Which preoperative assessment modalities best identify patients who are suitable for enhanced recovery after liver transplantation? – A systematic review of the literature and expert panel recommendations

Gonzalo Crespo, MD[1]; Amelia J. Hessheimer, MD[2]; Matthew J Armstrong, MD[3]; Annalisa Berzigotti, MD[4]; Diethard Monbaliu, MD, PhD[5,6]; Michael Spiro, MBBS, BSc, FRCA, FFICM[7,8], Dimitri Aristotle Raptis, MD, MSc, PhD[8,9], Jennifer C. Lai[10], MD, MBA. *On behalf of the ERAS4OLT.org Working Group*

Affiliations

1. Hepatology and Liver Transplant Units, Hospital Clínic, University of Barcelona, IDIBAPS, CIBERehd, Spain.
2. Hepatopancreatobiliary Surgery & Transplantation, General & Digestive Surgery Service, Hospital Universitario La Paz, IdiPAZ, Madrid, Spain.
3. Liver Transplant Unit, Queen Elizabeth University Hospital Birmingham, UK
4. Department for Visceral Surgery and Medicine, Inselspital, University Hospital of Bern, University of Bern, Switzerland
5. Department of Microbiology, Immunology, and Transplantation, and Laboratory of Abdominal Transplantation, KU Leuven, Leuven, Belgium
6. Department of Abdominal Transplant Surgery and Coordination, University Hospitals Leuven, Leuven, Belgium
7. Department of Anesthesia and Intensive Care Medicine, Royal Free Hospital, London, UK.
8. Division of Surgery & Interventional Science, University College London, UK.
9. Clinical Service of HPB Surgery and Liver Transplantation, Royal Free Hospital, London, UK
10. Department of Medicine, University of California, San Francisco (UCSF), San Francisco, CA

Correspondence: Jennifer C. Lai, UCSF Box 0538, San Francisco, CA 94143; Jennifer.lai@ucsf.edu

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Abbreviations

ERAS: Enhanced recovery after liver transplantation;

KPS: Karnofsky Performance Status

LFI: Liver Frailty Index

LT: Liver transplantation

MELD: Model for end-stage liver disease

SMI: Skeletal muscle index

Data statement: There is no data statement.

ABSTRACT

Background: To implement Enhanced Recovery After Surgery (ERAS) protocols for liver transplant (LT) candidates, it is essential to identify tools that can help risk stratify patients by their risk of early adverse post-LT outcomes.

Objective: We aimed to identify pre-LT tools that assess functional capacity, frailty, and muscle mass that can best risk stratify patients by their risk of adverse post-LT outcomes.

Methods: We first conducted a systematic review following PRISMA guidelines, expert panel review and recommendations using the GRADE approach (PROSPERO ID CRD42021237434). After confirming there are no studies evaluating assessment modalities for ERAS protocols for LT recipients specifically, the approach of the review focused on pre-LT modalities that identify LT recipients at higher risk of worse early post-LT outcomes (≤90 days), considering that this is particularly pertinent when evaluating candidates for ERAS.

Results: Twenty-two studies were included in the review, encompassing three different types of pre-LT modalities: evaluation of physical function (including frailty and general physical scores like the Karnofsky Performance Status (KPS), assessment of cardiopulmonary capacity, and estimation of muscle mass and composition. The majority of studies evaluated frailty assessment and muscle mass. Most studies, except for liver frailty index (LFI), were retrospective and single-center. All assessment modalities could identify, in different grade, LT recipients with higher risk of early post-LT mortality, length of stay or postoperative complications.

Conclusions: We identified 4 pre-LT assessment tools that could be used to identify patients who are suitable for ERAS protocols: 1) KPS (quality of evidence moderate, grade of recommendation strong), 2) LFI (quality of evidence moderate, grade of recommendation strong), 3) abdominal muscle mass by CT (quality of evidence moderate, grade of recommendation strong), and 4) cardiopulmonary exercise testing (CPET) (quality of evidence moderate, grade of recommendation weak). We recommend that selection of the appropriate tool depends on the specific clinical setting and available resources to

administer the tool, and that use of a tool be incorporated into the routine pre-operative assessment when considering implementation of ERAS protocols for LT.

Introduction

Enhanced Recovery After Surgery (ERAS) protocols are effective at improving outcomes after surgery[1-4], but no standardized ERAS protocols exist in liver transplantation (LT)[5, 6]. In addition, LT has some peculiarities with respect to other surgical procedures, given that per the intrinsic features of therapy, a large proportion of patients will be in poor condition (relative to elective surgery) at the moment of surgery. Therefore, patients awaiting LT will have difficulties in achieving the different components of ERAS pathways already established in routine surgery (e.g. colorectal). Thus, successful implementation of an effective ERAS protocol in LT involves identification of two groups of patients: 1) those who are most likely to progress rapidly under multi-modal peri-operative pathways to recovery post-LT (i.e. enhancing/accelerating the recovery of the most robust), and/or 2) those who are predicted to have worse early post-LT outcomes and thus that may theoretically benefit most from ERAS procedures (i.e. preventing LT complications of the most frail/vulnerable). Given that one key underlying principle of ERAS protocols is to reduce stress reactions to the operation itself, there is a need for tools that accurately stratify the risk of high stress reactions and/or complications after surgery to better identify patients. In LT, these complications might include acute kidney injury, prolonged need for mechanical ventilatory support or respiratory complications, prolonged hospitalizations, or physical disability / functional dependence, along with early post-LT death.

There are a range of assessment tools that can identify patients who are most vulnerable to peri- and immediate post-operative complications after LT. Such tools include those that can be readily conducted at the bedside or in the outpatient clinic to assess physical function, as a surrogate for physiologic reserve[7] to those that more directly—and potentially more objectively—measure cardiopulmonary reserve[8, 9], the trade-off, however, being the need for more specialized equipment, trained personnel, and testing time; or those that assess the quality and quantity of muscle mass[10].

The objective of this review was to answer this specific question: “Among patients undergoing LT, which pre-operative assessment modalities best identify patients who are suitable for ERAS?”. Within this question, we aimed to answer the following 2 sub-questions: 1. Does cardiovascular fitness and functional capacity assessment identify patients who are suitable for ERAS for LT?, 2. Does frailty assessment identify patients who are suitable for ERAS for LT?

This work was conducted in preparation for the ILTS - ERAS4OLT.org Consensus Conference on Enhanced Recovery for Liver Transplantation, January 2022, Valencia, Spain.

Methods

Protocol and registration

This study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A systematic literature review was performed on January 10, 2021, searching the online databases Ovid MEDLINE, Embase, Scopus, Google Scholar, Clinical.Trials.gov and the Cochrane Central Register of Controlled Trials. The systematic review protocol was registered on PROSPERO (CRD42021210374).

Eligibility criteria

Retrospective or prospective studies that evaluated specific preoperative assessment modalities to identify patients suitable for ERAS after LT were included. Only studies that included adults with end-stage liver disease listed for and that underwent deceased donor transplantation were included. Studies including fewer than 10 patients and case reports were excluded. After the systematic review and considering the absence of information that could directly answer the research question, the members of the panel performed another review of the literature specifically evaluating the association between pre-LT assessment modalities and post-LT short-term outcomes. We included studies that investigated the following pre-LT assessment modalities: 1) evaluation of physical function, 2) evaluation of cardiopulmonary reserve, 3) evaluation of muscle mass or composition. Short-term outcomes were restricted to those within the first 90 days after LT and/or LT episode hospitalization, and no other exclusion criteria except for case reports and studies including fewer than 10 patients were applied in this part of the review.

Information sources

We used the following bibliographic databases to apply the search strategy and extract all available records: Ovid MEDLINE, Embase, Scopus, Google Scholar, Clinical.Trials.gov and the Cochrane Central Register of Controlled Trials.

Search

Bibliographic searches were performed by professional academic librarians. Individual search strategies are shown in the Supplementary Methods. Eight authors (GC, AJH, MJA, AB, DM, AM, AS, JCL) were involved in determining eligibility for each citation by sequential review of titles, abstracts and full texts, using the predefined criteria. Disagreements were resolved by consensus after re-assessment. Reference lists from included studies were reviewed for additional citations not identified by the original search. EndNote was used for screening and reference citation management.

Quality of studies and Recommendations Grading

The “Grading of Recommendations Assessment, Development and Evaluation” (GRADE) approach was used for grading quality of evidence and strength of recommendations[(11)]. The GRADE system was designed to provide a comprehensive and structured approach to rating the quality of evidence (QOE) for systematic reviews, and to grade the strength of recommendations for development of guidelines in health care. We applied the modified GRADE approach for QOE assessment derived from systematic reviews using estimates summarised narratively[(12)]. The QOE was rated separately for each outcome. The direction and strength of recommendation was assessed individually by all authors and disagreements resolved by consensus[(13, 14)].

Results

Study selection

Among 2247 records obtained after database search in the systematic review, 52 full-text articles were assessed for eligibility. Forty-five of these articles were excluded, thus finally 7 studies were included in the systematic review (**Figure 1**). In addition, 15 more studies were included after the review performed by the panel. In the end, 22 studies were included in the review[15-36].

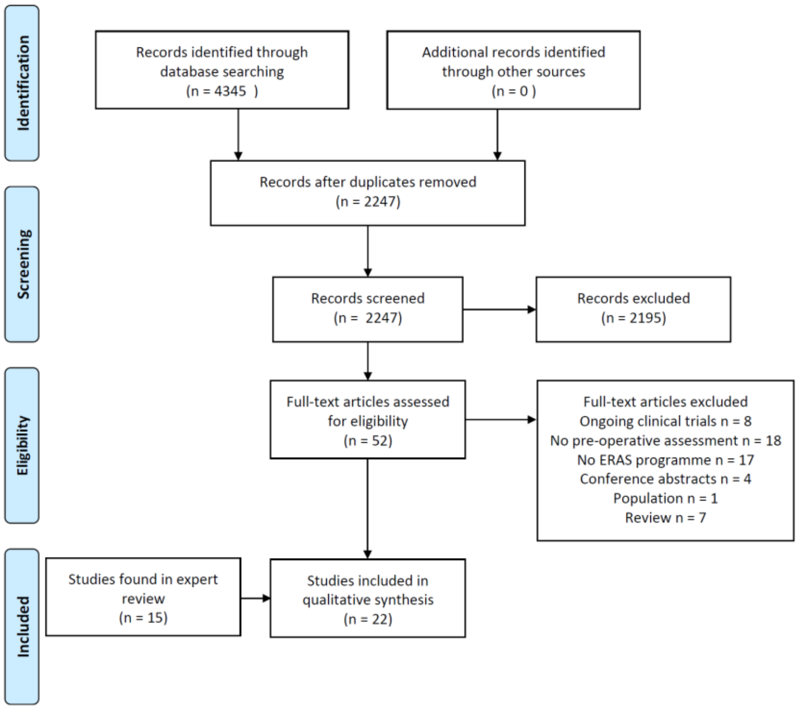

Figure 1. Flow diagram of the systematic review (exclusion criteria are not mutually-exclusive)

Study characteristics

The characteristics of the studies included are shown in **Table 1**. As stated in Methods, no study directly assessed the question of which pre-LT modality identifies patients suitable for ERAS, so in the end we evaluated 22 studies that assessed different preoperative assessment modalities and their impact on post-LT outcomes. Regarding the pre-transplant assessment modalities evaluated in the studies, 4 studies evaluated cardiopulmonary capacity by different means including 6-minute walking test and cardiopulmonary exercise

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testing (CPET)[15-18], 7 studies investigated physical function by using different frailty metrics or physiological scoring systems[19-25], and 10 utilized different quantitative morphomics modalities to estimate muscle mass and composition[27-36]. Finally, one study included quantitative morphomics for sarcopenia in addition to a frailty assessment[26]. With respect to post-transplant outcomes, most studies investigated intensive care unit (ICU) or hospitalization length of stay (LOS), eight studies evaluated (up to 90-day) post-transplant mortality, and five studies looked at respiratory complications. Lastly, we grouped together other less frequently investigated outcomes like rejection, economic costs or non-home discharge (**Table 2**).

Table 1. Study characteristics

Reference	Study type	Period of inclusion	No. of patients	Preoperative assessment modality investigated	Short-term post-transplant outcomes
(15)	Retrospective, single center	2012-2017	130 LT recipients	Functional status (ability to achieve 4 METS)	Post- LT tracheostomy
(16)	Prospective, single center	2002-2004	135 LT candidates (47 eventually underwent LT)	Peak VO2 by cardiopulmonary exercise testing (CPET)	Post-LT: length of stay and duration of oxygen use to maintain PaO2 60mmHg or SatO2 >92%
(17)	Prospective, single center, observational	N/R (3-year period)	182 LT candidates (60 eventually underwent LT)	Cardiopulmonary exercise testing (CPET)	Post-LT: 90-day mortality, length of ICU and hospital stay
(18)	Prospective cohort study, single center	2013-2015	100 LT recipients	6-minute walking test (6MWT) and 6-minute step test (6MST)	Post-LT respiratory complications (PRC, pneumonia, atelectasis, acute respiratory failure)
(19)	Retrospective, single center	1993-94	31 LT recipients	Physiological status scores (APACHE, SOFA) at WL inclusion and LT, status at WL inclusion	Post-transplant mortality Functional status
(20)	Prospective, single center, observational	2015-2017	50 LT candidates (29 eventually underwent LT)	Fried Frailty Score	Post-LT: length of stay, non-hospital discharge, 30-day mortality
(21)	Retrospective, U.S. national registry	2006-2011	24,505 LT recipients	Performance status as assessed by Karnofsky Performance Status (KPS) at the time of LT	30-day post-LT mortality
(22)	Retrospective, single center	2014-2016	241 LT recipients	Liver Frailty Index (LFI)	Acute cellular rejection after LT
(23)	Prospective, single center	2013-2016	214 LT recipients	Liver Frailty Index	Post-LT LOS Post-LT ICU days Hospitalized days within 90 days post-LT Non-home discharge

(24)	Prospective, multicenter	2012-2019	1166 LT recipients	Liver Frailty Index	Prolonged post-LT LOS ≥12 days Prolonged post-LT ICU ≥4 days Prolonged hospitalized days within 90 days post-LT ≥17 days Non-home discharge post-LT
(25)	Retrospective, England national LT registry	1997-2015	6968 LT recipients	Performance status as assessed by Eastern Cooperative Oncology Group score (ECOG)	Post-LT LOS Post-LT ICU days
(26)	Retrospective, single center	2017-2018	107 LT recipients	Gait speed, chair stands, Karnofsky Performance Status (KPS), smooth muscle index (SMI) on CT scan, cardiac double product in stress test	Post-LT: 30-day pulmonary infections, aspiration, reintubation and hospital stay
(27)	Retrospective, single center	2005-2008	338 LT recipients	Total skeletal muscle mass (CT scan at L3-L4)	Length of ICU stay, total LOS, number of days on a ventilator, patient and graft survival after LT. Disposition of the patient at discharge (home, nursing/medical or reha-bilitation facility, or death during transplant hospitalization)
(28)	Retrospective, single center	2016-2017	97 LT recipients	Sarcopenia (psoas muscle index, PMI) via CT	Postoperative complications, 1 month survival
(29)	Retrospective, single center	2011-2013	172 LT recipients	CT: total psoas area (TPA), psoas muscle index (PMI), skeletal muscle area (SMA), skeletal muscle index (SMI), psoas density (PD), skeletal muscle density (SMD)	Sepsis and Clavien-Dindo complications grade III-IV Length of stay
(30)	Retrospective, single center	2008-2014	262 LDLT recipients	Sarcopenia: psoas muscle mass index (PMI) and intramuscular adipose tissue content (IMAC) via CT	Post-LT 90 days mortality
(31)	Retrospective, single center	2008-2012	232 LT recipients	Psoas muscle mass index on CT at the level of the third lumbar vertebra (PMI-L3)	Hospital stay >20 days Post-LT in-hospital infections
(32)	Retrospective, single center	2003-2011	228 LDLT recipients	Sarcopenia, as determined by psoas muscle area at the caudal end of L3 vertebral level by CT	Post-operative sepsis
(33)	Retrospective, single center	2000-2012	248 LT recipients	Sarcopenia, as determined by L3 skeletal muscle index evaluated via CT scan	Post-transplant hospital LOS, infections during 1st 90 days, mortality
(34)	Retrospective, single center	1998-2014	368 LT recipients	Sarcopenia, as determined by L3 paraspinal muscle index	Post-transplant ICU stay
(35)	Retrospective, single center	2010-2017	225 LT recipients	Sarcopenia-Skeletal muscle index (SMI) L3 Visceral adiposity-Visceral fat area (VFA) Myosteatosis-Skeletal muscle radiation-attenuation	Post-LT 90-day major complications and mortality ICU and hospital stay Costs
(36)	Retrospective, single center	2002-2006	293 LT recipients	Sarcopenia-SMI Myosteatosis-muscle attenuation Visceral adiposity-VFA	Transplant episode length of stay Rehospitalization

Results of individual studies

The association between the different preoperative measures and the post-LT outcomes is shown in **Table 2**. No study compared the diagnostic/prognostic capacity of different techniques, and the aims of the studies were focused on predicting post-LT clinical outcomes associated with the pre-LT assessment modalities investigated.

In terms of the assessment of cardiopulmonary function, two studies evaluated relatively sophisticated methods like the anaerobic threshold or the peak VO_2 in CPET[16, 17], while one study looked at the predictive capacity of 6MWT[18] and another subjectively evaluated the capacity of patients to achieve 4 METS[15]. A low aerobic capacity as assessed by CPET or 6MWT was moderately associated with post-LT outcomes.

Regarding the association between pre-LT physical function estimates and post-LT outcomes, most data come from a multicenter, prospective project evaluating the Liver Frailty Index (LFI) in patients awaiting LT[22-24]. These data show an association between LFI as a measure of frailty and post-LT short-term outcomes, particularly length of stay and other complications such as rejection or post-LT frailty. In addition, other measures of physical function such as the Fried Frailty Index, gait speed, the ECOG scale or the Karnofsky Performance Status (KPS) also seem to be associated with different early post-LT outcomes including mortality, length of stay or pulmonary complications.

Finally, several studies have looked in different manners at muscle an muscle mass or characteristics. Most studies used imaging techniques that quantify psoas muscle mass or skeletal muscle mass at L3/L4 vertebral level normalized according to body surface (skeletal muscle index, SMI) as a measure of sarcopenia, while other studies have evaluated other muscle characteristics such as the muscle content of fat (myosteatosis). In terms of outcomes prediction, most studies show an association between the presence of sarcopenia and severe early post-LT events, particularly infections and length of stay, although the association between sarcopenia and early post-LT mortality was restricted to one study. In addition, the presence of myosteatosis, but not sarcopenia, was associated with 90-days major complications, survival and cost in one study.

Table 2. Study outcomes

Reference	Post-LT short-term mortality	Post-LT length of stay (ICU or overall)	Post-LT pulmonary complications	Other outcomes
15			Pre-LT functional capacity not associated with post-LT tracheostomy	
16		Patients with severely reduced AC (peak VO_2<60% than predicted) showed a trend towards longer hospital stay (23 vs 28 days, p=0.06)	Patients with severely reduced AC peak needed longer post-LT oxygen to maintain a PaO2 higher than 60 mm Hg or SaO2 >92% (3.3 vs. 7.2 days; p=0.035).	
17	Mean pre-LT anaerobic threshold (AT) independent predictor of post-LT 90-day mortality: 8.4 ml/min/kg in non-survivors vs 12 in survivors.	Lower pre-LT AT significantly associated with post-LT ICU stay (8.1 vs 2.8 days), but not with total hospital stay		
18			Higher 6MWT values associated with a reduced likelihood of PRCs in multivariate analysis: OR (95% CI) 0.589 (0.357–0.971) for each 50 m walked (p=0.03).	
19	No association between WL inclusion/immediate pre-LT APACHE II, APACHE III, SAPS scores or WL inclusion status coding and 30-day post-LT mortality			No association between WL inclusion/immediate pre-LT APACHE II, APACHE III, SAPS scores or WL inclusion status coding and post-LT functional status
20	No association between frailty and 30-day mortality	Frail patients (n=10) had longer hospital stay (14.5 vs 8 days), No association with post-LT ICU stay		Frail patients (n=10) had longer time to complete 1st complete physical therapy session (6 vs 4 days).
21	Increased odds of 30-day mortality in patients with KPS 50-70 (OR 1.40; 95% CI 1.10-1.78) and KPS 10-40 (OR 2.56; 95% CI 1.91-3.44).			
22				Pre-LT frail patients (46, 19%) had a higher risk of ACR in the first 3 post-LT months (15% vs 5%), significant in uni- and bi-variate analyses
23		Frail pre-LT patients (LFI ≥4.5) had longer median (IQR) post-LT LOS [9(7-14) vs. 7(5-11); p=0.004], post-LT ICU days [3(2-5) vs. 2(1-3); p=0.06],		Frail pre-LT patients had additional hospitalized days within 90 days post-LT [2 (0-9) vs. 0 (0-3); p=0.03], but similar rates of non-home discharge (9% vs. 4%; p=0.19).
24		Pre-LT frailty (LFI≥4.5) associated with increased odds of prolonged LOS (OR 2.00; 95% CI 1.47-2.73), prolonged ICU stay (OR 1.56; 95% CI 1.12-2.14).		Pre-LT frailty (LFI ≥4.5) associated with increased hospitalized days within 90 days post-LT (OR 1.72; 95% CI 1.25-2.37), non-home discharge (OR 2.50; 95% CI 1.58-3.97

25		Compared to ECOG 1, patients with ECOG 3 experienced a longer post-LT ICU (adjusted difference 1.2, 95% CI 0.4-2.0; -<0.001) and overall LOS (adjusted difference 7.21, 95% CI 4.81-9.61).		
26		No pre-LT test associated with post-LT LOS	Pre-LT gait speed and KPS associated with time to extubation; pre-LT gait speed associated with post-LT pulmonary infection and aspiration.	
27		Overall: total muscle mass predicted total and ICU LOS ($p<0.001$) Men: Total muscle mass to height squared predicts total length of stay, ITU stay and days ventilated ($p<0.05$)	Total muscle mass predicted days ventilated in the overall population and in women.	Muscle mass predicted going to medical facility/nursing home versus home ($p=0.04$). A 10% increase in muscle mass would decrease by 18% the likelihood of going to a medical facility or nursing home rather than home)
28	No association with post-LT graft of patient survival			The incidence of postoperative complications in patients with and without sarcopenia was 39.5% and 24.1% ($p=0.08$)
29		Skeletal muscle density ($p=0.04$) and psoas density ($p=0.02$) showed weak negative correlation with length of stay. No correlation of PMI, SMA or SMI with length of stay.		PD and SMD associated with Clavien-Dindo grade III/IV complications ($p=0.02$)
30	Pre-LT lower PMI and higher IMAC independent predictors of post-LT mortality. Muscle-MELD better than MELD alone and PMI alone for mortality prediction.			
31		PMI-L3 independent predictor of post-LT hospital stay > 20 days		PMI-L3 independent predictor of post-LT in-hospital infections
32				Sarcopenia was associated with a significantly increased risk of sepsis within 90 days post-LT (HR 5.31 ; 95% CI 1.53-18.4 ; $p=0.009$).
33	Pre-transplant sarcopenia not associated with increased post-transplant mortality	Pre-transplant sarcopenia associated with longer post-transplant hospital stay		Pre-transplant sarcopenia associated with more post-transplant bacterial infections
34		Pre-transplant sarcopenia associated with longer post-transplant ICU stay		
35	Pre-LT myosteatosis associated with 90-day post-LT mortality. No association between mortality and sarcopenia, visceral adiposity or sarcopenic obesity (low SMI + high VFA)	Myosteatosis associated with longer ICU and total hospital stay. No association with the rest of measurements-		Higher costs in patiens with myosteatosis. No association with the rest of measurements.

36		No association between pre-LT sarcopenia, visceral adiposity or myosteatosis and LOS or rehospitalization. Decrease in SMI while in the waiting list associated with longer post-LT LOS	.	

Quality of evidence

The summary of findings for the main outcomes, including the quality of evidence (QOE) assessment according to the GRADE approach are summarised in **Table 3**. The quality of evidence was highest for the outcome of length of stay, moderate for short-term post-LT mortality, and low for both pulmonary complications and other post-LT outcomes (e.g., post-LT functional status, time to complete physical therapy, acute cellular rejection, inpatient days within 90 days post-LT, non-home discharge, post-operative morbidity, post-LT infections).

Table 3. Summary of Findings leading to the Quality of Evidence Assessment according to the GRADE approach, categorized by pre-operative assessment metric

Summary of Findings								
Number of studies			Limitations	Inconsistency	Indirectness	Imprecision	Publication Bias	Quality of Evidence (GRADE)
RCT	Observational comparative	Observational non-comparative						
Pulmonary complications								
0	5	0	Serious	Serious	Not serious	Serious	Not serious	Low
Short-term post-LT mortality								
0	8	0	Not serious	Not serious	Not serious	Not serious	Not likely	Moderate
Length of stay (including ICU days)								
0	14	0	Not serious	Not serious	Not serious	Not serious	Not likely	Strong
Other outcomes (e.g., post-LT functional status, time to complete physical therapy, acute cellular rejection, inpatient days within 90 days post-LT, non-home discharge, post-operative morbidity, post-LT infections)								
0	12	0	Serious	Serious	Not serious	Serious	Not serious	Low

Recommendations

Our objective was to identify pre-operative assessment modalities that best identify LT recipients who are suitable for ERAS. While there were no studies in LT recipients that specifically evaluated outcomes after ERAS, we performed a thorough review of the literature to identify pre-operative assessment modalities that could stratify LT recipients at risk for early adverse outcomes after LT. In making our recommendations, our underlying assumption was that patients who were most vulnerable to adverse short-term post-LT outcomes would likely benefit most from a multi-dimensional approach to reducing physiologic stress in the setting of LT, as ERAS protocols are intended.

We recommend using one of four pre-operative assessment modalities (**Table 4**), as we felt these tools had the strongest evidence to support their ability to risk stratify LT recipients by their risk of adverse short-term post-LT oucomes. We have selected 4 tools (rather than a single tool) to allow for application of these pre-assessment modalities across a range of clinical scenarios (e.g., ambulatory versus hospitalized/non-critically ill versus hospitalized/critically ill and resource settings.

- Karnofsky Performance Status, a metric of performance status. *[Quality of evidence: moderate* | *Grade of recommendation: strong]*
- Liver Frailty Index, a metric of physical frailty. *[Quality of evidence: moderate* | *Grade of recommendation: strong]*
- Abdominal skeletal muscle mass by CT (psoas muscle mass/index or preferably skeletal muscle mass/index). *[Quality of evidence: moderate* | *Grade of recommendation: strong]*
- Cardiopulmonary exercise testing. *[Quality of evidence: moderate* | *Grade of recommendation: weak]*

Table 4a. Evidence for recommendation framework according to the GRADE approach

Question: Among patients undergoing liver transplantation, which pre-operative assessment modalities best identify patients who are suitable for ERAS for liver transplantation?

Recommendation: We recommend consideration of one of four pre-operative assessment modalities: Karnofsky Performance Status, Liver Frailty Index, Cardiopulmonary exercise testing, and abdominal muscle mass by CT scan.

Decision domain	**Judgment**		**Reason for Judgment**	***Subdomains influencing Judgment***
	Yes	No		
Balance between desirable and undesirable outcomes (estimated effects), with consideration of values and preferences (estimated typical)	✓		Given the best estimate of typical values and preferences, we are confident that the benefits outweigh the harms and burden.	The risk of administering these metrics is small relative to the potential benefits of avoiding early adverse post-LT outcomes. The weight of evidence supports the assessment of these metrics in the ambulatory setting, although two of these metrics (KPS and abdominal muscle mass) may technically be assessed in critically-ill patients.
Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)	✓		Evidence to support these pre-assessment modalities is moderate.	Limitations of the evidence is that no study directly evaluated the use of pre-operative assessment modalities to identify patients best suited for ERAS protocols in the LT setting. That being said, if pre-operative assessment is intended to risk stratify patients by their vulnerability to early adverse post-LT outcomes, we believe that there is moderately sufficient evidence to support the use of these 4 metrics.
Confidence in Values and Preference, and their Variability	✓		Populations under study are similar to the populations that will be considered for ERAS4OLT, so there is confidence in values and preference and variability.	
Resource implications	✓		Yes	Use of Liver Frailty Index, Karnofsky Performance Status are highly feasible and require few resources. Assessment of abdominal muscle mass requires CT scan and CPET requires specialized equipment which may pose moderate issues with resource limitations, but KPS or LFI offer alternatives.
Overall Quality of Evidence: ***Moderate***				
Recommendation: ***Strong***				

Table 4b. Evidence for recommendation framework according to the GRADE approach

Question: Does cardiovascular fitness and functional capacity assessment identify patients who are suitable for ERAS for liver transplantation? **Recommendation**: CPET may help risk stratify ambulatory patients by their risk of early adverse post-LT outcomes.				
Decision domain	**Judgment**		**Reason for Judgment**	***Subdomains influencing Judgment***
	Yes	No		
Balance between desirable and undesirable outcomes (estimated effects), with consideration of values and preferences (estimated typical)	✓		Given the best estimate of typical values and preferences, we are confident that the benefits outweigh the harms and burden.	The risk of administering these metrics is small relative to the potential benefits of avoiding early adverse post-LT outcomes.
Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)	✓		Moderate confidence in the magnitude of estimates in the ambulatory LT setting.	Limitations include the fact that CPET can only be administered in the ambulatory setting among patients who are healthy enough to complete the full testing.
Confidence in Values and Preference, and their Variability		✓	Low confidence in values, preference. Potentially high variability.	
Resource implications		✓	Requires specialized equipment and personnel.	Feasibility: Not likely feasible to implement across many centers given need for specialized equipment and personnel. Not generalizable to acutely/critically ill patients or perhaps even those with decompensated disease in the outpatient setting (due to inability to complete the testing).
Overall Quality of Evidence: ***moderate***				
Recommendation: ***weak***				

Discussion

Our review identified a number of tools that have been studied in LT patients that can be broadly categorized into metrics of: 1) performance/functional status, 2) frailty, 3) cardiopulmonary fitness, and 4) sarcopenia. In general, these metrics were strongly associated with early adverse post-LT outcomes, including early death, longer hospital and ICU LOS, as highlighted in **Tables 1** and **2**. This makes conceptual sense, as each of these metrics, in one way or another, capture physiologic reserve in an individual that would increase vulnerability to a major physiologic stressor such as LT surgery.

Table 4c. Evidence for recommendation framework according to the GRADE approach

Question: Does frailty assessment identify patients who are suitable for ERAS for liver transplantation?

Recommendation: The Liver Frailty Index may help risk stratify patients by their risk of early adverse post-LT outcomes.

Decision domain	Judgment		Reason for Judgment	*Subdomains influencing Judgment*
	Yes	No		
Balance between desirable and undesirable outcomes (estimated effects), with consideration of values and preferences (estimated typical)	✓		Given the best estimate of typical values and preferences, we are confident that the benefits outweigh the harms and burden.	The risk of administering these metrics is small relative to the potential benefits of avoiding early adverse post-LT outcomes.
Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)	✓		Evidence to support these pre-assessment modalities is strong.	Multi-center data, large number of patients.
Confidence in Values and Preference, and their Variability	✓		HIgh confidence in values, preference, and their variability.	
Resource implications	✓		Low cost, highly feasible to administer	Administration of Liver Frailty Index is highly feasible and requires few resources.

Overall Quality of Evidence: **Moderate**

Recommendation: **Strong**

Our recommendation of 4 tools, rather than a single one, was intentional. We aimed to provide a "suite" of tools to identify patients who would be suitable for ERAS protocols that could be tailored to the clinical scenario (e.g., ambulatory versus inpatient) and across a variety of resource settings. For example, CPET may be the most accurate marker of cardiopulmonary fitness, but it has limited generalizability given its requirement for specialized equipment/personnel and the inability to administer CPET in acutely-ill patients. It is possible that simpler methods such as the 6MWT could capture similar information about functional capacity as CPET, but at the current time, there lack adequate data in the LT setting to support the 6MWT to risk stratify LT patients for ERAS protocols. On the other end of the spectrum of cost/ease of use, KPS can be administered (or assessed by the clinician) across all settings at no cost, but is limited by a greater degree of subjectivity than a performance-based test such as CPET or LFI. In the middle of the spectrum are LFI, a performance-based metric that has been studied predominantly in ambulatory patients, and abdominal muscle mass by CT, which can be administered in hospitalized patients, which can offer valuable information regarding physiologic reserve and therefore be well-suited to risk stratify patients for ERAS4OLT protocols.

Ideally, ERAS protocols should be applied in all LT recipients. However, given resource limitations, implementation of multi-disciplinary, multi-modal ERAS protocols may not be feasible across all LT centers, despite potentially improved outcomes and potential cost savings. For this reason, we have recommended the pre-operative assessment modalities that can be used across a range of settings depending upon the clinical status of the patient (ambulatory versus hospitalized) and depending upon resources available. Key areas for future research include whether *longitudinal changes* in these assessment modalities prior to LT or a combination of these tests—i.e., Liver Frailty Index *plus* abdominal muscle mass—better identify patients who are most suitable for ERAS than a single baseline assessment using a single tool.

Limitations

The major limitation to our review was that no study specifically evaluated pre-operative assessment modalities for use in ERAS protocols in LT recipients. Even as we adapted our search to evaluate pre-operative assessment tools that identified LT recipients vulnerable to adverse post-LT outcomes, there were no RCTs, so the quality of evidence was moderate at best.

Conclusion

We recommend 4 pre-operative assessment modalities that can identify patients who are most suitable for ERAS4OLT protocols. These pre-operative assessment modalities are:

- Karnofsky Performance Status (Quality of Evidence; Moderate | Grade of Recommendation: Strong)
- Liver Frailty Index (Quality of Evidence; Moderate | Grade of Recommendation; Strong)

- Abdominal muscle mass by CT (Quality of Evidence; Moderate | Grade of Recommendation; Strong)
- Cardiopulmonary Exercise Test (Quality of Evidence; Moderate | Grade of Recommendation; Weak)

Group Authorship / Acknowledgments

Claus Niemann, San Francisco, CA, USA, Joerg-Matthias Pollok, London, UK, Marina Berenguer, Valencia, Spain, Pascale Tinguely, London, UK,.

Authorship

All authors qualify for authorship as per the International Committee of Medical Journal Editors (ICMJE) guidelines.

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