infected with HCV, 236 (45.7%) co-infected with HCV and hepatitis B virus (HBV), 11 (2.1%) co-infected with HCV and human immunodeficiency virus (HIV), and 15 (2.9%) co-infected with HCV, HBV, and HIV. The median model for end-stage liver disease (MELD) score at listing was 17 and HCC was present in 206 (39.8%) cases. HCV+ patients delisted were 442 (61.9%), 355 (80.3%) for LT. The mean waiting time to transplantation was 1.9 months; the percentage of death was 7.6%. Conclusions This snapshot of the waiting list for LT in the year before the advent of DAA drugs will allow us to assess whether and how they will change the waiting list for LT when we start to look at the impact of new therapies on the waiting list.

5. Waitlist morbidity (n=1 studies)

Cowling, T., et al. (2005). "MELD scores do not predict patient morbidity while on the liver transplant waiting list." Transplantation Proceedings 37(5): 2174-2178. https://pubmed.ncbi.nlm.nih.gov/15964371/

The goals of this study were to assess waitlist morbidity in terms of the frequency of health care services utilized by patients while on the liver transplant (LTX) waiting list and to determine whether that utilization can be predicted by the Model for End-Stage Liver Disease (MELD). Sixty-three noncomatose subjects were followed from waitlist placement until death, change in status, LTX, or study discontinuance. Health care events included doctor/clinic visits, labs, outpatient/inpatient tests and procedures, and hospital/intensive care unit days. Listing MELD scores and LTX MELD scores were examined against the number of health care event occurrences within 60 days of listing and 60 days of LTX, respectively, as were changes in MELD scores between listing and LTX and differences in the number of occurrences between the two time points. The only significant correlations noted were between LTX MELD scores and number of hospital days near LTX (r = .360, P = .046) and between LTX MELD scores and the sum total number of occurrences near LTX (r = .370, P = .044). These results suggest that MELD scores do not appear to predict morbidity in terms of health care utilization in patients awaiting LTX. Developing a system capable of predicting waitlist morbidity may lead to the implementation of medical interventions aimed at circumventing foreseeable complications and/or crises in patients awaiting LTX.

6. time spent on waiting list (n=3 studies)

Maluf, D., et al. (2003). "Non-resective ablation and liver transplantation in patients with cirrhosis and hepatocellular carcinoma (HCC): Safety and efficacy." American Journal of Transplantation 3(3): 312-317. https://dx.doi.org/10.1034/j.1600-6143.2003.00041.x

We investigated the efficacy of nonresective ablation techniques and the tumor-free survival of cirrhotic patients undergoing liver transplantation for hepatocellular carcinoma (HCC). In group 1, 11 HCC patients were treated with these techniques and transplanted. On the waiting list, patients were treated to complete ablation, judged by gadolinium-enhanced MRI and alpha-fetoprotein (AFP) levels. Group 1 was compared with a concurrent group of 10 liver transplant patients (group 2) with incidental HCC (stages T1 = three patients, T2 = seven patients). The group 1 patients received 36 procedures (4 alcohol ablations, 14 transhepatic artery chemo-embolizations, 15 trans-hepatic chemo-infusions, and 3 radio frequency ablations) for treatment of 13 liver masses. Tumor-node-metastasis (TNM) stage was reduced in eight patients (72.7%), unchanged in two patients and increased in one patient before transplantation. The mean waiting time for transplantation was 12.9 +/- 7.6 months. Both groups had a tumor-free survival of 100%, at 30 +/- 12 months post transplant. On pathology, 54.5% of explanted livers had residual viable HCC after tumor treatment, and 36.4% (4/11) explants had synchronous lesions. Non-resective ablation therapy is safe and effective in reducing the HCC progression in cirrhotic patients awaiting liver transplantation. The cancer-free survival rate in this treatment group is equal to that for incidental T1-T2 HCCs.

Molano, M., et al. (2020). "Impact of liver-directed therapy and non-therapy on the waiting time list of patient candidates for liver transplantation: retrospective survival analysis." Clinical & Experimental Hepatology 6(4): 304-312. https://dx.doi.org/10.5114/ceh.2020.102175

AIM OF THE STUDY: To determine whether liver-directed therapies (LDT) and no therapy affect waiting list times for liver transplant candidates from a single center.

MATERIAL AND METHODS: This retrospective study included patients > 12 years of age diagnosed with hepatocellular carcinoma between January 2014 and June 2019 and followed until the date of transplant, date of delisting, loss to follow-up, or date of death. Waiting list time and associated factors were analyzed using Kaplan-Meier and Cox proportional-hazards methods.
RESULTS: A total of 181 patients met the selection criteria. The mean age was 60 years with standard deviation (SD) of 7.8 years. Sixty-six percent underwent transplant, and 64% were classified within the Milan criteria. Men had a lower median waiting list time than women (191 days vs. 236 days, p = 0.0093). The overall median survival time or time to transplant for 50% of the population was 218 days (95% CI: 195-235). Men displayed a 3.1-fold (95% CI: 1.5-6.2) higher probability of transplantation than women (p = 0.002). Patients who received no therapy had a 5-fold higher probability of undergoing transplantation than patients under arterial LDT (HR [95% CI]: 5 [1.2, 20], p = 0.02). Patients under combined LDT displayed a 70% reduced probability of transplantation compared to patients who received arterial LDTs (p = 0.0009).
CONCLUSIONS: LDT was associated with a prolonged stay on the transplant list, likely due to the presence of an aggressive liver tumor. However, LDTs allow the patient to remain active on the liver transplant list, increasing their chances of undergoing transplantation.

Nicolini, D., et al. (2013). "Doxorubicin-eluting bead vs conventional transcatheter arterial chemoembolization for hepatocellular carcinoma before liver transplantation." World Journal of Gastroenterology 19(34): 5622-5632. https://dx.doi.org/10.3748/wjg.v19.i34.5622

AIM: To assess the possible effect of two different types of preoperative transcatheter arterial chemoembolization (TACE) on recurrence-free survival after liver transplantation (LT) in patients with hepatocellular carcinoma (HCC) and to analyze the effects of TACE on tumor histology. METHOD(S): We retrospectively analyzed the histologi-cal features of 130 HCC nodules in 63 native livers removed at transplantation. Patients who received any other type of treatment such as radiofrequency tumor ablation, percutaneous ethanol ablation or who were not treated at all were excluded. All patients in the present study were within the Milan Criteria at the last imaging findings before transplantation. Doxorubicin-eluting bead TACE (DEB-TACE) was performed in 22 patients (38 nodules), and conventional TACE (c-TACE) in 16 (25 nodules). Patients' and tumors' characteristics were retrospectively reviewed. We performed a per-nodule analysis of the explanted livers to establish the mean percentage of necrosis of any nodule treated by TACE (conventional or DEB) and a per-patient analysis to establish the percentage of necrosis in the cumulative tumor area, including 21 nodules not reached by TACE. Inflammatory and fibrotic changes in the tissue surrounding the tumor nodule were analyzed and categorized as poor/absent, moderate and enhanced reaction. Uni- and multivariate analysis of risk factors for HCC-recurrence were performed. RESULT(S): The number and diameter of the nodules, the time spent on the waiting list and the number of treatments were similar in the two groups. A trend towards higher appropriate response rates (necrosis >= 90%) was observed in the DEB-TACE group (44.7% vs 32.0%, P = 0.2834). The mean percentage of necrosis in the cumulative tumor area was 58.8% +/- 36.6% in the DEB-TACE group and 50.2% +/- 38.1% in the c-TACE group (P = 0.4856). Fibrotic and inflammatory reactions surrounding the tumor nodule were markedly more common in the DEB-TACE group (P < 0.0001, for both the parameters). The three-year recurrence-free survival was higher in DEB-TACE-treated patients than in conventionally treated patients (87.4% vs 61.5%, P = 0.0493). Other factors affecting recurrence-free survival included viable tumor beyond Milan Criteria on histopathological examination, the percentage of necrosis on CTA <= 50% and a pre-transplant serum alpha-fetoprotein level greater than 70 ng/mL. On multi-variate analysis, the lack of treatment with DEB-TACE, high levels of alpha-fetoprotein and viable tumor beyond Milan Criteria at histology examination were identified as independent predictors of tumor recurrence. CONCLUSION(S): DEB-TACE can effectively promote tumor necrosis and improves recurrence-free survival after LT in HCC.

6. Cost-effectiveness (n=3 studies)

Ahmed, A., et al. (2017). "Treatment of patients waitlisted for liver transplant with all-oral direct-acting antivirals is a cost-effective treatment strategy in the United States." Hepatology 66(1): 46-56. https://dx.doi.org/10.1002/hep.29137

All-oral direct acting antivirals (DAAs) have been shown to have high safety and efficacy in treating patients with hepatitis C virus (HCV) awaiting liver transplant (LT). However, there is limited empirical evidence comparing the health and economic outcomes associated with treating patients pre-LT versus post-LT. The objective of this study was to analyze the cost-effectiveness of pre-LT versus post-LT treatment with an all-oral DAA regimen among HCV patients with hepatocellular carcinoma (HCC) or decompensated cirrhosis (DCC). We constructed decision-analytic Markov models of the natural disease progression of HCV in HCC patients and DCC patients waitlisted for LT. The model followed hypothetical cohorts of 1,000 patients with a mean age of 50 over a 30-year time horizon from a third-party US payer perspective and estimated their health and cost outcomes based on pre-LT versus post-LT treatment with an all-oral DAA regimen. Transition probabilities and utilities were based on the literature and hepatologist consensus. Sustained virological response rates were sourced from ASTRAL-4, SOLAR-1, and SOLAR-2. Costs were sourced from RedBook, Medicare fee schedules, and published literature. In the HCC analysis, the pre-LT treatment strategy resulted in 11.48 per-patient quality-adjusted life years and $365,948 per patient lifetime costs versus 10.39 and $283,696, respectively, in the post-LT arm. In the DCC analysis, the pre-LT treatment strategy resulted in 9.27 per-patient quality-adjusted life years and $304,800 per patient lifetime costs versus 8.7 and $283,789, respectively, in the post-LT arm. As such, the pre-LT treatment strategy was found to be the most cost-effective in both populations with an incremental cost-effectiveness ratio of $74,255 (HCC) and $36,583 (DCC). Sensitivity and scenario analyses showed that results were most sensitive to the utility of patients post-LT, treatment sustained virological response rates, LT costs, and baseline Model for End-Stage Liver Disease score (DCC analysis only). Conclusion(s): The timing of initiation of antiviral treatment for HCV patients with HCC or DCC relative to LT is an important area of clinical and policy research; our results indicate that pre-LT treatment with a highly effective, all-oral DAA regimen provides the best health outcomes and is the most cost-effective strategy for the treatment of HCV patients with HCC or DCC waitlisted for LT. (Hepatology 2017;66:46-56). Copyright © 2017 by the American Association for the Study of Liver Diseases.

Axelrod, D. A., et al. (2014). "Assessing variation in the costs of care among patients awaiting liver transplantation." American Journal of Transplantation 14(1): 70-78. https://dx.doi.org/10.1111/ajt.12494

Previous economic analyses of liver transplantation have focused on the cost of the transplant and subsequent care. Accurate characterization of the pretransplant costs, indexed to severity of illness, is needed to assess the economic burden of liver disease. A novel data set linking Medicare claims with transplant registry data for 15 710 liver transplant recipients was used to determine average monthly waitlist spending (N = 249 434 waitlist months) using multivariable linear regression models to adjust for recipient characteristics including Model for End-Stage Liver Disease (MELD) score. Characteristics associated with higher spending included older age, female gender, hepatocellular carcinoma, diabetes, hypertension and increasing MELD score ($p < 0.05$ for all). Spending increased exponentially with severity of illness: expected monthly spending at a MELD score of 30 was 10 times higher than at MELD of 20 ($22 685 vs. $2030). Monthly spending within MELD strata also varied geographically. For candidates with a MELD score of 35, spending varied from $19 548 (region 10) to $36 099 (region 7). Regional variation in waitlist costs may reflect the impact of longer waiting times on greater pretransplant hospitalization rates among high MELD score patients. Reducing the number of high MELD waitlist patients through improved medical management and novel organ allocation systems could decrease total spending for end-stage liver care. Using a national cohort-linking registry and medical claims data, the authors find that the cost of end-stage liver care among patients awaiting liver transplant increases dramatically with changes in severity of illness. See editorial by Abouljoud et al on page 9. © 2013 The American Society of Transplantation and the American Society of Transplant Surgeons.

Northup, P. G., et al. (2009). "Addition of adult-to-adult living donation to liver transplant programs improves survival but at an increased cost." Liver Transplantation 15(2): 148-162. https://dx.doi.org/10.1002/lt.21671

Using outcomes data from the Adult-to-Adult Living Donor Liver Transplantation Cohort Study, we performed a cost-effectiveness analysis exploring the costs and benefits of living donor liver transplantation (LDLT). A multistage Markov decision analysis model was developed with treatment, including medical management only (strategy 1), waiting list with possible deceased donor liver transplantation (DDLT; strategy 2), and waiting list with possible LDLT or DDLT (strategy 3) over 10 years. Decompensated cirrhosis with medical management offered survival of 2.0 quality-adjusted life years (QALYs) while costing an average of $65,068, waiting list with possible DDLT offered 4.4-QALY survival and a mean cost of $151,613, and waiting list with possible DDLT or LDLT offered 4.9-QALY survival and a mean cost of $208,149. Strategy 2 had an incremental cost-effectiveness ratio (ICER) of $35,976 over strategy 1, whereas strategy 3 produced an ICER of $106,788 over strategy 2. On average, strategy 3 cost $47,693 more per QALY than strategy 1. Both DDLT and LDLT were cost-effective compared to medical management of cirrhosis over our 10-year study period. The addition of LDLT to a standard waiting list DDLT program is effective at improving recipient survival and preventing waiting list deaths but at a greater cost. © 2009 AASLD.