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# **A METHODOLOGICAL REVIEW OF CLINICAL OUTCOMES REPORTED IN LIVER TRANSPLANTATION TRIALS**

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## **REVIEW / ORIGINAL STUDY**

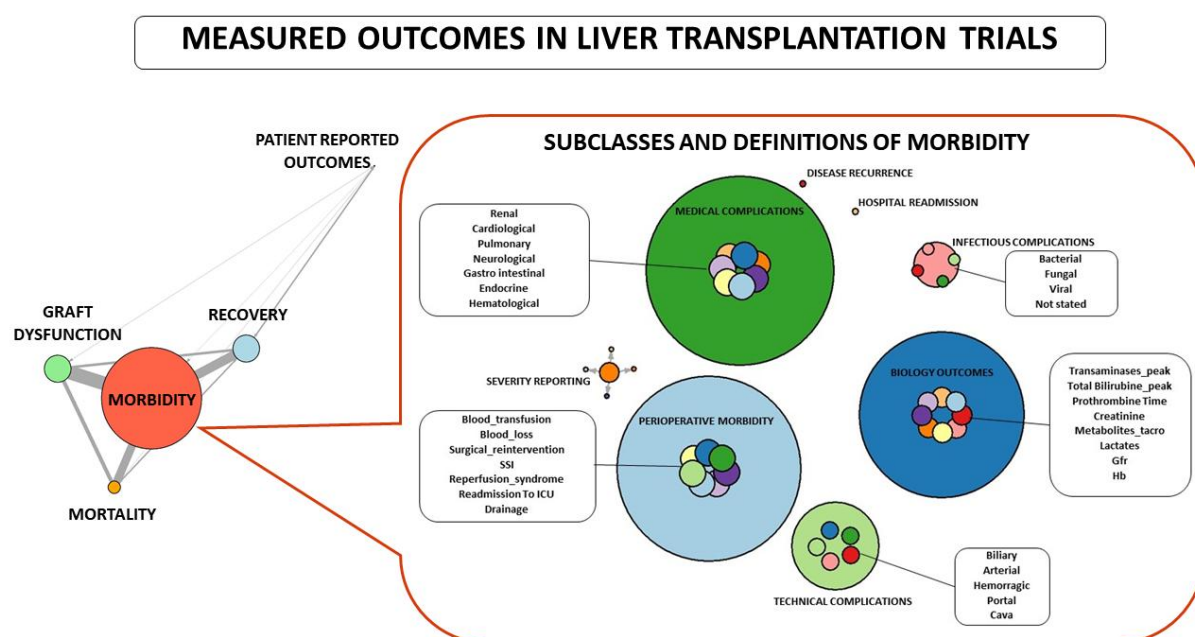
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## GRAPHICAL ABSTRACT



## **ABSTRACT**

### **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.

**PROSPERO:**CRD42018108146

## INTRODUCTION

Liver Transplantation (LT) is a life-saving treatment for end-stage liver disease (ESLD) <sup>1</sup>. Five decades after its introduction, more than 90 000 procedures have been performed in Europe <sup>2</sup>, with 1-year survival evolving from 64%-66% in 1985 to 90%-92% in 2015 both in Europe <sup>2-5</sup> and the US <sup>6,7</sup>. Despite improved survival, LT remains associated with serious morbidity, ranging from 2 to 40% across series <sup>8-14</sup>, related to co-morbidities, surgical challenges <sup>11,12</sup>, infectious complications and postoperative immunosuppression <sup>9,11-13</sup>. This morbidity is responsible for a mortality rate of 6-10% within the first month<sup>2</sup>, with extra-hepatic organ failures being the major causes of morbidity and graft loss.

The evaluation of appropriate clinical outcome measures, including complications and other patient-centred outcomes, rather than surrogates is crucial in comparative effectiveness research to compare results across studies and combine them in meta-analyses.

Unfortunately, the lack of standardisation of outcomes evaluated, as well as selective reporting of significant outcomes is very common, making data synthesis challenging <sup>15</sup>.

A possible solution to address these issues is the development and application of core outcome sets (COS), defined as an agreed minimum set of outcomes to be measured and reported in all studies of a specific condition <sup>15</sup>. COS development maximizes the usefulness of individual trials, by reducing heterogeneity in outcomes evaluated and allowing their combination in meta-analyses, thus increasing global research efficiency and reducing research waste <sup>15-17</sup>. The need for COS development was recently acknowledged in the field of complex surgery with COS being developed for colorectal <sup>18</sup>, bariatric <sup>19</sup>, oesophageal <sup>20</sup> and cardiac surgery <sup>21</sup>, as well as kidney transplantation <sup>22</sup>. To the best of our knowledge, no COS has yet been developed for liver transplantation.

The aim of this methodological review is to evaluate and classify short term outcomes (up to 1 year) reported in randomized clinical trials (RCTs) performed for adult LT, in order to inform COS development and provide recommendations for future study design.

## **METHODS**

We performed a methodological review of recently published and ongoing randomised controlled trials in liver transplantation. This review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis protocols (PRISMA-P) Statement<sup>23</sup>. The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on 12<sup>th</sup> September 2018 (CRD42018108146).

### **Search strategy**

We searched MEDLINE via PubMed for published trials via a multifaceted search equation using a combination of specific key-words and free-text words for liver transplantation, as well as the Cochrane filter to identify RCTs. Manual cross-referencing of the included studies was performed to identify relevant citations.

To focus on current practice and to ensure stability of survival rate, the search was limited to studies published during the last 5 years.

The search was conducted on 30/06/2018 and updated on 30/08/2018.

On 06/07/2018, we also searched for ongoing trials registered during the last five years at ClinicalTrials.gov with the following search terms: “liver transplantation” as condition, “interventional” as study type, “recruiting” as recruitment status, “phase 3”, “phase 4” and “non applicable” as phase.

### **Eligibility criteria**

Studies were selected using the following criteria:

#### *Participants*

We included studies on human adult patients (18 years or older) undergoing LT. Articles focussing on retransplantation or combined LT (with kidney, heart, lung, pancreas or intestine) were not considered because of different patterns of morbidity and mortality. Studies focusing on paediatric populations and experimental studies on cells, tissue or including animals were not considered for inclusion. Studies focusing on autotransplantation in cases of extreme liver surgery were also not considered for inclusion.

#### *Interventions*

No restriction on the type of intervention tested was considered, provided that the whole set of the target population included patients undergoing LT. The intervention could be

performed before, during or immediately after LT (during the in-hospital period). Any intervention without a clear clinical relation to liver transplantation, not patient-centred or related to a non-relevant therapeutic outcome was not considered (e.g. bio-equivalence or pharmacokinetic studies, pedagogic intervention on a simulated LT, or performance characteristics of two different monitoring strategies). Similarly, studies considering LT as an outcome measure was not considered (e.g. an intervention tested to avoid LT, using as an endpoint the time-to-LT or the number of LT-free patients).

### *Study design*

We included only randomised clinical trials. Abstracts, letters to the editor and conference posters were not considered for inclusion because of the incomplete description of study methodology and results.

### *Setting*

No restrictions on study location or settings were applied.

### *Follow-up*

We considered studies reporting follow-up up to 1 year after LT for inclusion. Studies focusing on longer term outcomes were considered for inclusion only if data on short term outcomes up to 1 year were reported. Post-hoc analyses or long-term follow-up of previously published RCTs were not considered.

### *Language*

We considered articles reported in English, French or Italian. Studies in other languages were included only if the translation could be accurately obtained through Google translate.

## **Selection process**

The results of the literature search were uploaded to Rayyan, a web-based reference manager<sup>24</sup>, to facilitate the selection process.

The titles and abstracts identified by the search were reviewed by one author (RB) to select reports for full text evaluation based on eligibility criteria. In case of duplicate or overlapping reports, the article including the largest number of patients and reporting the primary outcome was included. Doubtful inclusions were resolved through discussion with a senior reviewer (AD).

## **Data extraction**

A standardized data collection form, specifically designed with Google forms for the purpose of this study, was used for data extraction from published articles or for ongoing trials at ClinicalTrials.gov.

The following data were collected for each selected study:

- General characteristics: Study design, number of participating centers, total number of patients included for published trials, or expected sample size for ongoing trials at ClinicalTrials.gov, as well as the duration of the study. We assessed whether the authors clearly reported the presence of a funding source, as well as its private or public nature.
- Liver transplantation characteristics: Indication for LT and the type of graft used (whole or split graft, deceased or living donor).
- Intervention: Timing of intervention (preoperative, peri-operative or early postoperative-up to discharge), type of intervention (pharmacologic, non-pharmacologic or both) and whether the intervention belonged to one of the following categories
  - Anaesthesiology
  - Graft conditioning
  - Surgical technique
  - Intensive care
  - Immunosuppressive regimen
  - Postoperative recovery including rehabilitation
  - Other
- Methodological characteristics: The risk of bias for each included study, using the Risk of Bias tool developed by Cochrane <sup>25</sup>.
- Outcomes assessed: All primary and secondary outcomes reported in the methods section, or in the section 'Outcomes measures' at ClinicalTrials.gov. Outcomes were extracted with the related definition, the time point and the severity score when provided. For published articles, we assessed the consistency between outcomes reported in the methods and result section.

### **Classification of outcomes**

Outcomes were classified in the following categories <sup>2,26–28</sup>



- **Mortality**
  - *Short term mortality* defined as mortality within 90 days after LT
  - *Intermediate mortality* defined as mortality occurring up-to 1 year after LT.
- **Liver graft dysfunction**
  - *Graft loss*, defined as any medical or surgical condition requiring re-transplantation, such as primary graft dysfunction or non-function<sup>29</sup> and death.
  - *Early allograft dysfunction*<sup>29,30</sup>, defined as the presence of one or more of the following: (1) bilirubin>10 mg/dL of postoperative day 7; (2) INR >1.6 on postoperative day 7; (3) aminotransferase level (alanine aminotransferase [ALT] or aspartate aminotransferase [AST]) >2000 IU/mL within the first 7 postoperative days.
  - *Acute or chronic cellular rejection*, defined as the deterioration of allograft function with biopsy showing infiltration by T cells and other leukocytes, with evidence of ductular injury and endothelitis<sup>31</sup>
  - *Small for size syndrome*, defined as graft-recipient weight ratio (GRWRs) <0.8 %<sup>32</sup>
- **Morbidity.** All complications occurring up-to 1 year after LT reported in the included articles were examined:
  - *Perioperative morbidity* (e.g., blood loss, blood transfusion, reperfusion syndrome after declamping, readmission in ICU, surgical re-intervention, radiological or surgical drainage requirement, surgical site infection, primary closure or negative wound pressure etc).
  - *Biological morbidity* (e.g. end-procedure blood lactates, transaminase peak, bilirubin or prothrombin time at any time point, decreased glomerular filtration rate etc.)
  - *Technical complications*
    - Biliary complications (e.g. leakage, stenosis)
    - Vascular complications (e.g. haemorrhage, thrombosis or stenosis)
  - *Medical complications*
    - Neurologic (e.g., peripheral neuropathy, psychosis, convulsions, tremors, neurotoxicity, hemiplegia, hallucination)

- Pulmonary (e.g., endotracheal re-intubation, pneumonia, pleural effusion, pneumothorax, pulmonary embolism)
- Cardiovascular (e.g., cardiac arrhythmia, coronary artery disease, myocardial infarction)
- Gastrointestinal (e.g., diarrhoea, constipation, abdominal discomfort)
- Renal (e.g., acute kidney injury, renal failure, renal replacement therapy and dialysis)
- Infectious (e.g., Sepsis, septic shock)
- *Primary disease recurrence*
- *Hospital readmission*
- ***Recovery outcomes***
  - early (e.g. duration of LT and cold ischaemia time, time span from LT to extubation) <sup>33,34</sup>
  - intermediate (e.g. length of stay in ICU, length of stay in hospital, time to functional recovery, etc. ) <sup>33,34</sup>
- ***Patient reported outcomes*** (PRO) such as pain, disability, fatigue and quality of life.

## **Statistical analysis**

The statistical analysis was mainly descriptive. For continuous variables, we computed medians (quartile 1 [Q1] quartile 3 [Q3]), and for qualitative variables, frequencies (percentages). We described published and ongoing trials separately. Statistical analysis involved the use of R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria (<http://www.R-project.org/>).

## RESULTS

Among the 2685 references identified by the PubMed search, 55 were included. From the search on Clinicaltrials.gov, we identified 67 references and included 24 ongoing trials. The selection process is detailed in Figure 1, and the complete list of trials can be found in Supplementary\_material\_study\_list.

### Characteristics of the included trials

Among the included trials, 40 (73%) published and 15 (62%) ongoing were from single centres. Europe was the most frequent location of the trial's corresponding author (33% and 42% for published and ongoing trials, respectively). The trials included a median of 78 (40-120) patients for published trials and planned to include 117 (55-218) for ongoing trials. The experimental intervention was non-pharmacological in 20 published (36%) and 18 ongoing (75%) trials, and pharmacological in 35 published (64%) and in 6 ongoing trials (25%). The intervention was administered during the peri-operative period in 36 published (65%) and in 17 ongoing trials (71%).

Details on the type of graft used were provided by 27 published (49%) and 10 ongoing (42%) trials: cadaveric 13 published (24%) and 7 ongoing (29%) trials and LDLT in 19 published (35%) and 4 ongoing (17%) trials. More details are shown in Table 1.

The risk of bias for the 55 published trials is reported in Supplementary\_Table 1. Briefly, the risk of bias for random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessment and incomplete outcome data was rated as high in 22 (40%), 24 (44%), 29 (53%), 22 (40%) and 14 (25%) of trials, respectively.

### Outcomes evaluated

#### *Primary outcomes*

All the included trials reported primary outcomes in the methods section. Among published trials, 43 (76%) defined a single primary outcome, 4 (7%) trials two primary outcomes, 7 (13%) trials three primary outcomes and 2 (4%) trials four primary outcomes. Similarly, 19 (79%) ongoing trials defined a single primary outcome, and 5 (21%) two primary outcomes (Table 2). Among the 55 published trials, 51 reported the results for the primary outcomes described in the methods (93%).

### ***All outcomes***

The median number of all outcomes defined in the methods section was 5.0 (3.0-7.0) in published and 4.0 (3.0-8.0) in ongoing trials (Table 3).

For published trials, among the 397 outcomes reported in the method section, 283 (71%) had results reported.

The network relationship of outcomes used in the same trial is represented in the figure 2, as well as in the Supplementary\_Table\_2 (classification and timing of measured outcomes).

### ***Mortality***

Mortality was evaluated in 38 published (69%) and 13 ongoing (54%) trials: as primary outcome in one published (2%) and one ongoing (2%) trial; as secondary outcome in 37 published (67%) and 12 ongoing (50%) trials.

More than twelve different definitions were used, with the most frequent being “in hospital” for 9/36 (25%) published trials and both “3 months” or “one year” for 3/13 (23%) ongoing trials. The assessment of the time point for the outcome “mortality” was reported in 36 (65%) of published and 13 (93%) of ongoing trials.

### ***Morbidity***

Morbidity was assessed in 52 published (95%) and 20 ongoing trials (83%): as primary outcome in 37 published (67%) and 13 ongoing (54%) trials, and as secondary outcome in 18 published (18%) and 7 ongoing (29%) trials.

A severity score was assessed in 15/55 (27%) and 3/24 (12%) of published and ongoing trials, respectively. When looking at the most frequently reported morbidity classes, “peri-operative morbidity” was used as outcome in 35/52 (67%) published trials and “medical complications” in 11/20 (55%) ongoing trials. More details on morbidity outcomes and classification are reported in Table 4 as well as in the figure 3, this latter expressing the complex heterogeneity of morbidity classes and definitions.

### ***Graft dysfunction***

Graft dysfunction was assessed in 36 (65%) published and 11 (46%) ongoing trials: as primary outcome in 9 published (16%) and 6 ongoing (25%) trials, and as secondary outcome in 27 published (49%) and 5 ongoing (21%) trials.

Altogether, among the 72 (91%) trials assessing the graft dysfunction as an outcome, ten different definitions were reported. The most frequent used was “Acute cellular humoral

rejection” for 12/36 (33%) published trials and both “Early allograft dysfunction” or “Graft loss” for 4/24 (36%) of ongoing trials. Similarly, nine different time-point were reported for graft dysfunction assessment, with “7 days” being the most frequent by both 7/36-assessed (19%) published and 5/11 (45%) ongoing trials.

More details in Supplementary Table 2.

#### *Recovery outcomes*

Recovery outcomes were assessed in 31 (56%) published and 12 (50%) ongoing trials: as primary outcome in 7 published (13%) and 4 ongoing (17%) trials, and as secondary outcome in 24 published (44%) and 8 ongoing (33%) trials.

More than nine different “recovery outcomes” were reported, with the most frequent being “Length of stay in ICU” in 25 (81%) published trials and “Length of stay in Hospital” in 8 (67%) ongoing trials.

#### *Patient reported outcomes*

Patient reported outcomes were assessed in 7 (13%) published and 4 (17%) ongoing trials, but never as primary outcome. When looking at the different PRO classes, “symptoms” were considered in 6 (11%) published trials and “Quality of Life” in 3 (12%) ongoing trials.

#### *Intervention timing*

A subgroup analysis of number and type of outcomes was realized merging the intervention variables “preoperative and perioperative” versus early postoperative.

Overall, 767 pre and perioperative versus 260 outcomes were measured within the included trials. Recovery or graft dysfunction outcomes were reported in 38 (14.6%) and 34 (13.1%) of trials focusing on postoperative interventions, compared to 38 (5.0%) and 37 (4.8%) in trials on pre and perioperative interventions, respectively. (Supplementary Table 3)

## DISCUSSION

This methodological review of recently published and ongoing randomised clinical trials in liver transplantation found an important lack of standardisation of reported outcomes. Although morbidity and mortality were frequently considered, wide variation in the definitions used to describe the same outcome (e.g. 10 definitions for graft dysfunction, 9 for recovery outcomes), as well as heterogeneity in the timeframe of outcome assessment were evident (e.g. 12 different mortality time-points). We also found that patient-reported outcomes were very seldom reported and never as primary outcomes. Finally, we showed that some outcomes specified in the methods section were not reported in the results, suggesting a risk of selective outcome reporting.

Our results are consistent with previous methodological reviews conducted on other fields of surgery showing a lack of standardisation of outcomes and an overall poor quality of research. In a systematic review of 90 studies reporting the quality measurement of surgical wound infection, 41 definitions to define wound infection were identified<sup>35</sup>. More recently, a systematic review on 122 articles about outcomes after esophagectomy, reported ten different mortality measures across 115 studies, while definitions for at least one complication were given in only 27.6% of the studies<sup>36</sup>. This heterogeneity in outcome measures has important consequences as it prevents comparisons of results across studies and data synthesis in meta-analyses. This could be particularly true for mortality or recovery outcomes, for which the timing measure is more relevant than definition in itself.

Another problem is related to selective outcome reporting. We cannot exclude a risk of selective outcome reporting, as 7% of published trials did not report the results for the primary outcome and 29% of all outcomes (both primary and secondary) were not reported in the result section. This may also have a major impact on interpretation of results. Meta-research on 283 reviews regarding the impact of outcome reporting, found that among 42 meta-analyses with a statistically significant result, eight (19%) became non-significant after adjustment for outcome reporting bias and 11 (26%) would have overestimated the treatment effect by 20% or more<sup>37</sup>.

An increasingly attractive solution to improve outcome reporting is to develop and popularise the use of a “core outcome set” (COS). A core outcome set is an agreed minimum set of endpoints that have to be measured and reported in all studies of a given disease<sup>38</sup>. This allows cross-study comparisons, reduces heterogeneity and increases the ability to

perform data synthesis for the core set of outcomes. Investigators may of course add any outcome of particular interest to their study in addition to outcomes included in the COS <sup>36</sup>, and should be considered free to choose the most relevant outcome of interest (or time point), if none of the outcomes included in a given COS is adapted to the specific purpose of a trial. The COMET (Core Outcome Measures in Effectiveness Trials) initiative aims to collate and stimulate the development and application of COS. The initiative developed an online tool for presenting information on methodological reviews conducted and COS elaborated <sup>15</sup> with filters (general settings, health area, target population, methods, stakeholders involved, study type and publication year) to improve the efficiency of the search. A recent systematic review reported the development of 227 COS in the last three decades, with a wide range of disease categories including cancer, gastroenterology, rheumatology, anaesthesia but also intensive care and rehabilitation <sup>15</sup>.

There is no established COS for liver transplantation and this methodological review aims to be the base on which the COS developing process is built. Patient point of view is increasingly considered in COS development. In this study we found that only five trials (6.3%) had considered patient-reported outcomes, which is very low. Nonetheless, among them one was published and four are ongoing, suggesting a slight increase of researchers' awareness of this class of outcomes over time. Patient-important, patient-centred or patient-reported outcomes are increasingly considered as primary outcomes in many health domains, including cardiovascular disease, cancer, gastroenterology and surgery <sup>39</sup>. The measure of outcomes meaningful to patients is a cornerstone of comparative effectiveness research. This gives clinicians the ability to make better decisions by providing evidence on the effectiveness, benefits, and disadvantages of different treatments <sup>39</sup>.

We plan to organize an international working-group of experts, to develop a core outcome set, consisting of all relevant LT stakeholders (e.g. surgeons, hepatologists, anaesthetists, intensivists, and patients) to ensure that the COS is useful to evaluate this particular field of surgery and inform practice, as well as account for patient point of view. We will propose that a core outcome set for LT include at least one measure of each category reported, namely morbidity, graft dysfunction, mortality, recovery and patient-reported outcomes. Of course these measures may not be appropriated for all issues that researches wish to explore: for this reason, COS are intended to be complementary, and not a replacement of any of the outcome measure decided by investigators.

Besides the outcome reporting, this study offers a detailed picture on the recent panorama of trials in LT: the large majority are single center, with some national and even less international multicentre trials. This probably reflects logistical and methodological barriers of multicentre studies, not only in outcome reporting but in standardisation of preoperative and procedural variables across centers.

This review has several limitations. Firstly, the search was limited to studies published after 2014 and it is possible that trends in defining outcomes may have changed over the preceding years. Secondly, we decided to focus only on randomised clinical trials which are supposed to provide the highest level of evidence. The largest volume of published literature in the LT domain relies on cohorts or clinical series. It is possible that, had these other studies been included, the rate of each outcome class would have changed.

## **CONCLUSION**

This study highlights the lack of standardisation in outcomes reported in liver transplantation trials, as well as the low consideration of patient-reported outcomes. This has important consequences as it may prevent comparison across studies and data synthesis in meta-analyses. The need to develop a core set of outcomes for liver transplantation is urgent and should include patient-reported outcomes. Researchers should be compelled to measure and report the core outcome set as a minimum for all studies in this condition.



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## FIGURE TITLE AND LEGENDS

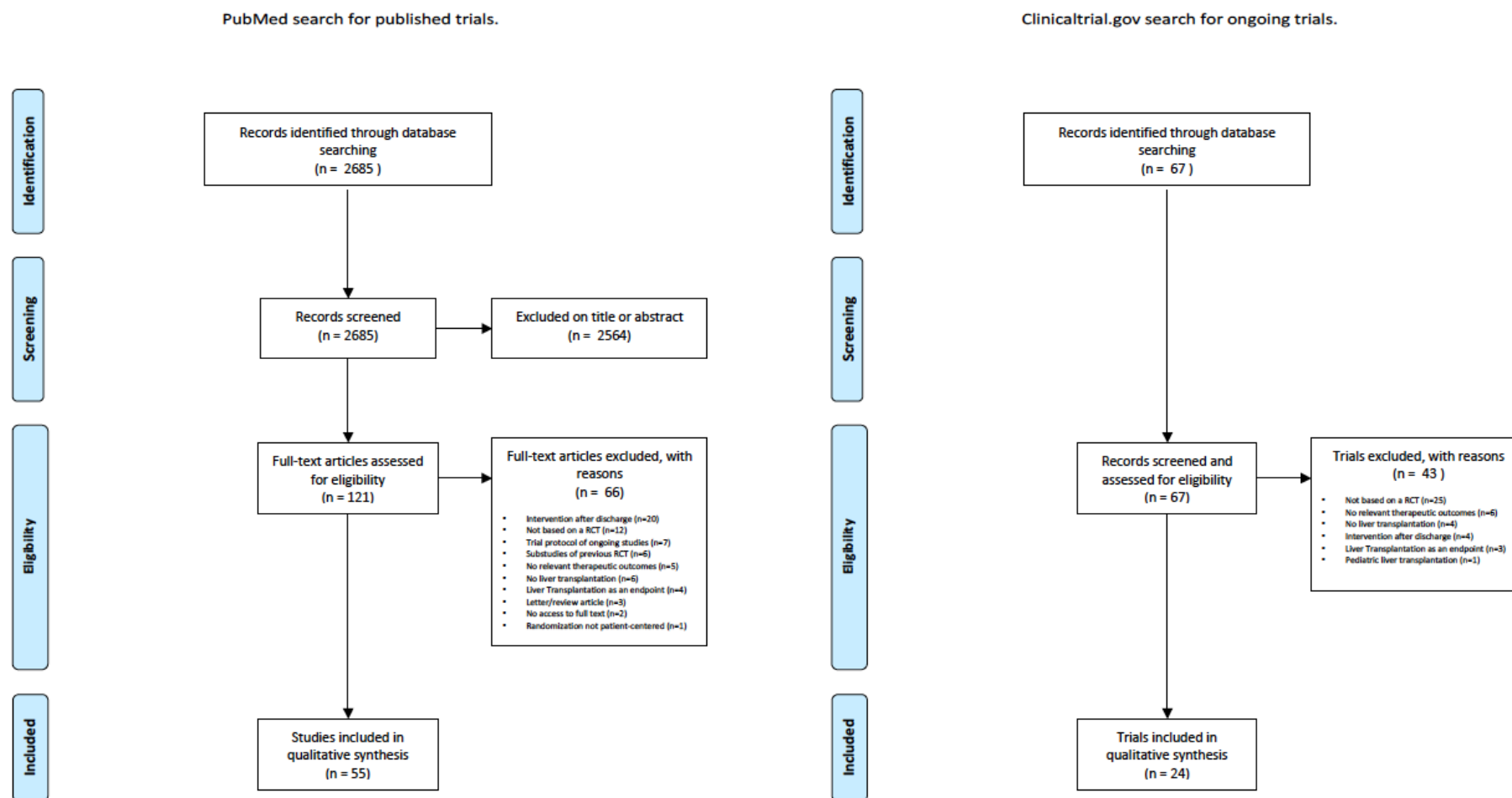
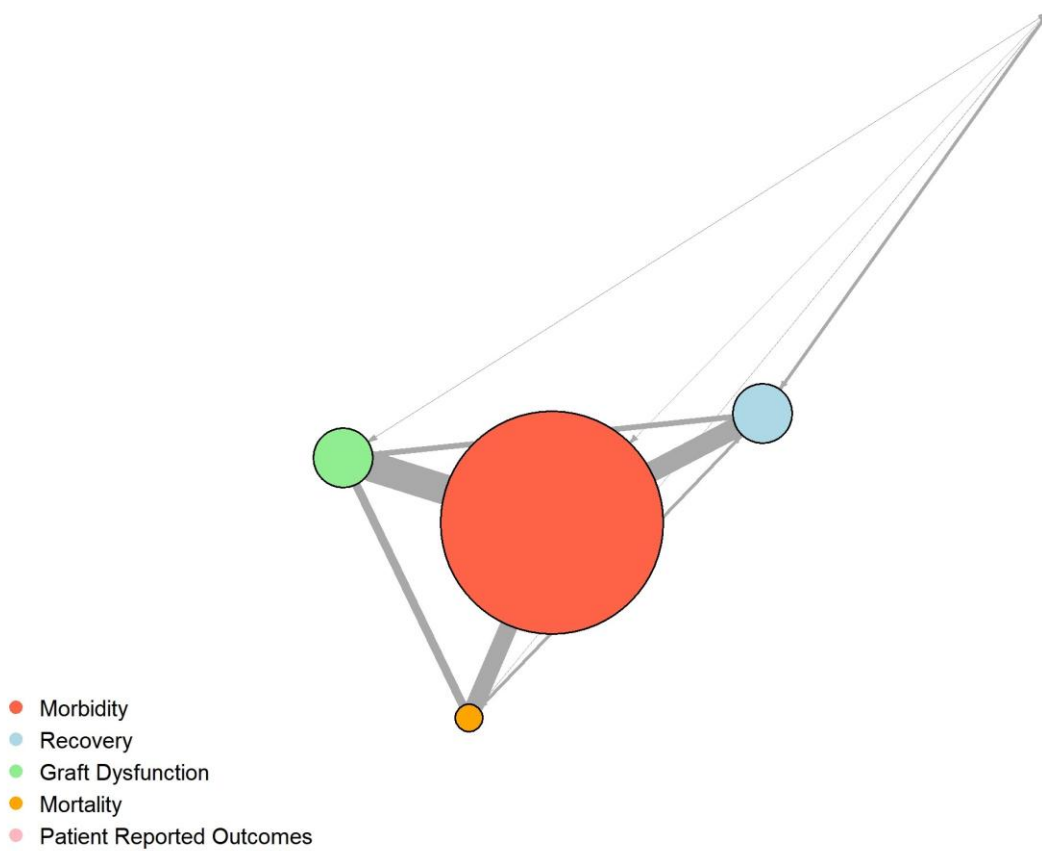


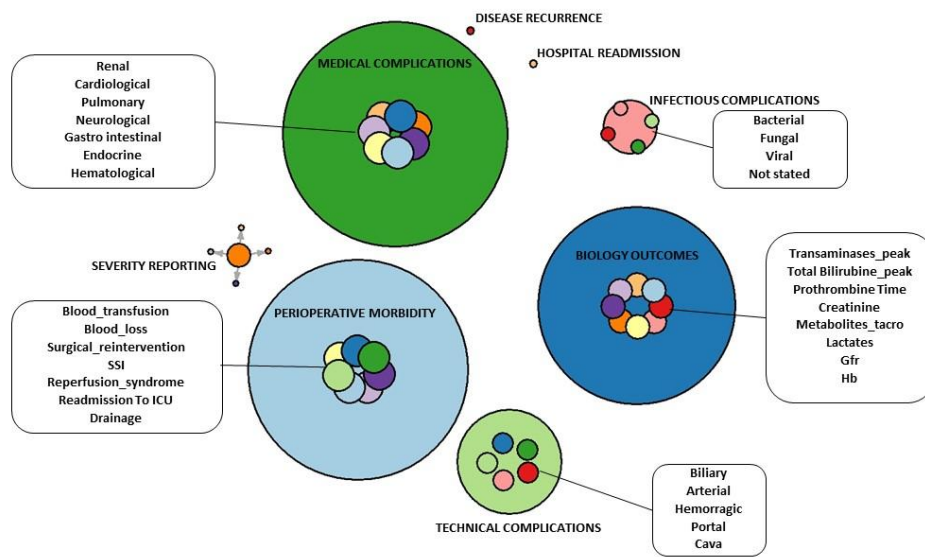
FIGURE 1

Flowchart selection of included published and ongoing studies.



**FIGURE 2**

**Network relations among outcomes reported in the same trial. The dot size is proportional to the rate of the outcome reported across all the included trials. The thickness of the line connecting the outcomes is proportional to the frequency of use of both outcomes in the same trial. As an example, the rate of trials reporting morbidity and graft dysfunction is higher than trials reporting morbidity and patient reported outcomes.**



**FIGURE 3**

The figure details the heterogeneity among morbidity classes and definitions reported across the included trials. The size of the eight main dots (corresponding to the classes of morbidity) are proportional to the number of trials reporting the morbidity classes. Inner dots represent the definitions used for each morbidity class. (SSI=Surgical Site Infection, ICU=Intensive Care Unit, GFR=Glomerular Filtration Rate, CCI=complication comprehensive index, MEAF=Model of Early Allograft Function score)

**Table 1. Characteristics of the selected trials**

Characteristics	Published Trials n (%) N= 55	Ongoing Trials n (%) N = 24
<b>Corresponding author location</b>		
Europe	18 (33)	10 (42)
Asia	10 (18)	4 (17)
North America	7 (13)	5 (21)
Africa	4 (7)	3 (12)
South America	3 (5)	2 (8)
India	5 (9)	0 (0)
Australia	4 (7)	0 (0)
Middle east	4 (7)	0 (0)
<b>Funding source</b>		
Public	13 (24)	19 (79)
Not reported	18 (33)	0 (0)
Private	9 (16)	2 (8)
No funding	9 (16)	0 (0)
Private and public	6 (11)	1 (4)
Unclear	0 (0)	2 (8)
<b>Patients enrolled (n)</b>		
Median (Q1-Q3), range	78 (40-120), 10-893	117 (55-218), 24-500
<b>Trial design, blinding</b>		
Open label (unmasked)	20 (36)	12 (50)
Double blinding	22 (40)	8 (33)
Single blinding	11 (20)	4 (17)
Partially blinded	2 (4)	0 (0)
<b>Trial design, centers</b>		
Single center	40 (73)	15 (62)
Multicenter, National	7 (13)	7 (29)
Multicenter, International	8 (15)	2 (8)



<b>Trial design, number of centers</b>		
Median (Q1-Q3)	1.0 (1.0-2.5), 1-72	1.0 (1.0-4.8),1-15
<b>Follow up, reported</b>	42 (76)	22 (92)
<b>Follow up, months.</b>		
Median (Q1-Q3), range	5.0 (1.5-9.5), 1-11	4.0 (1.8-8.0),1-36

#### LIVER TRANSPLANTATION CHARACTERISTICS

Type of graft detailed	27 (49)	10 (42)
Cadaveric	13 (24)	7 (29)
LDLT	19 (35)	4 (17)
Details on Abdominal incision	3 (5)	Not applicable
Duration of surgery reported	26 (47)	Not applicable
Duration of cold ischemia reported	32 (58)	Not applicable

#### INTERVENTION

##### Timing of intervention

Peri-operative	36 (65)	17 (71)
Early postoperative	16 (29)	4 (17)
Preoperative	3 (5)	3 (12)

##### Class of intervention

Anesthesiology/perioperative medicine	21 (38)	7 (29)
Graft_conditionning	9 (16)	6 (25)
Postoperative recovery including rehab'	8 (15)	4 (17)
Surgical technique	5 (9)	4 (17)
Immunosuppressive regimen	8 (15)	0 (0)
Other	1 (2)	3 (12)
Antifungal prophylaxis	2 (4)	0 (0)
Oncology	1 (2)	0 (0)

##### Intervention type

Non Pharmacologic	20 (36)	18 (75)
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Pharmacologic	35 (64)	6 (25)
Both	0 (0)	0 (0)

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Q=quartile, LDLT = Living Donor Living Transplantation

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**Table 2. Number and type of primary outcomes reported in the methods and results section of included trials**

Characteristics	Published Trials n (%) = 55	Ongoing Trials n (%) = 24
<b>Primary outcomes reported in the methods section <i>per</i> trial.</b>		
<b>Median (Q1-Q3), range</b>	<b>1.0 (1.0-1.0), 1-4</b>	<b>1.0 (1.0-1.0), 1-2</b>
Single primary outcome	43 (76)	19 (79)
Two primary outcomes	4 (7)	5 (21)
Three primary outcomes	7 (13)	0 (0)
Four primary outcomes	2 (4)	0 (0)
<b>Classification</b>		
<b>Morbidity</b>	<b>37 (67)</b>	<b>13 (54)</b>
Perioperative	16 (29)	5 (21)
Biology	7 (13)	1 (4)
Medical	5 (9)	3 (12)
Technical	4 (7)	2 (8)
Other	2 (4)	2 (8)
Infectious	3 (5)	0 (0)
<b>Graft dysfunction</b>	<b>9 (16)</b>	<b>6 (25)</b>
EAD	4 (7)	5 (21)
Rejection	5 (9)	0 (0)
Graft loss	0 (0)	1 (4)
<b>Recovery</b>	<b>7 (13)</b>	<b>4 (17)</b>
Intermediate recovery	5 (9)	2 (8)
Early recovery	2 (4)	2 (8)
<b>Mortality</b>	<b>1 (2)</b>	<b>1 (4)</b>

Early mortality	1 (2)	1 (4)
<b>Other</b>	<b>1 (2)</b>	<b>0 (0)</b>
Feasibility	1 (2)	0 (0)
<b>Primary outcome reported in result section</b>	<b>51 (93)</b>	<b>Not applicable</b>
EAD=early allograft dysfunction Q=quartile		

**Table 3. Number and type of outcomes reported in the methods and results section of included trials**

Characteristics	Published Trials n (%) = 55	Ongoing Trials n (%) = 24
<b>Outcomes reported in the method section <i>per</i> trial.</b>	<b>5.0 (3.0-7.0),2-13</b>	<b>4.0 (3.0-8.0),1-10</b>
<b>Median (Q1-Q3), range.</b>		
<b>Outcomes reported in the method section, <i>total number</i></b>	<b>397</b>	<b>185</b>
<b>Classification</b>		
<b>Morbidity</b>	<b>52 (95)</b>	<b>20 (83)</b>
Perioperative	35 (67)	7 (35)
Medical complications	32 (62)	11 (55)
Biology	27 (52)	6 (30)
Technical	23 (44)	5 (25)
Infectious	23 (44)	1 (5)
Other	11 (21)	2 (10)
<b>Graft dysfunction</b>	<b>36 (65)</b>	<b>11 (46)</b>
Acute cellular humoral rejection	12 (33)	1 (9)
Early allograft dysfunction	9 (25)	4 (36)
Graft loss	8 (22)	4 (36)
Biopsy Proven Allograft Rejection	2 (6)	0 (0)
Small For Size Syndrome	2 (6)	0 (0)
Allograft dysfunction	1 (3)	0 (0)
Ischemia reperfusion injury	0 (0)	1 (9)
MEAF	0 (0)	1 (9)
Primary non function	1 (3)	0 (0)

Rejection	1 (3)	0 (0)
<b>Mortality</b>	<b>38 (69)</b>	<b>13 (54)</b>
Intermediate Mortality	16 (9)	9 (5)
Early mortality	7 (4)	6 (3)
<b>Recovery</b>	<b>31 (56)</b>	<b>12 (50)</b>
Length of stay, hospital	24 (77)	8 (67)
Length of stay, ICU	25 (81)	6 (50)
Time to extubation	13 (42)	0 (0)
Other	4 (13)	4 (33)
<b>PRO</b>	<b>7 (13)</b>	<b>4 (17)</b>
Symptoms	6 (11)	1 (4)
QoL	1 (2)	3 (12)
<b>Outcomes reported in result section, total number</b>	<b>283 (71)</b>	<b>Not applicable</b>

Y=yes, Q=quartile, EAD=early allograft dysfunction, ICU=Intensive Care Unit, MEAF=Model of Early Allograft Function score, PRO=patient reported outcomes, QoL=Quality of life.

**Table 4. Detail of morbidity outcomes assessed and reported among the included trials**

	N	Published Trials n (%) = 55 (70)	Ongoing Trials n (%) = 24 (30)
<b>MORBIDITY</b>			
<b>Morbidity_assessed</b>	79	52 (95)	20 (83)
<b>Morbidity_perioperative</b>	72	35 (67)	7 (35)
Blood_transfusion	42	15 (43)	2 (29)
Blood_loss	42	15 (43)	1 (14)
Surgical_reintervention	42	12 (34)	0 (0)
SSI	42	5 (14)	2 (29)
Reperfusion_syndrome	42	2 (6)	2 (29)
Readmission to ICU	42	2 (6)	0 (0)
Drainage	42	1 (3)	0 (0)
<b>Biology outcomes</b>	72	27 (52)	6 (30)
Transaminases_peak	33	16 (59)	5 (83)
Total Bilirubine_peak	33	18 (67)	1 (17)
Prothrombine time	33	9 (33)	0 (0)
Creatinine	33	8 (30)	0 (0)
Metabolites_tacro	33	7 (26)	1 (17)
Lactates	33	5 (19)	1 (17)
GFR	33	6 (22)	0 (0)
Hb	33	2 (7)	0 (0)

<b>Complications_Technical</b>	72	23 (44)	5 (25)
Biliary	28	15 (65)	5 (100)
Arterial	28	12 (52)	0 (0)
Hemorrhagic	28	7 (30)	0 (0)
Portal	28	6 (26)	0 (0)
Cava	28	2 (9)	0 (0)
<b>Complications_Medical</b>	72	32 (62)	11 (55)
Renal	43	23 (81)	5 (45)
Cardiological	43	12 (38)	3 (27)
Pulmonary	43	13 (41)	1 (9)
Neurological	43	10 (31)	1 (9)
Gastro_Intestinal	43	5 (16)	2 (18)
Endocrine	43	2 (6)	3 (27)
Hematological	43	1 (3)	0 (0)
<b>Complications_Infectious</b>	72	23 (44)	1 (5)
Bacterial	19	12 (67)	0 (0)
Viral	19	8 (44)	0 (0)
Fungal	19	7 (39)	0 (0)
Not_Stated	19	4 (22)	1 (100)
<b>Disease_Recurrence</b>	10	7 (78)	1 (100)
<b>Hospital_Readmission</b>	10	2 (22)	0 (0)
<b>Severity_Reporting</b>	74	10 (18)	3 (16)
Dindo_Clavien	8	5 (83)	0 (0)
CCI	8	0 (0)	1 (50)
NCCI_adv_events	8	1 (17)	0 (0)
MEAF	8	0 (0)	1 (50)

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SSI=Surgical Site Infection, ICU=Intensive Care Unit, GFR=Glomerular Filtration Rate,  
CCI=complication comprehensive index, MEAF=Model of Early Allograft Function score

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## SUPPLEMENTARY MATERIAL

Supplementary\_Table 1. Risk of bias in the included published trials.

	Published Trials n (%) = 55
<b>Random sequence generation.</b>	
Low risk of bias	27 (49)
Unclear risk of bias	6 (11)
High risk of bias	22 (40)
<b>Allocation Concealment.</b>	
Low risk of bias	23 (42)
Unclear risk of bias	8 (15)
High risk of bias	24 (44)
<b>Blinding of participants and personnel.</b>	
Low risk of bias	18 (33)
Unclear risk of bias	8 (15)
High risk of bias	29 (53)
<b>Blinding of outcome assessment.</b>	
Low risk of bias	18 (33)
Unclear risk of bias	15 (27)
High risk of bias	22 (40)
<b>Incomplete outcome data.</b>	
Low risk of bias	21 (38)
Unclear risk of bias	20 (36)
High risk of bias	14 (25)

**Supplementary\_Table\_2. Classification and timing of measured outcomes**

	<b>Published Trials</b> n (%) = 55	<b>Ongoing Trials</b> n (%) = 24
<b>MORTALITY</b>		
Mortality, assessed	38 (69)	13 (54)
Mortality, reported	38 (69)	Not applicable
Mortality, reported cause of	22 (58)	Not applicable
Mortality, timing assessed	36 (65)	13 (54)
Mortality, timing		
in-hospital	9 (25)	0 (0)
1 month	4 (11)	1 (8)
5 weeks	0 (0)	1 (8)
3 months	4 (11)	3 (23)
6 months	4 (11)	4 (31)
9 months	1 (3)	0 (0)
1 year	5 (14)	3 (23)
2 years	0 (0)	1 (8)
29 months	1 (3)	0 (0)
3 years	2 (6)	0 (0)
5 years	1 (3)	0 (0)
Other	5 (14)	0 (0)
<b>MORBIDITY</b>		
Morbidity assessed	52 (95)	20 (83)
Medical complications	32 (62)	11 (55)
Biology	27 (52)	6 (30)
Technical	23 (44)	5 (25)
Infectious	23 (44)	1 (5)
Other	11 (21)	2 (10)
Severity score assessed	15 (27)	3 (12)
Severity reporting	10 (18)	3 (16)
Timing of complications assessed	27 (49)	20 (100)
Timing of complication		
<1h	0 (0)	3 (15)
1d	1 (4)	0 (0)
4d	1 (4)	0 (0)
5d	1 (4)	1 (5)
7d	3 (11)	5 (25)
2w	1 (4)	1 (5)
1m	5 (19)	1 (5)
3m	4 (15)	0 (0)
6m	4 (15)	4 (20)
9m	1 (4)	0 (0)
1y	6 (22)	0 (0)
3y	0 (0)	1 (5)

**GRAFT DYSFUNCTION**

Liver graft dysfunction, assessed	36 (65)	11 (46)
Liver graft dysfunction, reported	25 (69)	Not applicable
Liver graft dysfunction, measure		
Acute cellular humoral rejection	12 (33)	1 (9)
Early allograft dysfunction	9 (25)	4 (36)
Graft loss	8 (22)	4 (36)
Biopsy Proven Allograft Rejection	2 (6)	0 (0)
Small For Size Syndrome	2 (6)	0 (0)
Allograft dysfunction	1 (3)	0 (0)
Ischemia reperfusion injury	0 (0)	1 (9)
MEAF	0 (0)	1 (9)
Primary non function	1 (3)	0 (0)
Rejection	1 (3)	0 (0)
Liver graft dysfunction, timing		0 (0)
2 days	1 (4)	0 (0)
3 days	1 (4)	0 (0)
7 days	7 (28)	5 (45)
1 week	1 (4)	0 (0)
2 weeks	1 (4)	0 (0)
1 month	3 (12)	0 (0)
3 months	3 (12)	1 (9)
6 months	4 (16)	4 (36)
1 year	4 (16)	1 (9)

**RECOVERY OUTCOMES**

Recovery outcomes assessed	31 (56)	12 (50)
Classes of recovery outcomes		
Length of Stay, hospital	24 (77)	8 (67)
Length of stay, ICU	25 (81)	6 (50)
Time to extubation	13 (42)	0 (0)
Other	2 (6)	3 (25)
6mWT_VO2max	0 (0)	1 (25)
Discharge within 2 months	1 (25)	0 (0)
Duration of surgery	0 (0)	1 (25)
Liver frail index	0 (0)	1 (25)
Postoperative ileus	1 (25)	0 (0)
Recovery_from_neuromusc_block	0 (0)	1 (25)

**PATIENT REPORTED OUTCOMES**

PROS reported	7 (13)	4 (17)
PROS : symptoms	6 (86)	1 (25)

y=year, m=month, w=week, Q=quartile, EAD=early allograft dysfunction, ICU=Intensive Care Unit, MEAF=Model of Early Allograft Function score, PRO=patient reported outcomes, QoL=Quality of life.



**Supplementary\_Table 3. Number and type of outcomes reported in the results section of included trials depending on the timing of the intervention**

Characteristics	Pre and perioperative	Early postoperative
	n (%) = 767	n (%) = 260
<b>Morbidity</b>	<b>188 (24.5)</b>	<b>64 (24.6)</b>
Perioperative	76 (9.9)	13 (5.0)
Medical	45 (5.9)	31 (11.9)
Other	4 (0.5)	11 (4.2)
Biology	35 (4.6)	2 (0.8)
Technical	26 (3.4)	3 (1.2)
Infectious	0 (0)	3 (1.2)
<b>Recovery</b>	<b>38 (5.0)</b>	<b>38 (14.6)</b>
Intermediate recovery	25 (3.3)	32 (12.3)
Early recovery	13 (1.7)	6 (2.3)
<b>Graft dysfunction</b>	<b>37 (4.8)</b>	<b>34 (13.1)</b>
Graft Loss	15 (2.0)	10 (3.8)
EAD	15 (2.0)	0 (0)
Rejection	8 (1.0)	25 (9.6)
<b>Mortality</b>	<b>30 (3.4)</b>	<b>14 (5.4)</b>
In hospital	6 (10.2)	3 (15.0)
1 month	5 (8.5)	0 (0)
5 weeks	1 (1.7)	0 (0)
3 months	5 (8.5)	2 (10.0)
6 months	5 (8.5)	3 (15.0)
9 months	1 (1.7)	0 (0)
1 year	3 (5.1)	5 (25.0)
2 years	1 (1.7)	0 (0)
29 months	1 (1.7)	0 (0)
3 years	1 (1.7)	1 (5.0)
5 years	1 (1.7)	0 (0)
Other	4 (6.8)	1 (5.0)
<b>PRO</b>	<b>3 (0.4)</b>	<b>3 (1.2)</b>
QoL	3 (0.4)	1 (0.4)
Fatigue	0 (0)	1 (0.4)
Pain	0 (0)	1 (0.4)
<b>Other</b>	<b>2 (0.3)</b>	<b>0 (0)</b>
Feasibility	1 (0.1)	0 (0)

EAD=early allograft dysfunction, PRO=patient reported outcomes, QoL=Quality of life.

Supplementary material study list = Published trials included in the analysis			
First Author	Title	Publication year	PMID
Aliakbarian, M	Effects of N-Acetylcysteine Addition to University of Wisconsin Solution on the Rate of Ischemia-Reperfusion Injury in Adult Orthotopic Liver Transplant.	2017	26114393
Asrani, SK	De novo sirolimus and reduced-dose tacrolimus versus standard-dose tacrolimus after liver transplantation: the 2000-2003 phase II prospective randomized trial.	2014	24456026
Barros, MAP	L-Alanyl-Glutamine Attenuates Oxidative Stress in Liver Transplantation Patients.	2015	26518955
Beck-Schimmer, B	Conditioning With Sevoflurane in Liver Transplantation: Results of a Multicenter Randomized Controlled Trial.	2015	25769076
Bharathan, VK	Perioperative prostaglandin e1 infusion in living donor liver transplantation: A double-blind, placebo-controlled randomized trial.	2016	27152759
Bindi, ML	Solvent detergent vs. fresh frozen plasma in cirrhotic patients undergoing liver transplant surgery: a prospective randomized control study.	2013	23448618
Brescia, MD	Prospective Randomized Trial Comparing Hepatic Venous Outflow and Renal Function after Conventional versus Piggyback Liver Transplantation.	2015	26115520
Casciato, P	$\alpha$ -Lipoic Acid Reduces Post-Reperfusion Syndrome in Human Liver Transplantation - a pilot study.	2018	29974521
Celli, P	Adaptive support ventilation versus synchronized intermittent mandatory ventilation with pressure support in weaning patients after orthotopic liver transplantation.	2014	25150607
Cuervas-Mons, V	Impact of tacrolimus and mycophenolate mofetil regimen vs. a conventional therapy with steroids on cardiovascular risk in liver transplant patients.	2015	25924549
Demir, A	Impact of 6% Starch 130/0.4 and 4% Gelatin Infusion on Kidney Function in Living-Donor Liver Transplantation.	2015	26293067
Fayed, N	Effect of dexmedetomidine on hepatic ischemia-reperfusion injury in the setting of adult living donor liver transplantation.	2016	26856320
Fayed, N	Effect of perioperative terlipressin infusion on systemic, hepatic, and renal hemodynamics during living donor liver transplantation.	2013	23618777
Gedik, E	Blood glucose regulation during living-donor liver transplant surgery.	2015	25894177
Grat, M	Effects of continuous use of probiotics before liver transplantation: A randomized, double-blind, placebo-controlled trial.	2017	28506447
Janousek, L	Bile Duct Anastomosis Supplied With Biodegradable Stent in Liver Transplantation: The Initial Experience.	2016	27931575
Kaido, T	Effect of herbal medicine daikenchuto on oral and enteral caloric intake after liver transplantation: A multicenter, randomized controlled trial.	2018	29747091
Kandil, MA	Impact of terlipressin infusion during and after live donor liver transplantation on incidence of acute kidney injury and neutrophil gelatinase-associated lipocalin serum levels: A randomized controlled trial.	2017	28564127
Kim, JM	Early Enteral Feeding After Living Donor Liver Transplantation Prevents Infectious Complications: A Prospective Pilot Study.	2015	26554774

Kim, WH	Effect of remote ischemic postconditioning on patients undergoing living donor liver transplantation.	2014	25046844
Klintmalm, GB	Belatacept-based immunosuppression in de novo liver transplant recipients: 1-year experience from a phase II randomized study.	2014	25041339
Kong, HJ	Epsilon-aminocaproic acid improves postrecirculation hemodynamics by reducing intraliver activated protein C consumption in orthotopic liver transplantation.	2014	24142329
Kulik, L	Prospective randomized pilot study of Y90+/-sorafenib as bridge to transplantation in hepatocellular carcinoma.	2014	24681342
Lang, JD	A randomized clinical trial testing the anti-inflammatory effects of preemptive inhaled nitric oxide in human liver transplantation.	2014	24533048
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