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To Whom it may concern:

This is to certify that the study "International, Multicenter, Prospective, Non-competitive, Observational study to Validate and Optimize prediction models of 90-day and 1-year allograft failure after liver transplantation The IMPROVEMENT study" (id 4571) received a full approval by the local Ethics Committee during the meeting on December 2nd, 2021.

The President of the Ethics Committee
Prof. Andrea Bacigalupo

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International, Multicenter, Prospective, Non-competitive, Observational study to Validate and Optimize prediction models of 90-day and 1-year allograft failure after liver transplantation
The IMPROVEMENT study

Short Title: *Allograft failure after liver transplantation - The IMPROVEMENT study*

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For research purposes, the PI will be coadjuvated by a Co-PI, Prof. Vatche Agopian from University of California Los Angeles.

Rome, 27/11/2021 Alfonso W Avolio for the Steering Committee

1) SYNOPSIS

Allograft failure (AF) at 90 days after liver transplantation (LT) has been recently characterized thank to the development of kinetic models based on graft performance during the early post-operative days. Two scores, the North American (**L-GrAFT score**) and the European one (**EASE score**), allow the prediction of EAF with excellent C-statistics. Both were validated on external populations. L-GrAFT and EASE scores are calculated 10 days after LT, and a modification of the L-GrAFT seven days after. Both scores were designed to identify patients at high risk of AF who could benefit from early retransplantation and be rescued before other complications occur. In addition, a higher incidence of ischemic cholangiopathy has been reported with grafts from extended criteria donors (ECD) or from donors after cardiac death (DCD). This typically develops between 6 and 12 months after LT and causes AF in 5 to 15% of cases.

Other preoperative factors not routinely registered (e.g., frailty, sarcopenia, nutritional status, other organ failure, infections), often contribute to develop AF. Finally, the role of **graft steatosis** and the **protective effect of perfusion machines,** are yet to be analyzed in a large multicentric prospective study. Even if the quality of the organ remains a main determinant of the outcome, these factors may hamper or contraindicate a timely and efficacious re-transplantation. However, while the role of recipient **disease severity** and **comorbidities** is well known, to which extent machine perfusion machines and optimized post-operative management may mitigate the risk of AF prompt careful evaluation.

This is an **International, Prospective, Non-competitive, Observational study with the aim to validate and optimize prediction models** of AF at 90 days and 1 year after LT by comprehensively collecting data on current practice, various donor types (brain death donors [DBD] grafts; cardiac death donors [DCD] grafts; living donors [LD] grafts), with balanced international enrollment, homogeneous center volume, and various peri-operative mitigation strategies (e.g. machine perfusion). The study includes both a prospective cohort (high-volume liver transplant centers with >65 liver transplants per year) to develop new predictive models, and a retrospective cohort (intermediate and low-volume centers) to validate the newly developed models.

The secondary objectives are: 1. to validate the already existing predictive models and the newly developed algorithms on a retrospective cohort of patients from low to medium-volume transplant centers; 2. to develop a novel time-based dynamic algorithm, with increasing accuracy from the 3rd to 7th post-operative day; 3. to identify the best-time for re-transplant (after stratification according to the post-operative weeks, months, trimesters); 4. to investigate differences in the incidence of Allograft Failure at 90 and 365 days according to DBD, DCD, LD donor grafts; 5. to evaluate the effect of mitigation strategies on the precipitating factors of Allograft Failure at 90 and 365 days; 6. to investigate the association of kinetic algorithms with development of post-LT complications (acute kidney injury, ischemic cholangiopathy, other complications); 7. to identify risk factors for mortality that may contraindicate re-transplant.

The study has been designed to give a **precise snapshot of current practice** in Europe, Americas and Asia. Fifty consecutive first-transplants for each center enrolled in the prospective cohort (from January to August 2022) and seventy five in the retrospective cohort (from July 1, 2021 and June 30, 2019). Non-renal combined transplants, auxiliary and domino transplants are excluded. Retransplants can be included if the patient was already enrolled at the first transplant. A follow-up of at least 365 days is foreseen.

A graft biopsy of deceased donors should be obtained during the back-table check in the prospective cohort. The biopsy is not mandatory but strongly suggested. Biopsies of grafts from living donors will be also performed at the cut surface of the donor operation. All slices will be locally scanned and blindly reviewed centrally.

The study protocol has been defined by an international **steering committee.** Members will critically review the study protocol and promote/coordinate the participation of selected centers in their own area. Each center will include two investigators (one senior, one junior) in the author-line of the main manuscript.

Rome, 27/11/2021 Alfonso W Avolio for the Steering Committee

2) INTRODUCTION

a) Background

During the last decade, the expansion of the donor pool by using extended criteria donors (**ECD**) grafts and those after cardiac death (**DCD**) have redrawn the attention around allograft failure (AF) due to ischemia-reperfusion injury after liver transplantation. The prompt diagnosis of AF is of paramount importance to define the indication for early re-transplantation. Moreover, the grafts from ECD and DCD not only may develop AF during the initial 90 days (early allograft failure, EAF)[1-2] but also a slow-evolving type of failure, which presents up until 365 days.
The **evaluation times** and the **modalities** to promptly identify AF are still the object of research. At the same time, no consensus exists on the most accurate predictors of AF and on the possible mitigation strategies.[3-7] ECD and DCD grafts are burdened by a higher incidence of ischemic cholangiopathy,[8-9] that typically develops 6 to 12 months, which is also a cause of AF and need for retransplant.
Sophisticated models to estimate EAF, based on the **kinetics of different variables,** have been recently developed using retrospective data. Two scores, the North American (**L-GrAFT**)[1] and the European (**EASE**) score,[2] allow to predict AF at 90 with excellent C-statistics. Both scores have been validated on external populations.[10] L-GrAFT and EASE scores are calculated at day 10 after LT; furthermore, a modification of the L-GrAFT score at day 7 has been developed and validated.[11] Both scores are also proposed for quantifying the degree of graft recovery in translational studies. However, the prognostic role of **pre-transplant histopathology** of the graft as well as the detailed characterization of the dynamics that make retransplant sustainable or contraindicated and the possibilities to intervene to mitigate the graft related risk remain unmet needs. Finally, the **differences among phenotypic patterns of various transplant types** (DBD, deceased donor grafts after cardiac death [DCD] and living donor grafts [LD]) have not been investigated, nor a large prospective study has been undertaken.

b) Rationale

Timely prediction of AF is pivotal to identify patients potentially benefiting from a rescue retransplant before severe complications develop. When massive cytolysis and clear signs of liver failure occur within the first 2-4 days after LT, the indication for a retransplant is clear, independently from the evidence of the thrombosis of a hepatic vessel. Nevertheless, past 5 to 10 days after transplant, the decision whether or not to retransplant is often challenging. AF results from a complex interplay between donor, procurement-related, and recipient perioperative factors. All of them contribute to determine the severity and the capability to recover from the ischemia-reperfusion injury. However, several conditions and/or postoperative events may precipitate such capability (e.g., pre-operative cardiac ischemic damage, frailty-sarcopenia, graft rejection, drug toxicity, kidney failure, or severe infections or sepsis).[12-19] Only a part of these factors have been studied. Additionally, although L-GrAFT and EASE scores can predict AF after 7 to 10 days, the trajectories of the graft towards recovery, successful or unsuccessful retransplantion and death without retransplant, have not been fully characterized yet. Despite the excellent accuracy and the efficacious discrimination ability, the existing studies have not elucidated the individual role of these events, nor competitive models have been developed in the perspective of retransplantion.[1,2,11] Notably, literature is exclusively based on retrospective studies. Almost all these studies span an extended period of time, are often monocentric, do not consider the center volume effect, and are not balanced in the number of recruited patients in each center.[1,3-5] Finally, only a small number of DCD grafts and ECD grafts managed by perfusion machines have been included in previous studies.[1-2]

c) Objectives

Primary objective: to develop new algorithms for the timely prediction of Allograft Failure at 90 and 365 days *using a comprehensive prospectively collected dataset based on the current clinical practice of high-volume centers.*

The secondary objectives are:

1. to **validate** the already **existing predictive models** and the newly developed algorithms on a retrospective cohort of patients from low to medium-volume transplant centers;
2. to **develop** a novel **time-based dynamic algorithm**, with increasing accuracy **from the 3rd to 7th post-operative day**;
3. to **identify** the **best-time** for **re-transplant** (after stratification according to the post-operative weeks, months, trimesters);
4. to **investigate differences** in the incidence of **Allograft Failure** at 90 and 365 days according to **DBD, DCD, LD donor grafts**;
5. to **evaluate** the effect of **mitigation strategies** on the precipitating factors of Allograft Failure at 90 and 365 days;
6. to **investigate** the **association** of kinetic algorithms with development of **post-LT complications** (acute kidney injury, ischemic cholangiopathy, other complications);
7. to **identify risk factors** for **mortality** that may contraindicate re-transplant.

3) METHODS

a) Study design

Multicenter, international, observational two-cohort study.
The two cohorts include a first cohort with prospective patient enrolment and a second cohort with retrospective enrolment.

A steering committee was constituted to design the study. Members were identified according to their experience on the topic and their geographic area (Europe, Americas, Asia). A draft of the preliminary study design and subsequent questionnaires on controversial issues were circulated among members.

The **Ethics Committee of Fondazione Policlinico Universitario Agostino Gemelli**, Rome, and the **Institutional Review Board of the University of California**, Los Angeles, (respectively, the affiliations for AWA, principal investigator, and for VGA, co-principal investigator) are evaluating the study design and the provisional study protocol.
The provisional study protocol has been submitted to the European Society of Organ Transplantation (ESOT), the International Liver Transplant Society (ILTS), and the Asian Society of Transplantation (AST) for suggestions and promotion among the Liver Transplant Centers. The amended protocol should be circulated again among the steering committee members for approval. Finally, the members will submit the study protocol to the local institutional review boards for their approval.
No modification to the participating centers standard practice for the management of LT donors and recipients is required. The study has been structured according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[20]

b) Setting

The study will be conducted in 80 liver transplant centers from four continents, in XX nations. Two distinct datasets will be created to collect data from the participating centers, depending on which of the two cohorts their patients belong to.

- Prospective cohort. Two thousands liver transplant recipients will be enrolled in 40 high volume centers (defined as performing ≥65 LT a year). Each center will enroll 50 consecutive transplants according to the inclusion criteria. For each transplant a further 365-day period will be necessary for the follow-up.

- Retrospective cohort. A retrospective cohort has been conceived for medium-low volume centers (defining as performing <65 LT a year, that would otherwise require a prolonged enrolment time) to participate in the study using the data of LTs performed between during last three years.
A target number of 75 cases per center (40 Centers), enrolled backwards from July 1, 2021 and June 30, 2019 (36 months) will provide data for 3000 patients.
We expect to enroll approximately five thousand patients (2000 from the prospective cohort; 3000 from the retrospective cohort) by the end of 2022.
The study design includes two evaluation times (at 90 and 365 days after LT).
Participants will be followed-up during their post-transplant hospital stay and at the liver transplant outpatient clinic after discharge from hospital. Readmissions to the hospital for any cause will be recorded.

c) Participants

Inclusion criteria

1. Adult cases (≥18 years)
2. First transplant (retransplant cases should be enrolled if the first transplant is part of the study)
3. DBD grafts
4. DCD grafts (controlled and uncontrolled)
5. DBD and DCD grafts managed by perfusion machines
6. Living donor grafts (only right-side grafts; the inclusion of left side grafts and particularly their allocation to paediatric patients, constitutes an bias for the difficulty in distinguish small for size syndrome from other causes of early allograft failure)

Exclusion criteria

1. Non-renal combined grafts (e.g. liver-heart, liver-pancreas, multi-visceral grafts)
2. Domino grafts
3. Heterotopic grafts
4. Double grafts

The software of the eCRF will check the fulfillment of the eligibility criteria and whether the target number of cases for each Center has been reached.

Note. Due to some concerns regarding the differences in the prevalences of AB0 incompatible grafts among different countries, these patients can be enrolled concurring to the target number of cases for each center. During the statistical analysis, we should evaluate the opportunity to include them or not in the study population, being aware of the substantial equivalence in the survival results.[21-22]

d) Variables

Allograft failure was defined as graft failure (need for retransplant or death) for any reason at day 90 and at day 365 after LT. This definition also captures all late-occurring AFs (also known as delayed non-function)[23]. We consider as AF determinants all events potentially aggravating the process of graft function recovery, independently if they were or were not strictly associated with ischemia-reperfusion injury. Indeed, vascular (thrombosis of the hepatic artery or portal vein), biliary, toxic, and major hemodynamic events will be included because any of them interacting with parenchymal dysfunction can affect graft function recovery and favor graft failure and death.

The prospective cohort dataset includes 165 variables (see Appendix B). Main variable categories are:

- donor characteristics
- pre-operative data
- graft histology
- intraoperative data
- post-operative data

Less than half of them are numeric data. The remaining part is constituted by choice or dichotomic data, which can be entered quickly. The remaining part is constituted by choice or dichotomic data, which can be entered quickly on the electronic Case Report Form (eCRF). The eCRF has been developed using the REDCap ver 10.0.21 software hosted at https://redcap-irccs.policlinicogemelli.it/, which includes seven forms (IDENTIFICATION, DONOR, PRE-OPERATIVE, INTRAOPERATIVE, POSTOPERATIVE part I, POSTOPERATIVE part II, OUTCOME DATA). The eCRF allows easy calculation of scores including L-GrAFT and EASE scores.

The retrospective cohort dataset will include 75 variables (see Appendix B), previously registered in the local-center data sources. They will be used to validate previously published kinetic algorithms.

Histology obtained during the back-table graft preparation (i.e., the procedure performed before the implantation to check the viability of the graft) will constitute a key point although not mandatory condition for the enrolment. The histology slides will be scanned at the local centers, de-identified and uploaded on the eCRF and centrally read for research purposes.
Transplant candidates CT scan (DICOM files only) from the pre-listing work-up will be de-identified and uploaded on the eCRF and centrally read for research purposes.

The incidence and grade of ischemic cholangiopathy be measured through of a cholangio-MR at 10-12 months after LT. The DICOM files will be de-identified will and uploaded on the eCRF and centrally read for research purposes.

The list of the definitions and abbreviations is detailed in the Appendix A.
The list of the variables of both cohorts is detailed in the Appendix B.
The list of the formulas to compute the prediction scores is detailed in the Appendix C.

e) Data sources / measurement

Methodological aspects of data definition and measurements are detailed in Appendix A, B, C.
A customized eCRF (eletronic Case Report Form) has been be created for the study. The Investigator will be responsible to ensure that the eCRFs will correctly and completely be filled in. Study data will be collected and managed using REDCap electronic data capture tools hosted at Fondazione Policlinico Universitario A. Gemelli, IRCCS (https://redcap-irccs.policlinicogemelli.it/) provided by the Research Core Facility DATA COLLECTION of the Science and Technology Park of Fondazione Policlinico Gemelli IRCCS (GSTeP). REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing

1. an intuitive interface for validated data entry;
2. audit trails for tracking data manipulation and export procedures;
3. automated export procedures for seamless data downloads to common statistical packages;
4. procedures for importing data from external sources.[24-25]

Only users registered as study investigators or data managers will receive a user login to access the REDCap web platform and enter/manage data. CRFs must be completed for all patients who have given informed consent. Sources of information are the physician's patient record, hospital notes, original laboratory records, pharmacy records, and results of pathological examination. Data will be entered into the eCRF in a truthful, accurate and timely manner.

To guarantee the highest safety and quality of data collection and management some aspects must be highlighted:

1. RedCap was installed in GDPR compliance including database encryption and meets several security policies and user needs including compliance with 21 CFR Part 11, FISMA, HIPAA.

A two-step authentication login process has been implemented (In addition to username and password, a temporary password, sent by mail, to access the system is required);

2. The eCRF was built and will be managed according to ACCIT (Accuracy, Consistency, Completeness, Integrity and Timeliness) criteria.[26-28] All tricks in order to improve data quality have been included by design such as calculated field, branching and skip logic, alert related to specific condition, units conversion;

3. Only pseudo-anonymized data will be collected. Each center will be identified with a unique code and a progressive number will be automatically attributed by REDCap to each patient enrolled. More in depth:

a. The progressive number of the transplant in each Center (not of the patient) and the day of the transplant will be collected

b. The name and the surname of the patient is not recorded. However, for the convenience of the Center's operators, the first two initials of the surname and name could be optionally reported to facilitate the identification of the case during the postoperative follow-up. These initials will be visible only to the operators of the Center.

4. Each Center will only have access to its data. Only two operators/Center can access the eCRF, one junior and one senior. Either the junior or the senior can enter and modify the records. The senior operator has two additional features:

a. Records lock after validation (It can be done in a case-by-case mode or at the end of the study according to Center preference);

b. Dataset export for statistical analysis and other purposes;

NB: Only de-identified data of its own Center can be downloaded. De-identification allows to limit the amount of sensitive information that can be exported out of the project including one or more of the following:

1. Removing all tagged Identifier fields (tagged in Data Dictionary), unvalidated Text fields (e.g. text fields other than dates, numbers), Notes/Essay box fields.
2. Hashing the Record ID field (converts record name to an unrecognizable value).
3. Removing date and date time fields or shifting all dates by value between 0 and 364 days (shifted amount determined by algorithm for each record).

f) Bias

Centers participation on a voluntary basis.
Issue: some centers might withdraw their participation.
Solution: a large number of centers has been planned to accommodate potential withdrawals.

Prospective cohort composed only by high-volume centers.
Issue: the enrolment from high-volume centers might cause a loss of real-life description of the LT community situation.
Solution: only high-volume centers allow the collection of the required data to build new predictive models in a timely fashion. In addition, perfusion machines are utilized more commonly in high-volume centers. Nevertheless, data from medium-to-low volume centers will be used to validate the novel predictive model and the applicability to their clinical practice.

Delayed enrolment.
Issue: some high-volume centers might experience a reduction in their LT activity for various reasons.
Solution: granting extension to allow the centers to meet their enrolment expectation, up to six months extra.

Different prevalence of the graft subtypes.

Issue: despite the efforts to balance the numerosity of the various LT subgroups, the number of DBD grafts remains higher than that of LD and DCD.
Solution: the preliminary sample size / power analysis calculation demonstrated that the planned enrolment allows a sufficient numerosity to reveal the difference in the incidence of allograft failure at 90 and 365 days after LT.

g) Study size

The study size calculation was independently performed by the G-Step Statistical Facility of the Fondazione Policlinico Agostino Gemelli IRCCS (https://github.com/fernandoPalluzzi/EAF-LT/blob/main/Liver_EAF_power.R)

1. Prior knowledge

1.1. EAF incidence
- Incidence of Early Allograft Failure (EAF) according to the L-GrAFT study (2018): 11.1%[1]
- Incidence of EAF according to the EASE score study: 6.7%(2)
- Incidence of EAF according to the L-GrAFT validation study (2020) in UCLA: 7%[11]
- Incidence of EAF according to the L-GrAFT validation study (2020) in other US validation CENTERS: 11% 4
- Incidence of EAF according to the L-GrAFT validation study (2020) in European COPE cohort: 4%[11]

Notably, the COPE cohort consists of 222 grafts.

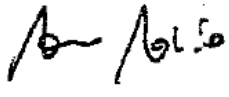
Research hypothesis stratified by donor type:
3% EAF in liver transplantation with living donors;
7% EAF in liver transplantation with standard deceased donors;
10% EAF in liver transplantation with high-risk deceased donors.

1.2. EASE and L-GrAFT score performance as AUC (95% confidence interval)
- EASE(10) AUC = 0.87 (0.83, 0.91)[2,3]
- L-GrAFT10 AUC = 0.72 (0.65, 0.78)[2,3]
- L-GrAFT7 AUC = 0.78 (0.75, 0.82)[4]

2. EASE score algorithm validation

Current target sample size (n):
- 4000-5000 subjects overall;
- 1600-2000 for the prospective study;
- 2400-3000 for the retrospective study.

Simulation 2.1: EASE(10) vs. L-GrAFT10
An overall population size n0 = 5000 subjects (i.e., the highest target sample size for this study), with an EAF incidence1 of p0 = 0.111, is set for the first simulation. During the simulation, n0 subjects were sampled from a binomial distribution to build a random dichotomous outcome vector y = {1: EAF, 0: non-EAF}.
Two simulated predictors, namely x1 and x2, are generated for L-GrAFT10 and EASE score, respectively. Predictor values are simulated by changing the y values (0-to-1 or 1-to-0) according to the probability p = P(x = k | y = k), where 1 – p is the probability for either the EASE or L-GrAFT10 score to yield a false positive or false negative (i.e., the prediction error). The value of p is such that the estimated AUC for either the EASE or the L-GrAFT10 score is equal to the observed AUC value. ROC curves for both EASE and L-GrAFT10 scores are generated using the roc function from the R package pROC.[29]



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AUCs and sample sizes for cases (EAF) and controls (non-EAF) are then estimated using the power.roc.test function from pROC 5. Taking the AUC1 = 0.72 of the L-GrAFT10 score as a reference, the sample sizes were estimated considering an AUC2 = 0.82 for the EASE score, under the null hypothesis of no difference between AUC1 and AUC2.
CONCLUSION
At a significance level = 0.05 and power = 0.8, the estimated sample size is about 350 subjects (36 EAF + 310 non-EAF subjects).

Simulation 2.2: EASE vs. L-GrAFT$_7$
This simulation was conducted with the same input arguments as the previous one, but considering a baseline AUC1 = 0.78, corresponding to the L-GrAFT7 score AUC 4. This modification is introduced to consider the possibility of achieving a higher AUC at day 7 of follow-up, after the transplantation, rather than day 10 (the current lower boundary). This has also the desired effect of reducing the difference AUC2 – AUC1, leading to a more conservative (i.e., larger) sample size estimation.
CONCLUSION
Under the null hypothesis of no difference between AUC1 and AUC2, at a significance level = 0.05 and power = 0.8, the estimated sample size is about 790 subjects (83 EAF + 705 non-EAF subjects).

3. Exploring different incidences of EAF

Current target sample size (n):
- Stratum A: 800 living donors grafts (3% EAF);
- Stratum B: 1000 subjects with standard deceased donors (7% EAF);
- Stratum C: 200 subjects with high-risk deceased donors [DCD or MP grafts] (10% EAF).

The aim of this estimation is to provide the minimum sample size to achieve the baseline AUC, considering a different EAF incidence for each stratum. To reach a conservative sample size estimation, the baseline (i.e., lowest) AUC = 0.72 of the L-GrAFT$_{10}$ score is considered, as a minimum performance requirement. The function power.roc.test from the R package pROC 5 is used also in this case.
CONCLUSION
Considering an AUC = 0.72, a significance level = 0.05, and a power = 0.8, the following sample sizes were estimated (with k = expected balance between non-EAF and EAF subjects):
- 442 grafts for stratum A
(living donors grafts, supposed incidence 3% EAF),
with k = (1 – pA)/pA
- 200 grafts for stratum B
(standard deceased donors, supposed incidence 7% EAF),
with k = (1 – pB)/pB
- 142 grafts for stratum C
(high risk deceased donors [DCD or MP grafts]),
with k = (1 – pC)/pC
where pA = 0.03, pB = 0.07, and pC = 0.10, correspond to the EAF proportion for stratum A, B, and C, respectively.

4. EASE score cut-off validation for class 5 subjects

Let us first consider a p5 = 0.0336 proportion of EAF cases belonging to EASE class 5 (highest L-GrAFT or EASE score). The aim is to estimate the minimum required sample size to observe a proportion p5 of EAF cases in class 5 and validate/improve the cut-off between class 5 and the other classes (1 to 4).

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CONCLUSION
To achieve a conservative sample size estimate, a minimum AUC = 0.7 is required for each class, at a significance level = 0.05, a power = 0.8, and a k = (1 – p5)/p5. Using the power.roc.test function from pROC 5, the minimum estimated sample size is 480.6 grafts (i.e., more than 480 subjects).

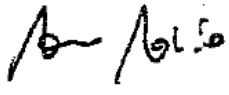
h) Quantitative variables

Quantitative variables will be first explored by missing analysis at three levels: at a center level; at a country level; at continental level.
Then, quantitative variables will be assessed by descriptive analysis in the overall population and according to three main graft types. In depth, they will be described either by mean and standard deviation (SD), whether normally distributed, or by median and interquartile range (IQR), otherwise. The Shapiro-Francia test will previously assess distribution of quantitative data.
Differences between the three main graft types 'subgroups will be investigated using either one-way ANOVA, if normally distributed, or otherwise by the Kruskal-Wallis non parametric test. The significance level will be set at <0.05.
Donor characteristics, pre-operative data, intraoperative data , graft histology, post-operative outcome-data will be also assessed as **potential predictors of the main outcome**, i.e., allograft survival, defined as graft failure at 90 and 365 days (codified by retransplant or death) for any reason, as well as of patients' survival at 90 and 365 days. The characteristics mentioned above will also be implemented in algorithms to chose the best time-window within which undergo re-transplant.
Notably, impact of donor age, graft percentage of macro-steatosis,[30-31], Donor Warm Ischemia Time,[32] Donor Asystolic Warm Ischemia Time[33-35], Recipient Warm Ischemia Time, Cold Ischemia Time, incidence of post-reperfusion syndrome,[36] length of stay in hospital[37-38] and incidence of vascular thrombosis and of biliary complications (anastomotic and non-anastomotic) will be evaluated paying attention to the graft type.[39] The definitions and the full list of variables are reported in Appendix A and B respectively.

The aforementioned characteristics will be also implemented in algorithms to choice the best time-window within which undergo to re-transplantation.

i) Statistical methods

First of all, a **cumulative incidence of allograft failure** will be calculated and in order to define the best time for re-transplant, different strategies may be implemented, based on the collected data at end of study. As first-choice, we could first draw a **Kaplan-Meier for each risk stratum**, i.e. each graft subtype. Then we will **analyze all potential risk factors for AF in each subtype by univariate and multivariate Cox regression models**. Finally, we will implement these results in a temporal algorithm based on Cox curves to identify **potential time-windows for re-transplant**. In the case of multiple drops in the initial KM curves of similar duration, we will build the algorithm so to uniform the duration of each time-window. Alternatively, we can implement a **change-point analysis model** derived from Kaplan-Meier estimation of the survival function followed by the **least-squares estimation of the change point**,[40] or a **wavelet analysis of change-points** based on a non-parametric hazard model.[41] We could also determine the **different time-windows** by using an extension of Glazer's method, using a mixture of two gamma distributions, hypothesizing two or more turning points.[42]Another possibility is represented by **using a Bayesian approach** to the problem of hazard change with unknown multiple change-points, by implementing a **stochastic approximation Monte Carlo algorithm** for efficient calculation of the posterior distributions.[43] Particularly used in graft failure prediction, also **a joint latent changepoint class model** could represent a potential way to improve the prediction of fixed time-windows for re-transplantation.[44,45] All these potential applications would depend on the data distribution at the end of data collection and follow-up period.



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i. Subgroups and interactions

Incidence of allograft failure at 90 and 365 as well as incidence of death at 90 and 365 days will be calculated. Differences between the three main graft types' subgroups will be investigated using either one-way ANOVA, if normally distributed, or otherwise by the Kruskal-Wallis non parametric test. The Chi square test will instead assess differences between qualitative variables. The significance level will be set at <0.05. Kaplan Meier curves will be calculated and differences will be investigated through log-rank test.

ii. Missing data management

A. Missing data in the calculation of the Area Under the Curve (AUC) and the slope of the kinetic model will be addressed as follows:

1. Patients who were retransplanted or died before day 10 were excluded from the calculation of the AUC and slope because of the real impossibility to calculate the score which is by definition computed at day 10. The number of this subgroup will be reported in the flow-diagram of the patients. These cases will be excluded from the patient population utilized for the development of algorithms. However, these cases will be considered for the calculation of the outcome measures (overall % of AF, % failure at 90 days; % failure at 365 days, length of stay, overall graft survival and overall patient survival).

2. Patients who have been discharged between day 8 and 10 and do not have the day 10 determination (missing value referring to the day 10 determination of AST or Platelet count or bilirubin). In these cases the values at day 7 will be used. The number of these cases will be reported in the flow-diagram. We are aware that this approach might overestimate the value of the AUC and consequently the score's value. However, as the number of patients without day-10 data is expected to be small, we believe that the effect will be minimal and not relevant for the purpose of the study.

3. Patients with missing data at day 2, or day 3 will be excluded being impossible the calculation of the score. Their number will be reported in the flow-diagram.

4. Patients with missing data at day 4 will be included. The AUC and the slope will be calculated using the trapezoid method not including day 4. Their number will be reported in the flow-diagram.

5. Patients with missing data at day 5 will be included. The AUC and the slope will be calculated using the trapezoid method not including day 5. Their number will be reported in the flow-diagram.

6. Patients with missing data at day 6 will be included. The AUC and the slope will be calculated using the trapezoid method not including day 6. Their number will be reported in the flow-diagram.

7. Patients with missing data on two consecutive days (day 4 and 5, or day 5 and 6, or day 6 and 7) will be included. The AUC and the slope will be calculated using the trapezoid method not including the two consecutive missing days. Their number will be reported in the flow-diagram.

8. Composite missing data (e.g., AST from one day and bilirubin from a different day) will follow the abovementioned rule. Their number will be reported in the flow-diagram.

9. Missing data in the descriptive analysis will be reported. Parameters of interest with percentage of missings higher than 8% will not be reported in tables neither will be considered for further univariate or multivariate analysis.

iii. Loss to follow-up

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The **count of cases lost to follow-up** will be reported together with in the numbers at risk tables below the Kaplan Meier curves.

4) RESULTS

a) Participants

A **flow-diagram** will show numbers of individuals at each stage of the study (potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed).
Reasons for non-participation at each stage will be reported.
A flow-diagram will be used.

b) Descriptive data

Characteristics of study participants will be reported. A preliminary descriptive analysis will be performed with stratification in the three major subgroups: DBD grafts, high risk DBD grafts (Extended Criteria Donor grafts), LD grafts. Donor Risk Index[46], Euro-transplant Donor Risk Index[47], MELD,[48], UK-DCD risk score,[49] MELDNa,[50] D-MELD[51-52], SOFT score[53], Balance Risk Score[54], and Liver Retransplantation Risk Score[55] will be computed.

c) Outcome data

Numbers of outcome events will be reported

d) Main results

Results will be described concerning to the primary and secondary endpoints. Evidences from univariate and multivariate will be used to built the model. The model will be adjusted for confounders.
A stratification of main results according to the four graft types (DBD, high-risk DBD, DCD, LD grafts) will be performed.

The study does not require dedicated funding from the National Health System as it will be conducted within the clinical practice of the Liver Transplant Unit of Policlinico Universitario A. Gemelli and of the other enrolled Liver Transplant Centers. Research funds from the Catholic University of Rome will cover the development of the eCRF, the data collection and the statistical analysis.

5) LOGISTIC ASPECTS

a) **Informed consent** and **data storage**

For the prospectively enrolled patients, **formal consent** to participate in the research project will be sought at patient admission for transplant. Patients will be informed of the study's observational design and that further analysis will be performed using de-identified aggregate data.
The data of transplant patients who did not give their consent will be anonymously recorded only for alignment of the progressive number and not included in the study. These patients will not be included in the Center's count of the target number of enrolled patients (50 patients).
The consent form will summarize the aim of the study, the list of parameters that should be collected, and the procedures that will be performed in the donor and in the recipient, including biopsy of the donor, CT scan of the recipient, tests for the calculation of frailty of the recipient. The consent forms will be stored at the participating centers' archives for 5 years, and then destroyed.
Due to the observational design of the study, **in the retrospective cohort no specific consent will be obtained**. At time of transplant, all patients signed a consent for the use of their clinical and outcome data.

b) **Biopsy of the graft**

Since biopsy of the graft in the donor is suggested, a systematic assessment of graft quality according to histopathological parameters (steatosis, vacuolization, necrosis, vacuolization, Suzuki score,[56] fibrosis)

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should be performed in the prospective cohort. Bile duct damage[57] will be evaluated on high-risk grafts [the risk threshold should be defined later according to the incidences] and on failed grafts. The biopsy will be performed at the back-table procedure. Two needle biopsies (left and right lobe) should done for research purposes. A further re-assessment of histopathological parameters should be performed in each case of graft dysfunction requiring a biopsy (rejection, cholangitis) in those with graft failure (graft hepatectomy in case of re-transplant, necroscopy in case of death without retransplant).
The quantification of steatosis degree and the calculation of the Suzuki score will be performed through centralized review of slides and uploaded on the eCRF.
In case of transplant from a living donor, the biopsy should be performed using a knife, to obtain a wedge biopsy 1 cm deep and 1 cm wide at the edge of the right lobe of the liver, close to the transection plane during the donor hepatectomy, just before parenchymal transection.
The biopsy specimens should be fixed in formalin, embedded in paraffin, and cut with serial sections of 3 to 4 μm thickness. The slides should be stained with hematoxylin-eosin and Masson's trichrome.
The slides obtained for each wedge biopsy should be uploaded, through a digital slide-scanner, on the web CRF for the centralized lecture. The acquisition should be set at 40x resolution (compressed modality); however, a 20x resolution is accepted.
A formal histopathological report will be uploaded on the eCRF within five working days by the pathologists at the coordinating center and be available to the data manager of the referring center for clinical use.
A similar approach will be adopted in any case of liver biopsy according to the center practice performed during the initial 10 post-operative days.
Moreover, centers should store five unstained sections for each liver biopsy to ensure high standard quality in case of an inadequate scanner or further studies.

c) Severity of disease and co-morbidities in the recipient

The conditions of the recipient at the time of transplant play a relevant role in the process of graft function recovery. Furthermore, to list patients for retransplant, the accurate evaluation of severity of liver disease and the degree of extra-hepatic involvement are crucial in the decision process. This aspect has not been investigated on a multicenter basis.

The components of the patient risk indicators (MELD,[49] MELDNa,[50] FRAILTY-index,[58-59], CAD-index,[60] modified Charlson comorbidity index,[61] ASA class,[62] and SOFA score[63]) will be recorded using keyboard input. To simplify the data collection, the eCRF will avoid re-inputing of data previously entered. The scores will be automatically calculated by the eCRF. All data should be recorded prospectively on a real time basis.

The quantification of sarcopenia and visceral adipose tissue will be obtained through centralized review of CT-scan uploaded on the eCRF.

Particular attention should be reserved to:

a. Nutritional evaluation of the recipient (prospective cohort)

The nutritional status will be assessed by:

1. the CONUT score[64] (calculated through albumin, cholesterol, and lymphocyte count during the workup and at listing for re-transplant)
2. the Visceral Adipose Tissue (VAT)[65] score (calculated through CT-scan). The CT-scan performed during the pre-transplant workup should be uploaded on the eCRF. Dicom images obtained through CT-scan will be analyzed for tissue cross sectional area (cm) using the Slice-O-Matic software (Tomovision, Montreal, Quebec, Canada).

b. Frailty evaluation of the recipient (prospective cohort)

The frailty evaluation will be based on to the Liver Frailty Index[58-59].

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The frailty evaluation should be performed within 60 days before transplant. Seven new data entries are required to calculate the frailty index (gender is not considered being recorded before).

c. **Sarcopenia evaluation of the recipient (centralized radiological review of CT-scans)** (mandatory in the prospective cohort and optional in the retrospective cohort)
Sarcopenia will be assessed measuring the Total Psoas Area (TPA) at the 3rd lumbar vertebra.[68-69] The values will be uploaded on the eCRF. Further CT-scans performed after transplant will be uploaded in case of listing for re-transplant. TPA will be calculated according to the formula: Psoas muscle area/height (mm^2/m^2). The psoas muscle area corresponds to the sum of the areas of the left and right psoas muscles.

d. **Cardiac risk evaluation of the recipient** (prospective cohort)
Cardiac risk evaluation will be based on the pre-transplant ejection fraction (ultrasounds) and Coronary Artery Disease Liver Transplant score.[59] At day 3 the ejection fraction will be evaluated and recorded together with noradrenalin dosages.

e. **Renal function evaluation of the recipient** (prospective cohort)
The evaluation of the RENAL RISK will be based on

1. the preoperative creatinine (at transplant)
2. kidney support during last 72 hours before transplant (no support, continuous arterial venous [CAV]; hemodialysis
3. creatinine at day 3, creatinine at day 5
4. albuminuria at day 3, albuminuria at day 5

The Acute kidney injury (AKI) risk score[69] will be calculated by the eCRF at day 1. The RIFLE score[70] and the albuminuria/creatinine ratio[71-72] at day 1 and day 3 will calculated by the eCRF. Consideration of time to dialysis independence post-LT will be evaluated in recipients with pre-LT renal failure or those who develop post-LT renal failure requiring RRT.

f. **ICU and respiratory risk evaluation of the recipient** (prospective cohort)
The evaluation of the ICU risk will be based on:

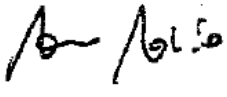
1. SOFA score[63] at ICU admission, day 3
2. lactate at ICU admission, day 3, day 5
3. Glasgow coma score[73] day 3
4. mean arterial pressure day 3
5. noradrenaline infusion, day 3
6. ejection fraction, day 3

The evaluation of the respiratory risk will be assessed on evidence of:

i. lung support during last 72 hours before transplant (no support, non-invasive ventilation [NIV], Continuous positive airway pressure therapy [CPAP], mechanical ventilation)
ii. on postoperative day 3 FiO_2, PaO_2, mechanical ventilation, extubation failure, weaning failure[74]

g. **Infectious risk evaluation of the recipient** (prospective cohort)
Infectious events[75] will be stratified as follows

- Bacteremia with fever and bacterial isolation which required antibiotic treatments;
- Liver and abdominal abscesses that required percutaneous or surgical drain and antibiotic treatments;
- Septic events with systemic relevance (e.g., multiple sites) without hemodynamic alterations;
- Septic shock with major hemodynamic alterations requiring ventilatory assistance and intravenous vasoactive drug administration.



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The site of infections should be identified. Relevant post-operative infectious events (liver parenchyma, bile tree, abdomen, lung, urinary tract, brain) should be registered in the prospective cohort.

h. Stratification according to postoperative complications

Postoperative complications will be stratified according to:

1. Clavien Dindo class[76] (if possible in the prospective and retrospective cohorts)
2. Comprehensive Complication Index[77-78] (only in the prospective cohort).

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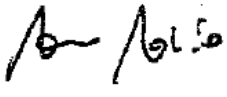

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Rome, 27/11/2021 Alfonso W Avolio for the Steering Committee

Prot. ID 4571
Chiar.mo Prof. Salvatore AGNES
Direttore U.O.C. CHIRURGIA GENERALE E DEL TRAPIANTO DI FEGATO

Chiar.mo Prof. Alfonso Wolfango AVOLIO
U.O.C. CHIRURGIA GENERALE E DEL TRAPIANTO DI FEGATO

S E D E

Riunione del 2/12/2021

Membri presenti :
Prof. Andrea BACIGALUPO, *Clinico Ematologo. Presidente*
Prof.ssa Stefania BOCCIA, *Biostatistico. Vicepresidente*
Dott. Paolo Angelo BONINI, *Esperto di Bioetica*
Prof. Emilio BRIA, *Clinico - Oncologia*
Prof. Alessandro CARUSO, *Clinico - Ostetricia e Ginecologia*
Dr. Antonello COCCHIERI, *Rappresentante dell'area delle professioni sanitarie*
Dott. Alessio DE LUCA, *Farmacista SSR1*
Dott. Francesco FILIDORO, *Farmacista esperto di Dispositivi Medici*
Avv. Danilo GALLITELLI, *Esperto in materia giuridica e assicurativa o Medico legale*
Prof.ssa Fiorella GURRIERI, *Esperto di Genetica*
Dott. Michele LEPORE, *Medico di Medicina Generale*
Prof.ssa Giuseppina LOFFREDI, *Rappresentante del Volontariato\ Associazione Tutela Pazienti*
Prof. Camillo MARRA, *Clinico - Neurologia*
Dott.ssa Barbara MEINI, *Farmacista SSR1*
Prof.ssa Nadia MORES, *Sostituto permanente del Direttore Sanitario*
Prof.ssa Ketty PERIS, *Clinico - Dermatologo*
Prof. Giacomo POZZOLI, *Farmacologo*
Prof. Riccardo RICCARDI, *Pediatra*
Prof. Dario SACCHINI, *Esperto di Bioetica*

Membri assenti :
Prof. Sebastiano FILETTI, *Clinico - Chirurgia*
Prof. Giovanni SCAMBIA, *Direttore Scientifico*

Membri esterni :
Avv. Filippo E. LEONE, *Responsabile Grant Office*

I componenti hanno preliminarmente dichiarato di non pronunciarsi per quelle sperimentazioni per le quali possa sussistere un conflitto d'interesse di tipo diretto o indiretto.

Il Comitato Etico, riunito lo 02/12/2021 per esprimere il proprio parere etico motivato sullo studio **Prot. THE IMPROVEMENT study** presentato dal prof. **Avolio Alfonso Wolfango**, relativo alla ricerca **'Studio internazionale multicentrico, prospettico, non-competitivo, osservazionale, finalizzato a validare e**

perfezionare i modelli predittivi a 90 giorni ed a un anno del fallimento dopo trapianto epatico'

ESAMINATA

la documentazione presentata in risposta alle criticità espresse da codesto Comitato Etico nella seduta dell'11/11/2021:

- Protocollo di studio in esteso (versione del 27/11/2021)
- Sinossi del protocollo (versione citata come 29/11/2021)
- Appendice A: definizioni e abbreviazioni
- Appendice B
- Appendice C
- STROBE Statement—Checklist of items that should be included in reports of *cohort studie*
- Lettera di risposta del PI
- Modulo per il consenso informato (versione 2.0 del 30/11/2021)
- Consenso per il trattamento dei dati personali (versione 2.0 del 30/11/2021)

e la documentazione presentata e approvata da codesto Comitato Etico nella seduta dell'11/11/2021:

- Modulistica Studi con Promotore No Profit
- Curricula del ricercatore e collaboratore
- Dichiarazione conflitto di interesse sperimentatore (versione del 14/10/2021)
- Elenco centri partecipanti
- Certificato corso GCP del PI

CONSTATATO CHE

il protocollo presentato:

- è giustificato scientificamente ed eticamente quanto al razionale, obiettivi;
- è giustificato quanto al disegno sperimentale;
- è giustificato quanto ai soggetti di sperimentazione;
- è giustificato quanto al rapporto rischi/benefici;
- è giustificato quanto alle informazioni fornite ai soggetti e alle modalità di richiesta del consenso;
- è giustificato quanto agli esami valutativi previsti;
- è giustificato quanto alla qualificazione del ricercatore e/o delle strutture e attrezzature disponibili;
- è giustificato quanto ai costi economici aggiuntivi per l'Ente;
- è giustificato in quanto alla numerosità campionaria e all'indagine statistica;
- è giustificato quanto alle garanzie assicurative;
- è rispettoso dei principi dell'Ente;
- fa riferimento ai codici deontologici (in particolare alla revisione corrente della dichiarazione di Helsinki e/o alle Norme di Buona Pratica Clinica (ICH-GCP) secondo l'all. 1 al D.M. 15.7.97) ed a tutta la normativa vigente;
- è conforme alle disposizioni di legge ed alle conseguenti raccomandazioni del Comitato Etico dell'Ente in materia di rispetto della privacy

ESPRIME PARERE FAVOREVOLE

Il presente parere è stato espresso all'unanimità.

Si ricorda allo sperimentatore con afferenza universitaria l'obbligo di notificare questa approvazione presso il proprio Dipartimento Universitario per gli adempimenti previsti.

Si richiede che questo Comitato Etico venga informato dell'inizio della sperimentazione, del suo svolgimento con una relazione annuale e della sua conclusione o eventuale interruzione. Inoltre dovrà essere informato di ogni successivo emendamento al protocollo.

Si dichiara che questo Comitato ricostituito ai sensi del DM 8 febbraio 2013 è organizzato ed opera nel rispetto delle norme di buona pratica clinica (GCP-ICH) e degli adempimenti previsti dalla normativa vigente.

Si fa presente che lo studio potrà avere inizio a seguito del rilascio della delibera amministrativa.

Il Presidente del Comitato Etico
Prof. Andrea Bacigalupo

APPENDIX A. Definitions

ALLOGRAFT FAILURE
The failure of the liver graft at 90 days or 365 days for any cause which lead to retransplant or death.[1-2]

DBD
donor after brain death

DCD
donor after cardiac death

SPLIT[3]
In the common approach of the split liver procedure, liver is divided into a left lateral segment graft (LLS, segments 1, 2 and 3) to be transplanted to a child and a right extended liver lobe graft for an adult recipient (4, 5, 6, 7, 8). In conventional techniques, usually the middle hepatic vein is retained with the left graft and the vena cava with the right graft. The indispensable division of the caudate lobe veins lead to uncertain variability of the segment 1, and resection might by necessary. Segment 1 could be included or not into the left lateral graft.
In a technically more challenging variant of this procedure, the principle is to split the liver into 2 hemigrafts and use the left side (segments 2, 3, 4) for a small adult or a teenager and the right (segments 5, 6, 7, 8) for a medium-sized adult patient.

PERFUSION MACHINES TYPES
- hypothermic machine perfusion (with or without active oxygenation)[4]
- dual hypothermic machine perfusion[5]
- normothermic machine perfusion[6]
- ischemia free organ transplant[7]

ISCHEMIA-FREE ORGAN TRANSPLANT (IFOT)[7]
In this novel procedure, the graft is procured, preserved, and implanted under continuous normothermic machine perfusion. The recipient will not suffer post-reperfusion syndrome or vasoplegia after revascularization of the allograft.

COLD ISCHEMIA TIME (minutes)
Cold ischemia time was defined as “the time between the cold perfusion of the liver is commenced at the cross-clamping and the time the organ is taken out from the cold storage for implantation.

WARM ISCHEMIA TIME (minutes)
Warm ischemia time was defined as “the time a tissue, organ, or body part remains at body temperature after its blood supply has been reduced or cut off”.

DONOR WARM ISCHEMIA TIME (minutes)
Donor WIT was defined as “time elapsed since the onset of hypotension (when systolic blood pressure falls <50 mm Hg) or hypoxemia (desaturation with SpO2 < 80% measured by pulse oximetry)—whichever comes first—until the cold arterial flush is started in the donor.[8]

DONOR ASYSTOLIC WARM ISCHEMIA TIME (minutes)
Donor Asystolic Warm Ischemia Time was defined as time from circulatory death to cold in-situ flush[9]

RECIPIENT WARM ISCHEMIA TIME
Recipient WIT was defined as “time elapsed since placing the graft in the abdomen of the recipient until the warm portal flow is started in the recipient”

SARCOPENIA
-Sarcopenia is the degenerative loss of muscle mass, strength, and function. It has been associated with worse short-term and long-term outcomes after liver transplantation and after surgery across a wide range of cancers, such as colorectal, gastric, esophageal, pancreatic, and liver.
-Sarcopenia was defined by reduced muscle mass and strength as recommended recently by the European Working Group on Sarcopenia in Older People (EWGSOP)[10]

FRAILTY
Aging-related syndrome of physiological decline, characterized by marked vulnerability to adverse health outcomes.[11]

RESPIRATORY FAILURE

Pts could present weaning failure (WF) if they not fulfill weaning criteria at 48 h after transplant or extubation failure (EF) patients if they were extubated within 48 hours but requires the reinstitution of mechanical ventilation (reintubation or non-invasive ventilation).[12]

HEART FAILURE/DYSFUNCTION
HF is a clinical syndrome with symptoms and or signs caused by a structural and/or functional cardiac abnormality and corroborated by elevated natriuretic peptide levels and or objective evidence of pulmonary or systemic congestion (European Society of Cardiology)

RENAL DYSFUNCTION
Renal dysfunction is defined as a glomerular filtration rate <60 mL/min and/or the presence of albuminuria >30 mg/d

RENAL FAILURE
Also known as end-stage kidney disease, is a medical condition in which the glomerular filtration rate is less than 15% of normal levels. (

POST REPERFUSION SYNDROME (PRP)
After unclamping the inflow (portal vein and or hepatic artery) we classified mild Post Reperfusion Syndrome as <30% decline of MAP or heart rate lasting <5 minutes that is responsive to an intravenous bolus dose of calcium chloride (1 g) or epinephrine (100 mg) without the need to start a continuous infusion of vasopressors. We also classified significant PRS as a >30% drop in MAP or heart rate, asystole, or hemodynamically significant arrhythmias or the need for continuous infusion of vasopressors during the intraoperative period.[14]

SEPSIS[15]
Sepsis should be defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. For clinical operationalization, organ dysfunction can be represented by an increase in the Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score of 2 points or more, which is associated with an in-hospital mortality greater than 10%.

SEPTIC SHOCK[15]
Septic shock should be defined as a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone. Patients with septic shock can be clinically identified by a vasopressor requirement to maintain a mean arterial pressure of 65mmHg or greater and serum lactate level greater than 2 mmol/L (>18 mg/dL) in the absence of hypovolemia.[14]

PATIENT SURVIVAL
Patient survival is defined as time from transplant to patient death, censoring for death at time of analysis.

GRAFT SURVIVAL
Graft survival is defined as time from transplant to graft failure or patient death, censoring for retransplant or death at time of analysis. The death of a patient for any reason will include by definition the failure of the graft and the end of both patient survival and graft survival.

eCRF
Electronic case report form.

POD
Post-operative day

NIV
Non invasive ventilation

CPAP
Continuous positive airway pressure therapy

CAV
Continuous arterial-venous hemodialysis

LENGTH OF STAY IN HOSPITAL[16]
Number of days in hospital considering either patients who are discharged and patients how die in the hospital.

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Table

List of the parameters in the two COHORTS

		PROSPECTIVE COHORT					**RETROSPECTIVE COHORT**	
N	**SECTION**	**Variable Name**	**Variable and code's decription**	**Variable Type**	**N**	**de**	**Variable Name**	**N**
1	**ID**	CENTER_ID	CENTER_ID (it will be attributed by the coordinator Center)	CODE	4		CENTER_ID	1
2	**ID**	CENTER_PROG_N	CENTER_PROG_N_of_transplant. All cases in the study period should be included	N	4		CENTER_PROG_N	2
3	**ID**	COUNTRY_CODE	**SPECIFY COUNTRY CODE according to telephone code**	Choice	4		COUNTRY_CODE	3
4	**ID**	RECIPIENT_CODE	Starting 4 letters of surname (SMIT for SMITH) optional	NOTE	4		RECIPIENT_4_LETTERS	4
5	**ID**	PROSPECTIVE_EN	0=PROSPECTIVE; 1=RETROSPECTIVE	Dichotomic	1		PROSPECTIVE_EN	5
6	**ID**	TX_DATE	Date of the Transplant (or re-transplant)	DATE	8		TX_DATE	6
7	**ID**	TX_Type	0=standard: 1=DOMINO; 5=ReTransplant; ~~2=KIDNEY COMBINED~~; 3=HEART COMBINED; 4=Living Donor Tx; 6=other	Choice	1		TX_Type	7
8	**DONOR**	Age_donor	Age of the donor (years)	Number	2		Age_donor	8
9	**DONOR**	Sex_donor	Sex of the donor (genotype)	Number	1		Gender_donor	9
10	**DONOR**	Weight_donor	Weight of the donor (Kg or lb)	Number	2		Weigth_donor	10
11	**DONOR**	Height_donor	Height of the recipient (cm)	Number	2		Heigth_donor	11
	~~**DONOR**~~	~~Girth_donor (optional)~~	~~Girth of the donor (cm)~~	~~Number~~				
12	**DONOR**	Ethnicity_donor	1=Caucasian; 2=African-American, 3=Asian, 4=Hispanic, 5=Other	Choice	1		Ethnicity	12
13	**DONOR**	Cause_Death	Cause of Death: Trauma, Anoxia, CerebroVascular Accident, Other	Choice	1		Cause_Death	14
14	**DONOR**	Location	Local, National, Regional	Choice	1		Location	15
15	**DONOR**	SPLIT_right_hemiliver	0=no SPLIT; 1=SPLIT_right_hemiliver	Dichotomic	1		SPLIT_right_hemiliver	16
	DONOR	**AB0_incompatible**	**0=no AB0_incompatible; 1=AB0_incompatible**	**Dichotomic**				
16	**DONOR**	DCD	0=no DCD; 1=DBD	Dichotomic	1		DCD	17
17	**DONOR**	Controlled_DCD	0=uncontrolled_DCD; 1=controlled DCD	Dichotomic			Controlled_DCD	18
18	**DONOR**	LDTx	0=no LD; 1=LDTx (LIVING DONOR GRAFT)	Dichotomic			LDTx	19
19	**DONOR**	MP	0=no MP; 1=MP	Dichotomic	1		MP	20
20	**DONOR**	MP_type	1=HOPE, 2=DUAL HOPE, 3=NORMOTHERMIC; **4=IN SITU NORMOTHERMIC REGIONAL PERFUSION**; 5=ISCHEMIA FREE; 6=OTHER	Choice	1		MP_type	21
___	**DONOR**	Macro_STEATOSIS_%	It should be populated after Central revision of slides	Number	3		Macro_STEATOSIS_%	22
___	**DONOR**	Suzuki_score	It should be populated after Central revision of slides	Number	2			
___	**DONOR**	BIOPSY_other	It should be populated after Central revision of slides	Note	30		BIOPSY_other	23
21	**DONOR**	DONOR_NOTE	DONOR_NOTE	Note	30		DONOR_NOTE	24
22	**DONOR**	DONOR_TLV	Donor Total Liver Volume (at CT-scan) /option NOT AVAILABLE	Number	4			
23	**DONOR**	Donor_**t**WIT	Donor Total Warm Ischemia Time* (minutes): from withdrawal of treatment to cold flush (in case of NRP: from withdrawal of treatment to initiation of NRP perfusion)	Number	3		Donor_TWIT	25
24	**DONOR**	Donor_**fWIT**	Donor Functional Warm Ischemia Time (minutes) is defined between		3		Donor_**fWIT**	26

			the timepoint where either/or: **▪ Spo2 <80%** **▪ MAP <60 mm Hg** **and the start of cold flush (in case of NRP: from either/or the Spo2 <80% MAP <60 mm Hg to the initiation of perfusion)**					
~~24~~	~~**DONOR**~~	~~Donor_AWIT~~	~~Donor Asystolic Warm Ischemia Time (minutes)~~	~~Number~~	~~3~~		~~Donor_AWIT~~	~~26~~
25	**DONOR**	Donor_HT	Time from flush to liver out of the body, for the standard super-rapid retrieval technique (minutes)	Number	2		Donor_HT	26bis
26	**DONOR**	GRWR	Graft-to-recipient weight ratio (GRWR) calculated field	Number	3	1	GRWR	
27	**Re pre-Op**	Age_recipient	Age of the recipient in years	Number	2		Age_recipient	27
28	**Re pre-Op**	Sex_recipient	Sex of the recipient (genotype)	Number	1		Sex_recipient	28
29	**Re pre-Op**	Weight_recipient	Weight of the recipient including ascites (Kg)	Number	2		Weigth_recipient	29
30	**Re pre-Op**	Height_recipient	Height of the recipient (cm)	Number	2		Heigth_recipient	30
31	**Re pre-Op**	Ethnicity_recipient	Caucasian, African-American, Asian, Hispanic, Other	Choice	1		Ethnicity	31
32	**Re pre-Op**	Indication_code	**SPECIFIED in TABLE**	Choice	1		Indication_code	32
33	**Re pre-Op**	Indication_note	Note	Note	1		Indication_note	33
34	**Re pre-Op**	HCC_coindication	0=no HCC; 1=HCC	Dichotomic	1		HCC_coindication	34
35	**Re pre-Op**	HCC_stage	0=T0; 1=T1; 2=T2; 3=T3	Choice	1		HCC_stage	35
36	**Re pre-Op**	PVT_Yerdel	1=Yerdel 1; 2=Yerdel 2; 3=Yerdel 3; 4=Yerdel 4	Choice	1		PVT_Yerdel	36
37	**Re pre-Op**	Bilirubin_Tx	Bilirubin at Transplant	Number	4			
38	**Re pre-Op**	Creatinine_Tx	Creatinine at Transplant	Number	3			
39	**Re pre-Op**	INR_Tx	INR at Transplant	Number	3			
400	**Re pre-Op**	Na_Tx	Na at Transplant	Number	3			
41	**Re pre-Op**	Albumin_Tx	Albumin at Transplant	Number	3		Albumin at Transplant	
42	**Re pre-Op**	AFT_Tx	Alpha-fetoprotein at transplant	Number	3			
43	**Re pre-Op**	LIST_DATE	DATE_OF_LIST	Date	8			
___	**Re pre-Op**	MELD_Tx	MELD at Transplant (calculated field)				MELD_Tx (alternative to MELD components)	37
___	**Re pre-Op**	MELDNa_Tx	MELDNa at Transplant (calculated field)				MELD_Na (alternative to MELD components)	38
44	**Re pre-Op**	PreTx-MAS	Pre-transplant-Major Abdominal Surgery	Choice	1		PreTx-MAS	39
45	**Re pre-Op**	PreTx-RRT	pre-transplant renal replacement therapy. 0=never, 1=sometimes in last month; 2=started during last 72h; 3=started during last week	Choice	1		optional	40
46	**Re pre-Op**	Diabetes	0=no diabetes; 1=diabetes	Dichotomic	1		optional	41
47	**Re pre-Op**	Insulin_Dependent_Diabetes	0=no Insulin Dependent Diabetes; 1=Insulin Dep Diabetes	Dichotomic	1		optional	42
48	**Re pre-Op**	Hypertension	0=no Hypertension; 1=Hypertension	Dichotomic	1		optional	43
49	**Re pre-Op**	Ejection Fraction %	Ejection Fraction % at pre-transplant echocardiography	Number	4			
___	**Re pre-Op**	CAD-LT_score	Coranary Artery Disease Score for Liver Transplant (calculated field)		1			
50	**Re pre-Op**	Tobacco_years	Tobacco Pack Years (1=0-20; 2=21-40; 3= >40)	Number	1			
51	**Re pre-Op**	Family_CAD	Family History of Coronary Artery Disease	Dichotomic	1			

52	**Re pre-Op**	Personal_CAD	Personal History of Coronary Artery Disease	Dichotomic	1			
53	**Re pre-Op**	Stent_Num	0=no; 1=1 stent; 2=2 stents; 3=3 stents	Number	1	1		
___	**Re pre-Op**	Frailty_Index (calculated field)	Lai J et al		3			
___	**Re pre-Op**	Sex (already recorded)	Sex (already recorded)					
54	**Re pre-Op**	Hand_strength_1	Hand grip strength (Kg) attempt 1	Number				
55	**Re pre-Op**	Hand_strength_2	Hand grip strength (Kg) attempt 2	Number				
56	**Re pre-Op**	Hand_strength_3	Hand grip strength (Kg) attempt 3	Number				
57	**Re pre-Op**	Sec_5_chair_sta	Time to do 5 chair stands	Number				
58	**Re pre-Op**	Sec_SIDE_posit	Seconds SIDE position	Number				
59	**Re pre-Op**	Sec_SEMI-TANDEM	Seconds SEMI-TANDEM position	Number				
60	**Re pre-Op**	Sec_TANDEM	Seconds TANDEM position	Number				
61	**Re pre-Op**	FRAILTY_assessment_date	FRAILTY_assessment_date	DATE	8			
___	**Re pre-Op**	TPA	Total Psoas Area = Psoas muscle area/height (mm2/m2) THE MODALITY OF CALCULATION (on CT-scan or MRI-scan; locally or centrally, should be defined)	Number	4			
___	**Re pre-Op**	VAT	Visceral Adipose Tissue THE MODALITY OF CALCULATION (on CT-scan or MRI-scan; locally or centrally, should be defined)	Number	4			
62	**Re pre-Op**	TPA/VAT_Imaging_date	Last CT-scan date	DATE	8			
63	**Re pre-Op**	ASA_PS_class_beside_liver	1 healthy patient; 2 patient with mild systemic disease; 3 a patient with severe systemic disease; 4 patient with severe systemic disease that is a consistent threat to life; 5 moribund patient who is not expected to survive without the operation	Choice	1	0		
64	**Re pre-Op**	Lung_support_previous_3_dd	0=no; 1=NIV; 2=CPAP; 3=Mechanical Ventilation	Choice	1		Lung_support_previous_3_dd	44
65	**Re pre-Op**	Kidney_supp_previous_3_dd	0=no; 1=CAV; 2=HD	Choice	1		Kidney_supp_previous_3_dd	45
___	**Re pre-Op**	Modified Charlson Comorbidity Index	Calculated Field	Choice	1			
66	**Re pre-Op**	Congestive Heart Failure	Congestive Heart Failure 0=no; 1=yes	Choice	1			
67	**Re pre-Op**	Coronary artery disese	Coronary artery disese 0=no; 1=yes (calculated field)	Choice	1			
68	**Re pre-Op**	Diabetes mellitus	Diabetes mellitus 0=no; 1=yes	Choice	1			
69	**Re pre-Op**	Peripheral vascular disease	Peripheral vascular disease 0=no; 1=yes	Choice	1			
70	**Re pre-Op**	Cerebral vascular accident	Cerebral vascular accident 0=no; 1=yes	Choice	1			
71	**Re pre-Op**	Chronic obstructive pulmonary dis	Chronic obstructive pulmonary dis 0=no; 1=yes	Choice	1			
72	**Re pre-Op**	Connective tissue disease	Connective tissue disease 0=no; 1=yes	Choice	1			
73	**Re pre-Op**	Creatinine >1.5	Calculated field					
74	**Re pre-Op**	History of Malignancy	History of Malignancy 0=no; 1=yes	Choice	1			
75	**Intra-Op**	Hold Donor DCD parameter	Hold Donor DCD ischemia parameter (to be defined)	Number	3		Hold Donor DCD parameter	46
76	**Intra-Op**	CIT	Cold Ischemia Time	Number	3		CIT	47
77	**Intra-Op**	rWIT	recipient Warm Ischemia Time	Number	3		WIT	48
78	**Intra-Op**	PRBC	Packed Red Blood Units transfused during surgery	Number	2		PRBC	49

79	**Intra-Op**	Cell_Saver	Cell_Saver_Use (yes/no)	Choice	1			
80	**Intra-Op**	FFP	Fresh Frozen Plasma Units transfused during surgery	Number	1		FFP (optional)	50
81	**Intra-Op**	PLT	Platelets Units transfused during surgery	Number	1		PLT (optional)	51
82	**Intra-Op**	Portal reconstruction	Jump graft (Yes or not)	Choice	1		optional	52
83	**Intra-Op**	Arterial reconstruction	Number of arterial anastomosis (1-4)	Number	1		optional	53
84	**Intra-Op**	AHC	Aorto-Hepatic Conduit (Yes, No)	Dichotomic	1		optional	54
85	**Intra-Op**	AL	Arcuate_Legament_Management (preservation of gastroduodenal artery; release of arcuate legament, aorto-celiac anastomosis, standard Center anastomosis)	Choice	4		optional	55
86	**Intra-Op**	PRS	Post-Reperfusion Syndrome (none, **mild**, severe)	Choice	1		optional	56
87	**Intra-Op**	BA	Biliary anastomosis (duct to duct interrupted sutures; duct to duct continuous sutures, Roux en Y)	Choice	3		optional	57
88	**Intra-Op**	**Cardiac_Arrest_Reperfusion**	**CARDIAC ARREST AT REPERFUSION**	Choice	1		optional	
89	**Intra-Op**	IntraOp_NOTES	Intraoperative details (VVBP, Veno-venous bypass; TPC, Temporary Porto-cava shunt, ...)	Note	30		IntraOp_NOTES	58
90	**Post-Op**	PaO2_1_POD	PaO2 day 1 post-operative	Number				
91	**Post-Op**	FiO2_1_POD	FiO2 day 1 post-operative	Number				
92		Glasgow EYE 1 POD	Glasgow Coma EYE 1 POD					
93		Glasgow VERBAL RESPONSE 1 POD	Glasgow Coma VERBAL RESPONSE 1 POD					
94	**Post-Op**	Glasgow MOTOR RESPON 1 POD	Glasgow Coma BEST MOTOR RESPON 1 POD	Choice	1			
		GLASGOW_COMA_SCALE 1 POD	(CALCULATED FIELD)					
95	**Post-Op**	MAP70_1_POD	Mean arterial pressure > or < 70 at day 1	Choice	1			
96	**Post-Op**	Dopamine_1_POD	dopamine day 1 ≤ 5 µg/kg/min or dobutamine (any dose) dopamine day 1 > 5 µg/kg/min OR epinephrine ≤ 0.1 µg/kg/min OR norepinephrine ≤ 0.1 µg/kg/min	Choice	1			
97	**Post-Op**	SOFA_1_POD	SOFA day 1 ICU – calculated field	Number				
98	**Post-Op**	PaO2 3 POD	PaO2 day 3 post-operative	Number	3			
99	**Post-Op**	FiO2 3 POD	FiO2 day 3 post-operative	Number	3			
100	**Post-Op**	Glasgow Coma EYE 3 POD	Glasgow Coma EYE Scale day 3 post-operative94	Choice	1			
101		Glasgow Coma VERBAL RESPONSE 3 POD						
102		Glasgow Coma BEST MOTOR RESPON 3 POD						
		GLASGOW_COMA_SCALE 3 POD	(CALCULATED FIELD)	GLASGOW_COMA_SCALE				
103	**Post-Op**	MAP70_3_POD	Mean arterial pressure > or < 70 at day 1	Choice	1			
104	**Post-Op**	Dopamine_3_POD	dopamine day 3 ≤ 5 µg/kg/min or dobutamine (any dose)	Choice	1			

			dopamine day 3 > 5 µg/kg/min OR epinephrine ≤ 0.1 µg/kg/min OR norepinephrine ≤ 0.1 µg/kg/min					
105	**Post-Op**	SOFA score 3 POD	SOFA day 3 post-operative – calculated field					
106	**Post-Op**	Mechanical Ventilation 3 POD (already recorded)	Mechanical Ventilation day 3 post-operative (already recorded)					
107	**Post-Op**	Platelets 3 POD (already recorded)	Platelets day 3 post-operative (already recorded)					
108	**Post-Op**	Bilirubin 3 POD (already recorded)	Bilirubin (ICU admission day 3 post-operative					
109	**Post-Op**	Creatinine 3 POD	Creatinine day 3 post-operative	Number				
___	**Post-Op**	RIFLE day 3 POD	RIFLE (or AKIN) day 3 calculated field					
___	**Post-Op**	Albuminuria/creatinine ratio_d3	Albuminuria/creatinine ratio day 3 post-operative (calculated field)					
110	**Post-Op**	Albuminuria 5 POD	Albuminuria at day 5 post-operative					
111	**Post-Op**	Creatinine 5 POD	Creatinine at day 5 post-operative	Number				
___	**Post-Op**	Albuminuria/creatinine ratio_d3	Albuminuria/creatinine ratio at day 5 (calculated field)					
___	**Post-Op**	RIFLE day 5 POD	RIFLE (or AKIN) day 3 calculated field					
112	**Post-Op**	Lactate 1 POD	Lactate day 1	Number				
113	**Post-Op**	Lactate 3 POD	Lactate day 3	Number				
114	**Post-Op**	Lactate 5 POD	Lactate day 5	Number				
115	**Post-Op**	Ejection_fraction_3_POD	Ejection_fraction_day_3	Number				
116	**Post-Op**	Noradrenalin_dose_3_POD	Noradrenalin dose day 3	Number				
117	**Post-Op**	AST_1_POD	AST at day 1 post-operative	Number	5		AST_1_POD	59
118	**Post-Op**	AST_2_POD	AST at day 2 post-operative	Number	5		AST_2_POD	60
119	**Post-Op**	AST_3_POD	AST at day 3 post-operative	Number	5		AST_3_POD	61
120	**Post-Op**	AST_5_POD	AST at day 5 post-operative	Number	5		AST_5_POD	62
121	**Post-Op**	AST_6_POD	AST at day 6 post-operative	Number	5		AST_6_POD	63
122	**Post-Op**	AST_7_POD	AST at day 7 post-operative	Number	5		AST_7_POD	64
123	**Post-Op**	**AST_10_POD**	AST at day 10 post-operative	Number	5		AST_10_POD	65
124	**Post-Op**	ALT_1_POD	ALT at day 1 post-operative	Number	5		ALT_1_POD	66
125	**Post-Op**	ALT_2_POD	ALT at day 2 post-operative	Number	5		ALT_2_POD	67
126	**Post-Op**	ALT_3_POD	ALT at day 3 post-operative	Number	5		ALT_3_POD	68
127	**Post-Op**	ALT_5_POD	ALT at day 5 post-operative	Number	5		ALT_5_POD	69
128	**Post-Op**	ALT_6_POD	ALT at day 6 post-operative	Number	5		ALT_6_POD	70
129	**Post-Op**	ALT_7_POD	ALT at day 7 post-operative	Number	5		ALT_7_POD	71
130	**Post-Op**	**ALT_10_POD**	ALT at day 10 post-operative	Number	5		ALT_10_POD	72
131	**Post-Op**	PLAT_1_POD	Platelets count at day 1 post-operative	Number	3		PLAT_1_POD	73
132	**Post-Op**	PLAT_3_POD	Platelets count at day 3 post-operative	Number	3		PLAT_3_POD	74
133	**Post-Op**	PLAT_5_POD	Platelets count at day 5 post-operative	Number	3		PLAT_5_POD	75
134	**Post-Op**	PLAT_6_POD	Platelets count at day 6 post-operative	Number	3		PLAT_6_POD	76
135	**Post-Op**	PLAT_7_POD	Platelets count at day 7 post-operative	Number	3		PLAT_7_POD	77
136	**Post-Op**	PLAT_10_POD	Platelets count at day 10 post-operative	Number	3		PLAT_10_POD	78
137	**Post-Op**	BIL_1_POD	Bilirubin at day 1 post-operative	Number	4		BIL_1_POD	79

138	**Post-Op**	BIL_3_POD	Bilirubin at day 3 post-operative	Number	4		BIL_3_POD	80
139	**Post-Op**	BIL_5_POD	Bilirubin at day 5 post-operative	Number	4		BIL_5_POD	81
140	**Post-Op**	BIL_6_POD	Bilirubin at day 6 post-operative	Number	4		BIL_6_POD	82
141	**Post-Op**	BIL_7_POD	Bilirubin at day 7 post-operative	Number	4		BIL_7_POD	83
142	**Post-Op**	**BIL_10_POD**	**Bilirubin at day 10 post-operative**	Number	4		BIL_10_POD	84
143	**Post-Op**	Crea_7_POD	Creatinine at day 7 post-operative	Number	4			
144	**Post-Op**	**INR_1_POD**	**INR at day 1 post-operative**	Number	3	1	**INR_1_POD**	
145	**Post-Op**	**INR_3_POD**	**INR at day 3 post-operative**	Number	3	1	**INR_3_POD**	
146	**Post-Op**	**INR_5_POD**	**INR at day 5 post-operative**	Number	3	1	**INR_5_POD**	
147	**Post-Op**	**INR_6_POD**	**INR at day 6 post-operative**	Number	3	1	**INR_6_POD**	
132	**Post-Op**	**INR_7_POD**	**INR at day 7 post-operative**	Number	3	1	**INR_7_POD**	
133	**Post-Op**	**INR_10_POD**	**INR at day 10 post-operative**	Number	3	1	**INR_10_POD**	
134	**Post-Op**	RIFLE_7_POD	RIFLE (or AKIN) day 3 calculated field	Number	3	1		
135	**Post-Op**	Bleeding_complication	Bleeding complication requiring surgical intervention	Dichotomic	1			
136	**Post-Op**	Thrombosis_HV	Thrombosis of a hepatic vessel (artery, portal vein, cava)	Dichotomic	1		Thrombosis_HV	85
137	**Post-Op**	Respiratory_complication	1=Extubation failure; 2=Respiratory failure	Choice	1			
138	**Post-Op**	Days of invasive ventilation	Days of invasive ventilation (sum of different periods)	N	2			
139	**Post-Op**	Thrombosis type	**1**=Artery, **2**=PV,**3**= Cava; **4**=1+2; **5**=2+3	Choice	1		Thrombosis type	86
140	**Post-Op**	Endovascular treatment	0=no; 1=yes	Choice	1		Endovascular treatment	87
141	**Post-Op**	Endovascular treatment details	notes	Note	30		Endovascular treatment details	88
142	**Post-Op**	Anti-thrombotic prophylaxis	1.i.v. heparin; 2.subcutaneous heparin; 3.other	Choice	1		Anti-thrombotic prophylaxis	89
143	**Post-Op**	Rejection	0=no rej; 1=rej; 2=steroid resistent rej	Number	1			
144	**Post-Op**	Infection sites	1=liver; 2=abdominal extra-liver; 3=lung; 4=heart; 5=other	Multiple Choice	1			
145	**Post-Op**	Bacteremia_episodes	Number_of_bacteremia_episodes (0 to N)	N	1			
146	**Post-Op**	Sepsis_episodes	0=no; 1=yes	Dichotomic	1			
147	**Post-Op**	Septic shock	0=no; 1=yes	Dichotomic	1			
148	**Post-Op**	Viral infection	0=no; 1=yes	Dichotomic	1			
149	**Post-Op**	Viral_infection_note	Viral_infection_note	Note	30			
150	**Post-Op**	Post-operative course	Brief description of complicated post-operative course	Note	30		Post-operative course	90
151	**OUTCOME**	Clavien-Dindo	1=1; 2=2; 3=3A; 4=3B; 5=4A; 6=4B	Choice	3		Clavien-Dindo	91
152	**OUTCOME**	CCI	Comprehrensive Complication Index	Choice	3		Optional	92
153	**OUTCOME**	ICU_stay	days	Number	1		ICU_stay	93
154	**OUTCOME**	Hospital_stay	days	Number	1		Hospital_stay	94
155	**OUTCOME**	HOLD_field	HOLD_field	HOLD				
156	**OUTCOME**	GRAFT_FAILURE	0=NO FAILURE; 1=FAILURE	Dichotomic	1		GRAFT_FAILURE	95
157	**OUTCOME**	GRAFT_SURVIVAL_DAY	LAST FOLLOWUP DAY	DATE	8		GRAFT_SURVIVAL_DAY	96
158	**OUTCOME**	CAUSE_OF_FAILURE	**SPECIFY CAUSES OF FAILURE according to Table**	Choice	1		CAUSE_OF_FAILURE	97
159	**OUTCOME**	PATIENT_EXITUS	0=ALIVE; 1=DEATH	Dichotomic	1		PATIENT_EXITUS	98
160	**OUTCOME**	PATIENT SURVIVAL_DAY	LAST FOLLOW-UP DAY	DATE	8		PATIENT SURVIVAL_DAY	99

161	**OUTCOME**	CAUSE_OF_DEATH	**SPECIFY CAUSES OF DEATH according to Table**	Choice	1		CAUSE_OF_DEATH	100
162	**OUTCOME**	RETX_DATE	DATE_OF_RETRANSPLANT	DATE	8		RETX_DATE	101
163	**OUTCOME**	MRI_chol_90_DAYS_RESULT	NORMAL, ANAST_STENOSIS, NON ANAST_STEN, MULTIPLE_ANAST_ST; NORMAL HEPATIC ARTERY, HEPATIC ARTERY STENOSIS, HEPATIC ARTERY THROMBOSIS	Multiple choice	1		MRI_chol_12MO_RESULT	
164	**OUTCOME**	MRI_chol_90_DAYS_TEXT	Brief description of MRI_cholangiogram	Note	90		Brief description of MRI_cholangiogram	
165	**OUTCOME**	MRI_chol_90_DAYS	NORMAL, MULTI-FOCAL PROGRESSIVE, DIFFUSE NECROSIS; CONFLUENCE DOMINANT; MINOR FORM	CHOICE				
166	**OUTCOME**	STENT_90_DAYS	NO STENT; STENT	Dichotomic				
167	**OUTCOME**	STENT_#_90_DAYS_	NUMBER OF STENTS	N				
168	**OUTCOME**	AP_90_DAYS	ALKALINE_PHOSFATASIS_AT_12 months	N				
169	**OUTCOME**	gammaGT_12_MO	gammaGT at 12 months	N				
170	**OUTCOME**	MRI_chol_12_MO_RESULT	NORMAL, ANAST_STENOSIS, NON ANAST_STEN, MULTIPLE_ANAST_ST; NORMAL HEPATIC ARTERY, HEPATIC ARTERY STENOSIS, HEPATIC ARTERY THROMBOSIS	Multiple choice	1		MRI_chol_12MO_RESULT	102
171	**OUTCOME**	MRI_chol_12_MO_TEXT	Brief description of MRI_cholangiogram	Note	90		Brief description of MRI_cholangiogram	103
172	**OUTCOME**	MRI_chol_12_MO	NORMAL, MULTI-FOCAL PROGRESSIVE, DIFFUSE NECROSIS; CONFLUENCE DOMINANT; MINOR FORM	CHOICE				
173	**OUTCOME**	STENT_12_MO	NO STENT; STENT	Dichotomic				
174	**OUTCOME**	STENT_NUMBER_12_MO	NUMBER OF STENTS	N				
175	**OUTCOME**	AP_12_MO	ALKALINE_PHOSFATASIS_AT_12 months	N				
176	**OUTCOME**	gammaGT_12_MO	gammaGT at 12 months	N				
177	**OUTCOME**	NOTE_MISTAKE	Identification of cause of no-Retx erroneous choice	NOTE	30		NOTE	104
178	**OUTCOME**	Contraindication to retransplant	1.Frailty; 2.Sarcopenia; 3:Cardiac; 5.Sepsis; 5.Renal; 6.Technical; 7=Other (multiple answers)	CHOICE	1		NOTE	105
179	**OUTCOME**	Other contraindication to retransplant	Please specify	NOTE	20		NOTE	106
180	**OUTCOME**	REGISTRATION PROBLEMS	NOTE on techinical problems (data entry and image upload)	NOTE	30		NOTE	107

APPENDIX C – FORMULAS of scores and calculated parameters

1. DONOR RISK INDEX (DRI) predict quantitatively the risk of post-transplant graft failure in liver transplantation. Seven donor factors and two procurement factors were incorporated into the DRI model to calculate a quantifiable DRI.
These factors include donor age, race, height, death from cerebrovascular accident (CVA), donation after cardiac death (DCD), cause of death classified as "other" (excluding trauma, CVA, or anoxia), split or partial graft, cold ischemia time, and location of organs based on donor service area.
Calculation: DRI 5 exp([0.154 if age is <40 to < 50 years] 1 [0.274 if age is < 50 to < 60 years] 1 [0.424 if age is <60to < 70 years] 1 [0.501 if age is <70 years] 1 [0.079 if COD 5 anoxia] 1 [0.145 if COD 5 CVA] 1 [0.184 if COD 5 other] 1 [0.176 if race 5 African American] 1 [0.126 if race 5 other] 1 [0.411 if DCD] 1 [0.422 if partial/split] 1 [0.066 ([170 – height]/10)] 1 [0.105 if regional share] 1 [0.244 if national share] 1 [0.010 3 cold time]).

2. Suzuki Score for the Assessment of Liver Damage Following Hepatic Ischemia/Reperfusion

score	congestion	vacuolization	Necrosis
0	none	none	none
1	minimal	minimal	single cell necrosis
2	mild	mild	-30%
3	moderate	moderate	-60%
4	severe	severe	>60%

Suzuki S, Toledo-Pereyra LH, Rodriguez FJ, Cejalvo D. Neutrophil infiltration as an important factor in liver ischemia and reperfusion injury. Modulating effects of FK506 and cyclosporine. Transplantation, 1993; 55(6): 1265–72.

3. BRUNNER SCORE (bile duct damage)

Common bile duct epithelium shows considerable damage after cold ischemia with further damage occurring after reperfusion. The extent of epithelial dam- age can be quantified by our newly developed bile duct damage score and is a prognostic parameter for biliary complications and graft loss.

grade	description
o	regular monolayer of high prismatic cylinder epithelium
1	flattened but still present epithelial cells
2	Destroyed biliary epithelium but pre- served subepithelial connective tissue
3	destroyed biliary epithelium combined with disrupted connective tissue without nuclei, indicating necrosis of the BD

Grade 0, grade 1 and less than 10% grade 2 or 3 damage were defined as group with ''no relevant'', and specimens with more than 10% grade 2 or 3 damage were classified as group with ''major'' dam- age.

Brunner SM, Junger H, Ruemmele P, Schnitzbauer AA, Doenecke A, Kirchner GI, Farkas SA, Loss M, Scherer MN, Schlitt HJ, Fichtner-Feigl S. Bile duct damage after cold storage of deceased donor livers predicts biliary complications after liver transplantation. J Hepatol. 2013 Jun;58(6):1133-9. doi: 10.1016/j.jhep.2012.12.022. Epub 2013 Jan 12. PMID: 23321317.

4. CONUT score

Controlling Nutritional Status Score calculation.

The Controlling Nutritional Status (CONUT) score is a screening tool to identify undernourished patients in the hospitalized population. The score is derived from the values of serum albumin, total cholesterol and lymphocyte counts.

For the calculation of CONUT score the following table is included.

Laboratory parameters	None	Light	Moderate	Severe
Serum albumin (g/dL)	Serum albumin (g/dL)	3.00-3.49	2.50-2.99	<2.50
Score	0	2	4	6
Total lymphocyte count	≥1600	1200-1599	800-1199	<800
Score	0	1	2	3
Total cholesterol (mg/dL)	≥180	140-179	100-139	<100
Score	0	1	2	3

(Ulíbarri, J. et al. CONUT: a tool for controlling nutritional status. First validation in a hospital population. Nutrición Hospitalaria 20, 38–45 (2005)

5. CARDIAC RISK SCORE

parameters: Age Gender Diabetes Hypertension Tobacco Pack Years Family History of Coronary Artery Disease* *Defined as history of coronary artery disease in a first-degree family member. Personal History of Coronary Artery Disease* *Defined as history of percutaneous coronary intervention, coronary artery bypass grafting and/or myocardial infarction.

For the calculation of cardiac risk score

factors	points
age	
<30	0

30-39	2
40-49	4
50-59	6
60-70	8
>70	10
sex	
male	0
female	-2
diabetes	
yes	2
no	0
tobacco pack years	
0-20	15
21-40	1
>40	2
family history of coronary artery disease	
yes	2
no	0
personal history of cad	
yes	7
no	0

Low risk: (-2) -- 3
Intermediate-Risk: 4-8
High Risk: 9-25
(Rachwan RJ, Kutkut I, Timsina LR, Bou Chaaya RG, El-Am EA, Sabra M, Mshelbwala FS, Rahal MA, Lacerda MA, Kubal CA, Fridell JA, Ghabril MS, Bourdillon PD, Mangus RS. CAD-LT score effectively predicts risk of significant coronary artery disease in liver transplant candidates. J Hepatol. 2021 Jul;75(1):142-149. doi: 10.1016/j.jhep.2021.01.008. Epub 2021 Jan 18. PMID: 33476745.)

6. SARCOPENIA EVALUATION

Patients prospectively enrolled should undergone an assessment of sarcopenia using two measurements:

A - Total Psoas Area (TPA) at the third lumbar vertebra.
TPA was measured according to the formula:
Psoas muscle area/height (mm^2/m^2).
Psoas muscle area corresponds to the sum of the areas of the left and right psoas muscles.
B. - Skeletal Muscle Index (SMI) (optional)
SMI was measured according to the formula: Skeletal Muscle Area/height (mm^2/m^2).
the Skeletal Muscle Area corresponds to the sum of the areas of the psoas, paraspinal, and abdominal wall muscles.

A temporal limit of up to 3 months between the single evaluated CT scan and the Liver Transplant date should be adopted.
All the measurements should be done at the intermediate part of the third lumbar vertebra. The vertebra level was identified on each scan based on midline sagittal images that were reformatted from the unenhanced axial CT dataset. On the corresponding axial image, the total cross-sectional areas of the psoas, paraspinal (left and right quadratus lumborum), and abdominal wall muscles (rectus abdominis, oblique, and transversus abdominis) should be determined.

7. RIFLE (RENAL DYSFUNCTION)

In the RIFLE criteria, the stratum of injury is defined by a doubling of serum creatinine or a reduction of urinary output below 0.5 ml/kg per h during at least 12 h. Importantly, of the patients who develop injury, >50% later will develop established renal failure
In RIFLE, failure is defined as a three-fold increase of serum creatinine or decrease in GFR of >75% or a urine output of <0.3 ml/kg per h for >24 h or anuria for >12 h. Alternatively, failure also is defined by a serum creatinine of >4 mg/dl (353.6 µmol/L) with an acute rise of 0.5 mg/dl (42.2 µmol/L).
For the calculation of RIFLE score the following table is included.

RIFLE score	GFR criteria	UO criteria	
Non-ARF	GFR decrease ≤ 25%	UO ≥ 0.5 mL/kg/h	0
Risk	Increase Crx1.5 or GFR decrease > 25%	UO < 0.5 mL/kg/h × 6 h	1

Injury	Increase Crx2 or GFR decrease > 50%	UO < 0.5 mL/kg/h × 12 h	2
Failure	Increase Crx3 or GFR decrease > 75% or Cr > 4 mg/dL	UO < 0.3 mL/kg/h × 24 h	3
Loss	Complete loss of kidney function > 4 week	–	–
End-stage renal disease	End-stage renal disease (> 3 months)	–	–

Hoste EA, Clermont G, Kersten A, Venkataraman R, Angus DC, De Bacquer D, Kellum JA: RIFLE criteria for acute kidney injury are associated with hospital mortality in critically ill patients: A cohort analysis. Crit Care10 :R73– R83,2006

8. Modified Charlson Comorbidity INDEX (Volk et at. Liver Tx 2007)

The Charlson Comorbidity Index (CCI) was originally created to assess the survival rate of patients with chronic diseases (10-year survival), although it was modified and adopted in LTx recipients as CCI-OLT.
The Charlson Comorbidity Index is a method of categorizing comorbidities of patients based on the International Classification of Diseases (ICD) diagnosis codes found in administrative data, such as hospital abstracts data. This index take into account:

Addition of the selected points:

Variable	Definition	Points
Myocardial infarction	History of definite or probable MI (EKG changes and/or enzyme changes)	1
Congestive heart failure	Exertional or paroxysmal nocturnal dyspnea and has responded to digitalis, diuretics, or afterload reducing agents	1
Peripheral vascular disease	Intermittent claudication or past bypass for chronic arterial insufficiency, history of gangrene or acute arterial insufficiency, or untreated thoracic or abdominal aneurysm (≥6 cm)	1
Cerebrovascular accident or transient ischemic attack	History of a cerebrovascular accident with minor or no residua and transient ischemic attacks	1
Dementia	Chronic cognitive deficit	1
Chronic obstructive pulmonary disease	-	1
Connective tissue disease	-	1
Peptic ulcer disease	Any history of treatment for ulcer disease or history of ulcer bleeding	1
Mild liver disease	Mild = chronic hepatitis (or cirrhosis without portal hypertension)	1
Uncomplicated diabetes	-	1
Hemiplegia	-	2
Moderate to severe chronic kidney disease	Severe = on dialysis, status post kidney transplant, uremia, moderate = creatinine >3 mg/dL (0.27 mmol/L)	2
Diabetes with end-organ damage	-	2
Localized solid tumor	-	2
Leukemia	-	2
Lymphoma	-	2
Moderate to severe liver disease	Severe = cirrhosis and portal hypertension with variceal bleeding history, moderate = cirrhosis and portal hypertension but no variceal bleeding history	3
Metastatic solid tumor	-	6
AIDS*	-	6

Plus 1 point for every decade age 50 years and over, maximum 4 points.
Note: liver disease and diabetes inputs are mutually exclusive (e.g. do not give points for both "mild liver disease" and "moderate or severe liver disease").

The 1-yr mortality rates for the different scores were: "0", 12% (181); "1-2", 26% (225); "3-4", 52% (71); and "greater than or equal to 5", 85% The percent of patients who died of comorbid disease for the different scores were: "0", 8% (588); "1", 25% (54); "2", 48% (25); "greater than or equal to 3", 59% (18).

Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-83. doi: 10.1016/0021-9681(87)90171-8. PMID: 3558716.

Definition:

1) Congestive heart failure—documented decreased left ventricular function or mean pulmonary artery pressure _25 mm Hg as determined by stress echocardiography, including patients with portopulmonary hypertension.
2) Coronary artery disease—documented history of myocardial infarction, or coronary disease on angiography. All men above age 40 yr and all women above age 50 yr, as well as patients of any age with risk factors for coronary artery disease underwent a stress test. Patients with a positive stress test but negative angiography were not considered as having coronary artery disease.
3) Diabetes mellitus—chronic hyperglycemia requiring outpatient medications at any time during the month preceding transplantation.
4) Peripheral vascular disease— documented arterial disease by angiography or ankle-brachial index.
5) Cerebral vascular accident—history of stroke with residual neurological deficit.
6) Chronic obstructive pulmonary disease (COPD)—chronic lung disease with requirement for medications, documented forced expiratory volume in 1 second _1.5 L, or a history of intubation for respiratory failure.
7) Connective tissue disease—diagnosis by a rheumatologist of systemic lupus, rheumatoid arthritis, scleroderma, or seronegative spondyloarthropathy. Patients with osteoarthritis, or arthralgias without objective evidence of inflammatory arthritis, were not considered as having connective tissue disease.
8) Renal insufficiency—serum creatinine of 1.5 mg/dL or greater on most recent pretransplantation testing, or a history of renal transplantation.
9) Malignancy—history of malignancy, excluding nonmelanoma skin cancer and hepatocellular carcinoma.

NOTES

- The CCI was calculated by assigning a weight of 2 to diabetes, stroke, renal insufficiency, and malignancy, and a weight of 1 to the other comorbidities, as previously described.[15]
- When each comorbidity was examined individually, no weighting was used.

9. Glasgow coma score

The Glasgow come score was calculated assigning points for each of the sections reported below (Eye opening, from 0 to 4; verbal response, from 0 to 5; best motor responce, from 0 to 6).

Eye opening

Criterion	Observed	Rating	Score
Open before stimulus	✔	Spontaneous	4
After spoken or shouted request	✔	To sound	3
After finger tip stimulus	✔	To pressure	2
No opening at any time, no interfering factor	✔	None	1
Closed by local factor	✔	Non testable	NT

Verbal response

Criterion	Observed	Rating	Score
Correctly gives name, place and date	✔	Orientated	5
Not orientated but communication coherently	✔	Confused	4
Intelligible single words	✔	Words	3
Only moans / groans	✔	Sounds	2
No audible response, no interfering factor	✔	None	1
Factor interferring with communication	✔	Non testable	NT

Best motor response

Criterion	Observed	Rating	Score
Obey 2-part request	✔	Obeys commands	6
Brings hand above clavicle to stimulus on head neck	✔	Localising	5
Bends arm at elbow rapidly but features not predominantly abnormal	✔	Normal flexion	4
Bends arm at elbow, features clearly predominantly abnormal	✔	Abnormal flexion	3
Extends arm at elbow	✔	Extension	2
No movement in arms / legs, no interfering factor	✔	None	1
Paralysed or other limiting factor	✔	Non testable	NT

10. ICU risk SOFA II (early post-operative care)

Sequential Organ Failure Assessment (SOFA) severity of illness score for hospital mortality is a morbidity severity score and mortality estimation tool developed from a large sample of ICU patients throughout the world. Unlike other scoring systems, such as the SAPS II and APACHE II systems, the SOFA was designed to focus on organ dysfunction and morbidity, with less of an emphasis on mortality prediction. The authors designed the system with an emphasis on bedside applicability and simplicity using widely available variables.

For the calculation of SOFA score the following table is included.

-Respiratory system

PaO2/FiO2 [mmHg (kPa)]	SOFA score
≥ 400 (53.3)	0
< 400 (53.3)	+1
< 300 (40)	+2
< 200 (26.7) and mechanically ventilated	+3
< 100 (13.3) and mechanically ventilated	+4

-Nervous system

Glasgow coma scale	SOFA score
15	0
13–14	+1
10–12	+2
6–9	+3
< 6	+4

-Cardiovascular system

Mean arterial pressure OR administration of vasopressors required	SOFA score
MAP ≥ 70 mmHg	0
MAP < 70 mmHg	+1
dopamine ≤ 5 µg/kg/min or dobutamine (any dose)	+2
dopamine > 5 µg/kg/min OR epinephrine ≤ 0.1 µg/kg/min OR norepinephrine ≤ 0.1 µg/kg/min	+3
dopamine > 15 µg/kg/min OR epinephrine > 0.1 µg/kg/min OR norepinephrine > 0.1 µg/kg/min	+4

-Liver

Bilirubin (mg/dl) [µmol/L]	SOFA score
< 1.2 [< 20.53]	0
1.2–1.9 [20-32]	+1
2.0–5.9 [33-101]	+2
6.0–11.9 [102-204]	+3
> 12.0 [> 204]	+4

-Coagulation

Platelets×103/µl	SOFA score
≥ 150	0
< 150	+1
< 100	+2
< 50	+3
< 20	+4

-Kidneys

Creatinine (mg/dl) [µmol/L] (or urine output)	SOFA score
< 1.2 [< 110]	0
1.2–1.9 [110-170]	+1
2.0–3.4 [171-299]	+2
3.5–4.9 [300-440] (or < 500 ml/d)	+3
> 5.0 [> 440] (or < 200 ml/d)	+4

Interpretation:

SOFA Score	Mortality if initial score	Mortality if highest score
0-1	0.0%	0.0%
2-3	6.4%	1.5%
4-5	20.2%	6.7%
6-7	21.5%	18.2%
8-9	33.3%	26.3%
10-11	50.0%	45.8%
12-14	95.2%	80.0%
>14	95.2%	89.7%

Mean SOFA Score	Mortality
0-1.0	1.2%
1.1-2.0	5.4%
2.1-3.0	20.0%
3.1-4.0	36.1%
4.1-5.0	73.1%
>5.1	84.4%

1. Vincent JL, de Mendonça A, Cantraine F, et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. Crit Care Med. 1998;26(11):1793-800. PMID 9824069.
2. Ferreira FL, Bota DP, Bross A, et al. Serial evaluation of the SOFA score to predict outcome in critically ill patients. JAMA. 2001;286(14):1754-8.

11. Clavien Dindo (7 classes) – OUTCOME (hospital morbidity)

The therapy used to correct a specific complication is the basis of this classification in order to rank a complication in an objective and reproducible manner.
It consists of 7 grades (I, II, IIIa, IIIb, IVa, IVb and V). The introduction of the subclasses a and b allows a contraction of the classification into 5 grades (I, II, III, IV and V) depending on the size of the population observed or the of the focus of a study.
Complications that have the potential for long-lasting disability after patient's discharge (e.g.: paralysis of a voice cord after thyroid surgery) are highlighted in the present classification by a suffix ("d" for disability). This suffix indicates that a follow-up is required to comprehensively evaluate the outcome and related long-term quality of life.
(Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004; 240(2):205-213)

Grade I Any deviation from the normal postoperative course without the need for phcohortacological treatment or surgical, endoscopic, and radiological interventions.
Allowed therapeutic regimens are as follows: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside
Grade II Requiring phcohortacological treatment with drugs other than those allowed for grade I complications
Blood transfusions and total parenteral nutrition are also included
Grade III Requiring surgical, endoscopic, or radiological intervention
IIIa Intervention not under general anesthesia
IIIb Intervention under general anesthesia
Grade IV Life-threatening complication (including CNS complications)* requiring IC/ICU management
IVa Single-organ dysfunction (including dialysis)
IVb Multiorgan dysfunction
Grade V -Death

*Brain hemorrhage, ischemic stroke, and subarachnoid bleeding, but excluding transient ischemic attacks. CNS indicates central nervous system; IC, intermediate care; ICU, intensive care unit.

12. Comprehensive Complication Index

For the calculation of CCI the following table is included.

wC = Weight of Complication

$CCI^{®} = \sqrt{(wC_1 + wC_2 \ldots + wC_x)}/2$

CCI®	wC	CCI® Single Value
Grade I	300	8.7
Grade II	1750	20.9
Grade IIIa	2750	26.2
Grade IIIb	4550	33.7
Grade IVa	7200	42.4

The Comprehensive Complication Index (CCI®) is based on the complication grading by Clavien-Dindo Classification and implements every occurred complication after an intervention. The overall morbidity is reflected on a scale from 0 (no complication) to 100 (death).

13. GRWR (graft/recipient weight ratio)

GRWR was calculated from the following equation (graft weight or volume in gram or ml/recipient weight in kg × 10)

14. L-GrAFT$_{10}$ score

L-GrAFT$_{10}$ score =
+ 9.77 +
- 0.429 x (AUC calculated from $\log_e$ of AST in 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 POD) +
+ 0.005 x (AUC^2 calculated from $\log_e$ of AST in 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 POD) +
+ 4.607 x (slope calculated from $\log_e$ of AST in 1, 2, 3, 4, 5, 6, 7 POD) +
+ 4.413 x (slope^2 calculated from $\log_e$ of AST in 1, 2, 3, 4, 5, 6, 7 POD) +
+ 0.890 x ($\log_e$ max of INR in 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 POD) +
- 0.049 x (AUC calculated from $\log_e$ of total bilirubin in 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 POD) +
+ 0.004 x (AUC^2 calculated from $\log_e$ of total bilirubin in 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 POD) +
+ 5.336 x (slope calculated from $\log_e$ of total bilirubin in 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 POD) +
- 0.046 x (AUC calculated from $\log_e$ of platelet count in 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 POD) +
- 5.249 x (slope calculated from $\log_e$ of platelet count in 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 POD) +
+ 13.086 x (slope^2 calculated from $\log_e$ of platelet count in 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 POD)

15. EASE score

EASE score =
- 0.058 +
+ 0.000534 x (AUC^2 calculated from $\log_e$ of AST in 1, 2, 3, 7, 10 POD) +
- 0.093 x (AUC calculated from $\log_e$ of platelet count in 1, 3, 7, 10 POD) +
- 7.735 x (slope calculated from $\log_e$ of platelet count in 1, 3, 7, 10 POD) +
+ 0.735 x (slope calculated from bilirubin level in 1, 3, 7, 10 POD) +
+ 0.044 x MELD at transplant)+
+ 0.065 x (number of PACKED RED BLOOD CELL transfused units during surgery) +
+ 2.567 (if arterial or portal thrombosis during days 1-10) +
- 0.402 (if center volume ≥70 cases x year)

Abbreviations. AUC, area under the curve; POD, post-operative day.

Notes. Forty data-entries are necessary to calculate the L-GrAFT$_{10}$ score and 17 data-entries to calculate the EASE-score. Differently from the L-GrAFT$_{10}$ score, for the EASE score the logarithmic transformation of bilirubin was not adopted.

The – 0.058 constant of the EASE score results from the algebraic sum of the constant obtained by the logistic regression (-0.958) and the constant added to calibrate the unsustainable risk cutoff at the 0 threshold (+ 0.3560).