Perioperative Care Exposures Multiorgan Outcomes and Functional Recovery in Liver Transplantation

A Single Center Prospective Clinical Cohort Study

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1. Research Background

1.1 Objectives and Significance

1.1.1 Background

Perioperative research in liver transplantation must address whether patients survive, whether organ injury occurs, and whether patients regain mobility and independent living after surgery. Clinical decisions concerning circulatory management, fluids and transfusion, anesthesia and analgesia, ventilation, and temperature management extend throughout surgery and early recovery. The International Liver Transplantation Society consensus on enhanced recovery integrates preoperative assessment and optimization, intraoperative surgery and anesthesia, and postoperative management into a single care pathway [1]. Research on this pathway requires linkage of the treatment actually received, the patient's physiological condition at the time, and subsequent outcomes.

The clinical question addressed by this study is which perioperative care exposures and physiological changes are associated with multiorgan injury and delayed recovery after accounting for preoperative disease severity, organ function, and graft characteristics, and whether these associations vary with the patient's baseline condition. Surgical procedures, bleeding and transfusion, medication use, and organ support all occur at identifiable times. Physiological abnormalities may prompt treatment adjustments, and treatment may in turn alter subsequent physiology. Information on the patient's condition before treatment, the treatment delivered, and subsequent changes is therefore needed to interpret observed associations.

Recovery assessment must also include activities that patients perceive and can actually perform. A prospective study of 180 recipients at five Spanish centers showed incomplete improvement in physical frailty after transplantation and differences between subjective judgment and objective functional assessment [2]. Mortality, length of stay, and graft laboratory results alone cannot fully describe early recovery experiences or later living abilities. This cohort therefore includes organ-specific outcomes, the Quality of Recovery-15 (QoR-15), days at home, and long-term functional follow-up to assess clinical events, early subjective recovery, and return to daily life, respectively.

Addressing these questions requires linkage of preoperative status, perioperative care, and postoperative recovery in the same patients. Routine records provide information on disease, surgery, medications, investigations, and hospitalization. However, without accurate procedural times, continuous physiological recordings, or preoperative functional baselines, retrospective review cannot fully recover this information. Patient-reported outcomes and functional assessments also require prespecified measurement times. Prospective consecutive enrollment permits recording rules to be established before outcomes occur, includes severely ill recipients and those temporarily unable to undergo assessment, and documents why data are missing.

This study will establish a single-center longitudinal clinical cohort with standardized care-exposure recording, organ-outcome adjudication, and functional follow-up, and will assess the consistency of associations across patient conditions. Circulatory, respiratory, temperature, and electroencephalographic recordings will characterize physiological responses during care. The evidence generated will identify perioperative management factors, recovery assessment times, and high-risk populations requiring further validation and will inform subsequent interventions addressing specific clinical questions.

1.1.2 Study Objective

To establish a single-center prospective clinical cohort of adult liver transplant recipients, linking preoperative recipient status and graft characteristics, perioperative care exposures and dynamic physiological changes, multiorgan outcomes, and functional recovery within the same population; to identify factors associated with organ injury and recovery difficulties; and to inform subsequent clinical validation and intervention studies.

1.1.3 Significance

This study will describe early multiorgan events, organ support, and functional recovery among liver transplant recipients at this center, and identify recovery patterns across preoperative risk groups. By linking actual care exposures and physiological changes with subsequent outcomes, it will evaluate management components associated with adverse outcomes or delayed recovery and inform the selection of questions for interventional validation.

Including QoR-15, days at home, mobility and independent living, cognition, and quality of life will assess recovery beyond clinical events. Standardized collection and follow-up will reduce duplicate registration and allow substudies on surgery, circulation and transfusion, anesthesia and analgesia, respiratory and temperature management, and rehabilitation to use a shared data foundation.

Outputs will primarily comprise outcome proportions, effect estimates, recovery trajectories, and the populations to which findings apply. Observational associations will generate and test clinical hypotheses; causal relationships and benefits of specific management strategies require further validation.

1.1.4 Innovation

The study examines care processes together with injury and recovery. Preoperative status, graft characteristics, actual care exposures, and subsequent outcomes will be recorded in the same recipients, allowing evaluation of both early organ events and patient recovery.

Perioperative information will be organized by actual event time. Surgical and anesthetic events will be linked to circulatory, respiratory, temperature, and EEG recordings to assess exposure timing, duration, and recovery. Each modality will be analyzed according to the corresponding clinical question; no single signal is required to summarize overall physiological status.

Clinical outcomes will be combined with repeated functional measurements. QoR-15, days at home, and long-term functional data will be obtained within common observation windows. Death, inability to assess, and loss to follow-up will be distinguished when assessing the relationship between organ injury and recovery.

Consistent and comparable observation will be maintained through standardized definitions, outcome adjudication, and follow-up, while retaining differences in equipment, care, and populations. These data will support association studies and prediction validation of appropriate complexity. Residual clinical materials will provide supplementary interpretation only for specific questions.

1.2 Current Research in China and Internationally

1.2.1 International Research

The scope of research has expanded to perioperative management and patient recovery. The ILTS enhanced recovery consensus evaluated evidence for 32 elements and issued recommendations covering preoperative, intraoperative, and postoperative management [1]. It informs selection of observations; actual care exposures across baseline risk groups and their relationships with recovery still require longitudinal clinical data.

Associations between perioperative exposures and organ outcomes depend on observation methods and populations. In an analysis of 1,576 recipients, Cywinski et al. found no statistical association between intraoperative hypotension and AKI severity, major cardiovascular events, or early allograft dysfunction [3]. Bieze et al., analyzing 1,153 recipients, found associations between certain hypotension exposures over the entire operation and AKI, but results were not consistent after phase-specific adjustment [4]. Exposure thresholds, duration, surgical phase, preoperative risk, and adjustment variables therefore require explicit definition. Differences across studies cannot directly establish causal evidence for a treatment target.

Early clinical events and functional recovery require separate assessment. The Spanish multicenter study assessed frailty preoperatively and at 3 and 6 months, observing differences in recovery over time [2]. QoR-15 and its Chinese validation provide a short-term patient-reported recovery measure; days-at-home research incorporates hospitalization, readmission, and survival on one time scale [5,6,7]. Prior validation of these instruments does not establish transplant-specific validity. This cohort will report completion feasibility, measurement distributions, and limitations of applicability.

Continuous physiological recordings can supplement care-process information. Alongside hemodynamics, respiratory, temperature, and brain-function recordings characterize responses in different systems. For example, Rice et al. retrospectively evaluated frontal EEG use in 77 first-time isolated liver transplant recipients without demonstrating a lower incidence of postoperative delirium [8]. Use of a monitoring technique and patient benefit must be assessed separately. The value of multimodal recordings should be tested by whether they explain clinical associations or add risk information.

Definitions or consensus statements are available for early allograft dysfunction, AKI, myocardial infarction, ARDS, and perioperative neurocognitive change [9-15]. Risk research must also specify prediction times, account for repeated observations within patients, and assess calibration, overall error, and applicability [16-18]. This cohort will standardize outcomes and timing while retaining scope for independent analyses of care domains and organ outcomes.

1.2.2 Research in China

Chinese liver transplantation research has used preoperative and intraoperative data to identify factors associated with specific complications and to develop risk models. The Beijing Tsinghua Changgung Hospital team studied prediction of AKI within 48 hours using data from 453 recipients, providing local evidence on preoperative organ status, perioperative variables, and risk prediction [19]. Such studies help identify variables requiring continuous recording and emphasize assessment of models according to the target outcome and intended clinical use time.

For neurological outcomes, a study of 211 recipients at the Third Xiangya Hospital of Central South University reported a postoperative delirium incidence of 20.4%; associated factors included preoperative infection, liver disease severity, and hepatic encephalopathy [20]. A team at the Third Affiliated Hospital of Sun Yat-sen University conducted machine-learning research on perioperative neurocognitive outcomes with external validation [21]. These studies highlight the need to account for preoperative status in organ-outcome adjudication and to distinguish acute complications from longer-term functional change.

These studies primarily address individual organ outcomes or risk models and provide a basis for the questions and variables in this study. Their questions differ from this cohort's intended examination of relationships among care processes, multiple organ outcomes, and longitudinal recovery. Consecutive registration, treatment-event recording, and fixed-window follow-up at this center will supplement existing data on event timing, repeated measurements, and patient recovery. Availability and direct reusability of existing records will be verified at initiation.

1.2.3 Research Gaps and Rationale for the Cohort

Baseline risk and actual care processes need to be distinguished within the same analysis. Preoperative scores describe some patient differences, while intraoperative management is influenced by illness, surgical phase, and graft characteristics. The study must determine which exposures and physiological changes remain associated with organ outcomes and recovery after accounting for this context, avoiding the assumption that greater treatment intensity in severely ill patients means treatment caused injury.

Temporal relationships among exposures, interventions, and outcomes require prospective recording. The same total drug or transfusion dose can reflect different administration times, bleeding contexts, and physiological responses. Retaining actual event times and conditions before and after treatment enables

phase comparisons and reduces use of post-outcome data to explain earlier risk. Unrecorded raw signals and procedural times cannot be collected retrospectively.

Organ injury must be linked longitudinally to recovery. Early hepatic, renal, cardiopulmonary, and neurological events have different observation windows; recovery quality, mobility, cognition, and quality of life may also follow different trajectories. Preoperative baselines, inpatient assessments, and 12-month follow-up within one cohort will allow evaluation of early events in relation to subsequent recovery and reduce comparability limitations caused by different populations and methods.

Shared research questions require a consistent population and definitions. Consecutive screening and standardized adjudication retain patients who are severely ill, have missing signals, or cannot temporarily complete scales. Common windows and definitions help distinguish real differences in care from differences in recording.

The cohort is needed to prospectively collect event timing, preoperative functional baselines, and continuous follow-up that are incompletely captured in routine records, producing data from one population for studying associations of care exposures with injury and recovery. Core data are selected according to these clinical questions, and substudies will analyze the shared data independently. Availability of any individual physiological signal or residual material will not determine implementation of the parent cohort.

1.3 Institutional Resources and Readiness

The proposed team comprises eight investigators. Principal investigator Yi Duan will oversee design, medical supervision, ethics coordination, and quality management; executive lead Zhifeng Gao will oversee implementation and institutional coordination. The other six investigators will cover screening and baseline assessment, perioperative collection, clinical outcome adjudication, follow-up and functional assessment, data and signal management, and statistical analysis, as detailed under study design.

The Beijing Tsinghua Changgung Hospital team's AKI prediction study in 453 liver transplant recipients provides a reference for clinical variable selection and risk research [19]. Consecutive enrollment is planned for 5 years. At approximately 100 adult liver transplants annually, around 500 procedures may be screened; capacity will be assessed through consecutive screening logs.

Before launch, ethics and institutional review, personnel training, verification of passive equipment interfaces and time synchronization, data permissions, and follow-up arrangements will be completed. The first 45 participants will assess feasibility of signal recording, transfer, and assessments. Anesthesia, transplant surgery, intensive care, laboratory, pathology, and statistical personnel will collaborate according to responsibilities. Research collection and functional testing will remain subordinate to clinical care.

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2. Study Objectives and Content

2.1 Study Objectives

2.1.1 Overall Objective

To establish a single-center prospective clinical cohort of adult liver transplant recipients, linking preoperative recipient status and graft characteristics, perioperative care exposures and dynamic physiological changes, multiorgan outcomes, and functional recovery in the same population; identify factors associated with organ injury and recovery difficulties; and inform subsequent clinical validation and intervention studies.

2.1.2 Primary Objective

The primary objective is to establish a standardized prospective cohort of adult liver transplant recipients, systematically recording perioperative care exposures, dynamic physiological characteristics, 30-day multiorgan clinical outcomes, and functional recovery through 12 months. The patient-level composite of all-cause mortality or at least one prespecified major organ complication within 30 days will be the core descriptive measure. Its proportion and 95% confidence interval will be estimated, and each component and its severity reported separately. Analyses of specific care-exposure associations and risk prediction are secondary or exploratory objectives requiring separate prespecified analysis plans and assessment of available information.

2.1.3 Secondary Objectives

To describe hepatic, renal, cardiopulmonary, and neurological events, organ support, and hospitalization outcomes; assess associations of care exposures and physiological features with organ-specific outcomes; and evaluate relationships between early clinical events and subsequent day-7 QoR-15, DAH-30/90, and mobility, frailty, cognition, and quality of life at day 90 and months 6 and 12.

A prespecified sleep and emotional recovery substudy will assess sleep quality, anxiety and depressive symptoms, and their changes before surgery and at postoperative days 30 and 90, and examine associations with care exposures, early organ events, and other recovery indicators. This extended follow-up module will not alter the primary outcome or parent-cohort eligibility.

Risk estimation using routine clinical data will be compared with estimation after addition of prespecified dynamic physiological features, assessing calibration and discrimination. Patient and graft survival, functional trajectories, and assessment feasibility will be reported separately.

2.1.4 Exploratory Objectives

To investigate physiological and recovery differences across surgical phases, donor types, and baseline risk groups and generate hypotheses for independent validation. Where materials and authorization permit, approved testing of residual clinical serum and tissue will be explored in relation to specific exposures and outcomes. High-dimensional features, complex time-varying treatment effects, and supplementary testing each require adequate information and appropriate conditions.

2.2 Study Content

2.2.1 Preoperative Recipient Status and Graft Characteristics

Demographics, liver disease etiology and severity, prior organ disease, infection, and organ support will be collected. Nutrition, frailty, daily living abilities, cognition, and quality of life will establish the baseline for interpreting exposures and outcomes. For patients unable to complete assessments, actual clinical status and reasons for limitation will be retained.

Clinically available and authorized donor and graft information will be linked, including donor type and age, graft type, routine pathology, cold and warm ischemia times, preservation, and machine perfusion. The study will assess how recipient reserve and graft characteristics relate to early organ events and recovery differences. Donor information will be limited to research needs without copying direct identifiers.

2.2.2 Perioperative Care Exposures and Dynamic Physiological Responses

Clinical exposures will include surgical procedures, vascular clamping and release, bleeding and transfusion, fluids and vasoactive drugs, anesthesia and analgesia, ventilation and temperature management, and postoperative sedation, organ support, and immunosuppression. Actual timing, dose, duration, and reasons for adjustment will be retained, distinguishing patient condition, clinical decisions, and post-treatment responses.

Clinically exportable raw signals and numerical data for circulation, respiration, temperature, and EEG will be collected synchronously. Duration, deviation burden, and recovery rate will be calculated by surgical phase and event. Relationships with clinical events and explanatory or predictive information beyond routine records will be examined. Valid duration and applicability will be documented separately for each modality.

2.2.3 Multiorgan Outcomes and Patient Recovery

Fixed definitions will identify EAD, AKI, cardiovascular and pulmonary complications, delirium, and other acute neurological events. Organ support, hospitalization, survival, and graft outcomes will be recorded. Associations of shared exposures with different organ events will be analyzed while retaining timing, severity, and overlap.

QoR-15 will assess early subjective recovery; DAH-30/90 will describe survival and time at home. Activity milestones, symptoms, daily living abilities, long-term cognition, frailty, and quality of life will characterize recovery trajectories. Analyses will respect temporal order and handle death, inability to assess, and loss to follow-up separately.

The sleep and emotional recovery substudy will use the Pittsburgh Sleep Quality Index (PSQI) and Hospital Anxiety and Depression Scale (HADS) before surgery and at days 30 and 90. Sleep quality, anxiety, and depression will be separate substudy recovery indicators, interpreted separately from QoR-15 and quality-of-life measures [28-30].

2.2.4 Nested Substudies Supported by Shared Data

Substudy	Shared data	Main analytical boundaries
Surgery and graft characteristics	Recipient baseline, procedure, clamping and release, ischemia and preservation, routine liver function, complications	Retain actual procedures and times; account for donor and recipient differences
Circulation fluids and transfusion	Blood pressure and waveforms, vasoactive drugs, bleeding and transfusion, fluids, surgical phases, hepatic renal and cardiopulmonary outcomes	Account for pretreatment status and indications; treatment intensity does not directly establish causation
Anesthesia analgesia and early recovery	Drug doses and times, postoperative sedation and analgesia, pain, nausea and vomiting, QoR-15, delirium	Distinguish drugs and phases; research does not allocate anesthesia regimens
Respiratory and temperature management	Ventilation, oxygenation, clinical blood gases, temperature sites, warming, transfusion, pulmonary outcomes	Retain equipment and sites; blood gases from routine testing only
Organ injury and functional recovery	Organ-specific events, organ support, QoR-15, DAH-30/90, longitudinal function	Distinguish concurrent associations from subsequent recovery; account for death and assessability
Sleep and emotional recovery	PSQI, HADS-A, HADS-D, linked care organ-event and recovery data	Assess preoperatively and at days 30 and 90; distinguish recall periods; consecutive invitation and reasons for nonassessment
Brain function	Hepatic encephalopathy, cognition, sedation and anesthesia, EEG, delirium, follow-up	EEG is one available observation; define delirium and long-term cognition separately
Clinical risk prediction	Baseline and graft data, care events, prespecified physiology, fixed outcomes	Limit prediction times and parameter counts; patient-level internal validation
Residual clinical material research	Authorized residual serum and tissue, source, processing and assay records	No required pairing or extra collection; no open-ended long-term storage

Before accessing outcome data, each substudy will define its clinical question, primary exposure, target outcome, analysis time, adjustment variables, and sample-size rationale. Shared core collection prioritizes reasonably burdensome information reusable across questions that cannot be fully recovered retrospectively. Physiological signals will come exclusively from routine monitoring; no additional equipment, electrodes, or invasive procedures will be introduced. Research scales, functional testing, and residual-material assays will follow specific questions and approvals. Activities beyond the parent protocol's purpose, procedures, or authorization require reassessment of classification and risk and corresponding review or amendment.

2.3 Key Questions

1. How are preoperative organ function, frailty, and graft characteristics related to early organ injury and subsequent recovery trajectories, and which patients experience persistent recovery difficulties?

2. After accounting for baseline risk and clinical indications, how are surgery, circulatory management, fluids and transfusion, anesthesia and analgesia, and respiratory and temperature management associated with postoperative organ outcomes, including timing, phase, and dose characteristics?

3. How are early organ events associated with subsequent QoR-15, days at home, long-term mobility, cognition, and quality of life, and how do death and inability to assess affect interpretation?

4. Can dynamic circulatory, respiratory, temperature, and EEG information supplement routine clinical data for risk and recovery assessment, and with what applicability and uncertainty?

5. Are associations consistent across donor types and preoperative risk states, and which findings warrant independent validation or interventional research?

3. Study Protocol

3.1 Study Design

3.1.1 Overview

This study will assess associations of preoperative recipient status and graft characteristics, perioperative care exposures, and dynamic physiological changes with postoperative multiorgan injury, early quality of recovery, and long-term functional recovery, identifying potentially modifiable factors for further interventional research. Baseline risk, actual care, and recovery will be recorded together to provide longitudinal data for association and risk analyses.

This is a single-center prospective observational clinical cohort with consecutive enrollment. At approximately 100 adult liver transplants per year, around 500 procedures are expected to be screened over 5 years, with a target of 450 first-time isolated liver transplant recipients. Each recipient will be followed for 12 months; final follow-up is expected approximately 6 years after the first enrollment. Retransplantation and combined-organ recipients may enter an extended registry for separate analysis.

Shared data include preoperative recipient status, donor and graft characteristics, surgery, anesthesia, other care exposures, and dynamic circulation, respiration, temperature, and EEG information, linked to early organ outcomes and repeated functional assessment. EEG is one brain-function observation collected alongside other modalities. Each substudy will define exposures and populations according to its question. Unavailability of a signal or scale does not affect parent-cohort enrollment.

The main study relies on clinical data, physiological recordings, and follow-up. Supplementary assays will use only approved residual serum and tissue intended for disposal after routine care. No additional blood volume, tubes, or sampling frequency, tissue excision, puncture, or biopsy will be required. No biobank will be established.

Item	Protocol arrangement
Study type	Single-center prospective observational clinical cohort with consecutive enrollment
Main population	Recipients aged ≥18 undergoing first isolated liver transplantation
Extended registry	Retransplantation and combined-organ recipients registered and analyzed separately
Enrollment and follow-up	Enrollment for 5 years; 12-month follow-up per recipient
Screening and target	Approximately 100 procedures annually and 500 screened over 5 years; target 450 main-cohort recipients
Shared question	Associations of baseline and graft conditions care exposures and physiological changes with organ injury and recovery
Primary outcome	All-cause mortality or at least one prespecified major organ complication within 30 days after surgery starts

Item	Protocol arrangement
Key secondary outcomes	Organ-specific outcomes, day-7 QoR-15, DAH-30/90, duration of organ support, long-term function cognition and quality of life
Core observations	Surgery anesthesia and other care exposures; circulation respiration temperature and EEG
Sample-size basis	Precision of the primary outcome proportion; separate information assessment for association and prediction substudies
Research biological sampling	Additional blood volume 0 mL; additional tissue sampling 0 procedures
Supplementary assays	Optional residual clinical serum and tissue assays; do not determine enrollment or primary-analysis eligibility

3.1.2 Design and Implementation Period

Anesthesia, transplant surgery, intensive care, laboratory, pathology, and statistical personnel will collaborate under a single-center prospective observational design. A common protocol, data dictionary, outcome definitions, and training requirements will be used to record actual care. The study will not allocate anesthesia methods, blood pressure targets, respiratory strategies, organ preservation, or immunosuppression. Clinicians will independently determine monitoring, investigations, and treatment. Intraoperative EEG, circulation, respiration, and temperature data will come from routine monitoring without changes to monitoring items, timing, duration, displays, or alarms.

Team and responsibilities. Eight investigators are planned. The principal investigator will oversee medical supervision and quality; investigators 2-4 will cover implementation coordination, screening and baseline assessment, and perioperative collection; investigators 5-8 will cover outcomes, follow-up, data, and statistics. Investigators may assist with bedside assessment and source verification within their authorization. Investigator 6 will coordinate training, follow-up, and completion tracking. Existing clinical services will provide laboratory testing, pathology, and routine nursing.

No.	Role	Main responsibilities
1	Principal investigator Yi Duan	Overall design medical oversight ethics and institutional coordination safety reporting quality management and disputed-outcome adjudication
2	Executive lead Zhifeng Gao	Implementation and progress screening enrollment care and event recording institutional coordination
3	Screening and baseline assessment	Screening consent preoperative clinical collection baseline assessment follow-up assistance source verification
4	Perioperative collection	Clinical and physiological collection treatment-event recording bedside assessment follow-up assistance source verification
5	Clinical outcome adjudication	Organ events infections complications graft and pathology verification independent review

No.	Role	Main responsibilities
6	Follow-up and functional assessment	Scale training visit scheduling survival days at home functional follow-up sleep and emotion module loss-to-follow-up tracing
7	Data and signal management	Electronic case report forms data dictionary time synchronization signal quality feature extraction queries permissions
8	Statistical analysis	Sample-size review analysis planning missing-data handling association analysis model validation reporting

Observations comprise shared core records and extensions addressing explicit questions. Core records include recipient and graft baselines, care, available multimodal physiology, major organ outcomes, and functional follow-up. Assessability of EEG, another signal, or a scale affects only analyses requiring that measure. Residual-material testing is not essential to the main study.

Enrollment will last 5 years with 12 months of follow-up per recipient. The first 45 participants will assess feasibility of recording, transfer, and assessment; they will count toward the final cohort if formal criteria and primary outcome definitions are identical. Collection completeness, measurement reliability, overall event frequencies, and signal availability will inform operational improvements and feasible model complexity. Exposure-outcome association strength will not guide feature selection or replacement of the primary outcome.

Skin incision will define follow-up time zero. Records will retain calendar date, actual time, and time relative to surgery start. General reperfusion analyses will reference first restoration of graft blood flow, recording portal vein and hepatic artery release separately. Analyses of a particular vessel must name the reference event and not conflate it with first reperfusion. Actual anatomical and flow-reconstruction events will be retained for different procedures. Exposure and outcome-risk windows will be explicit; events already occurring will not be treated as new events predicted by subsequent treatment.

3.2 Study Population

Recipients will be screened during waiting-list registration, inpatient preoperative assessment, or transplant preparation. Consecutive logs will record eligibility, enrollment, refusal, inability to complete emergency consent, cancellation, and other nonenrollment reasons. Research scales, functional assessments, and collection must not delay transplantation, anesthesia, or necessary care. No extra electrodes will be placed.

Main-cohort inclusion criteria: age ≥18 years; planned first isolated liver transplantation at this center; completion of ethics-approved informed consent by the recipient or a legally authorized representative. Emergency transplantation, preoperative hepatic encephalopathy, ICU care, mechanical ventilation, and renal replacement therapy are eligible. Donor type and disease severity will be retained for stratification.

Main-cohort exclusion criteria: age <18; prior liver transplantation; combined-organ transplantation; refusal; or inability to obtain valid authorization under the approved consent procedure. Retransplantation and combined-organ recipients may enter a separate extended registry under the same ethics scope and will not enter the main first-isolated-transplant analysis or its sample-size denominator.

Eligible recipients will not be excluded because cognitive testing cannot be completed, language or cultural adaptation is difficult, raw signals fail, routine monitoring is limited, postoperative death occurs, residual material is unavailable, or supplementary testing is refused. These limitations affect only specific measures or substudies.

Consenting recipients who do not undergo transplantation will not enter post-transplant outcome analyses, but screening and relevant safety records will be retained. Retransplantation after enrollment will be an outcome of the initial transplant and will not add a new independent patient to the main cohort.

3.3 Withdrawal Suspension and Loss to Follow-up

Recipients may withdraw future contact, individual assessments, authorization for residual-material use, or all participation without affecting care. No corresponding new data or assays will be added after withdrawal. Existing data and materials will be handled according to consent, ethics requirements, and applicable retention duties. Deletion of irreversibly anonymized data or data already included in aggregate results will not be promised.

Death is an outcome, not loss to follow-up or grounds for exclusion. Assessments may be paused during instability, fatigue, delirium, or sedation, with reasons recorded. Follow-up will preferentially coincide with routine visits; authorized telephone contact will obtain survival, hospitalization, and living status when attendance is impossible. At least three contact attempts on different dates within each window, together with approved record checks, will precede classification as lost for a specific outcome.

Post-discharge events will be verified using multiple sources. Telephone contact will primarily obtain survival, home status, quality of life, and clues to medical encounters. Graft failure, retransplantation, readmission, and other objective events will preferentially be verified through this hospital's records, investigations, external discharge records, or diagnostic documentation. Inconsistent or insufficient evidence will receive independent adjudication and, where needed, verification during routine visits without research-only hospital attendance. Insufficient evidence will be coded as indeterminate, not absent. Delirium will primarily rely on contemporaneous standardized inpatient assessments and records, not post-discharge recollection.

3.4 Definitions of Care Exposures and Physiological Features

Preoperative status. Record age, sex, height, weight, education, main language, liver disease etiology, hepatocellular carcinoma, original Child-Pugh and MELD variables, prior organ disease and function, encephalopathy, infection, support, medication, nutrition, and function. MELD-Na and MELD 3.0 will use standardized versioned calculations. Highly correlated scores and all their components will not be included simultaneously in one adjustment model [22].

Surgical and graft exposures. Record procedure, donor and graft features, graft procurement, native liver removal, vessel clamping, portal and hepatic artery release, anhepatic-period start and end, vena cava management, bypass, cold and warm ischemia, preservation, and perfusion. Blood loss, salvaged blood, and transfusions will retain actual quantities, measurement or estimation methods, and phases.

Donor and graft classification. Donor source, graft morphology, and implantation method will be separate. Source includes living donation, donation after brain death, donation after circulatory death, and actual registration category. Morphology includes whole or partial liver; partial grafts further identify split, reduced-size, living-donor partial grafts, and segments. Auxiliary transplantation and domino source will have separate fields rather than mutually exclusive categories at the same level as partial grafts. Special procedures retain indications and anatomy with prespecified stratified or sensitivity analyses.

Ischemia and reperfusion times. Retain actual dates and times for withdrawal of donor life support, circulatory arrest, recorded hypotension or hypoxemia thresholds, cold flush, procurement, cold-storage start and end, implantation start, portal release, and hepatic artery release. Inapplicable events will be marked. For DCD donors, available blood pressure, SpO_2, and onset/end of SBP <50 mmHg will be extracted where possible. Functional donor warm ischemia will be calculated only when data support prespecified pressure or oxygenation thresholds, duration, and endpoints; durations from different thresholds will be analyzed separately [35].

For static cold storage, cold ischemia is defined as donor cold-flush start to final removal of the graft from cold storage for implantation. Recipient implantation warm ischemia is the subsequent interval to first graft blood-flow reperfusion. First reperfusion is not necessarily portal release and will follow actual sequence; portal and hepatic artery release remain separate. The total cold-flush-to-first-reperfusion interval will also be recorded and not conflated with time to removal from ice. Machine or regional perfusion will retain segment starts and ends, temperature, and method, with actual cold-storage, perfusion, and implantation intervals calculated separately. Warm perfusion will not count as cold ischemia.

Bypass. Record use and type, including venovenous bypass, temporary portocaval shunt, and other methods, with indications, cannulation or anastomotic route, start and stop, anticoagulants and doses, and confirmed bleeding, thrombosis, or other events. Nonuse will be explicit.

Anesthesia and other exposures. Record actual administration times, doses, and routes for sedative-hypnotics, opioids, neuromuscular blockers and reversal, infusion starts, stops and rate changes, and inhaled agents with end-tidal concentrations. Record vasoactive drugs, fluids, blood products, diuretics, anticoagulant and hemostatic drugs, insulin, calcium, antimicrobials, postoperative sedation and analgesia, organ support, and immunosuppression. Clinically documented treatment reasons and pretreatment status will be retained; care will not be changed to complete variables.

Domain	Core exposure records	Derived measures and interpretation
Surgery and ischemia	Clamping release anhepatic period cold and warm ischemia preservation perfusion	Actual durations calculated separately using uniform definitions stratified by procedure and preservation
Fluids and transfusion	Crystalloids colloids blood products salvaged blood blood loss urine	Phase-specific and cumulative amounts with original units product specifications and reference weight; recorded balance does not directly measure intravascular volume
Vasoactive drugs	Drug route starts stops boluses infusion-rate changes	Drug-specific duration and cumulative doses; conversion rules locked beforehand; interpret with hypotension and indications
Anesthesia and analgesia	Intravenous and inhaled anesthesia analgesia sedation reversal rescue	Retain drugs and phases; analyze cumulative and time-varying exposure separately; doses drug-specific
Respiration and temperature	Ventilation modes and setting changes oxygen concentration temperature site warming	Record management settings separately from physiological responses with timing and context
Early postoperative care	Organ support sedation analgesia immunosuppression other treatment	Retain starts stops doses; outcome-specific cutoffs distinguish pre-event care from rescue after events

Prespecified physiological features. The following five low-dimensional features support shared physiological association analyses. Thresholds describe exposures and are not treatment targets. Each feature retains valid duration, quality grade, and equipment conditions and is selected according to the clinical question.

Domain	Prespecified feature	Definition and required records
Circulation	Time-weighted MAP deficit below 65 mmHg	Integrate positive values of 65 minus actual MAP over time and divide by valid monitoring duration; unit mmHg; sensitivity thresholds 55 and 60 mmHg

Domain	Prespecified feature	Definition and required records
Oxygenation	Time burden of SpO_2 below 92%	Quality-flagged cumulative minutes and proportion of valid recording below threshold; exclude artifacts such as probe detachment
Ventilation	Proportion of time with end-tidal CO_2 outside 30-50 mmHg	Calculate only during assessable invasive ventilation; retain tidal volume respiratory rate dead-space context and actual clinical blood gases
Temperature	Time-weighted core-temperature deficit below 36°C	Integrate positive values of 36 minus temperature and normalize by valid duration; retain site and equipment
Brain function	Proportion of EEG suppression time	Duration classified as suppressed by a unified algorithm divided by valid EEG; also report valid duration and suppressed minutes; lock algorithm leads and filters before outcome association and review blinded

Extended features include blood pressure variability, respiratory and temperature changes, EEG spectra, interchannel relationships, cross-modality associations, and recovery rates around events. Each requires a prespecified question and extraction method. BIS, entropy, and suppression ratios across devices are not equivalent. Without uniform raw EEG, only appropriate clinical or within-device analyses will be undertaken. Comparability in other modalities likewise depends on original measurement methods.

Phase windows include induction to incision; incision to the anhepatic phase; the anhepatic phase; 0-5 minutes, 5-30 minutes, and 30 minutes to surgery end after first graft reperfusion. An assessable 5-minute pre-reperfusion baseline will also be retained. Missing phases remain unassessable and are not replaced by adjacent recordings. Before inspecting associations, substudies will specify primary exposure, scale, risk window, and adjustment, avoiding repeated searches for optimal thresholds or cutoffs in the complete data.

Postreperfusion syndrome. PRS will be recorded as an intraoperative event. Its prespecified hemodynamic definition is a MAP reduction >30% relative to the mean valid MAP in the final minute before first graft reperfusion, occurring in the first 5 minutes afterward and lasting continuously ≥1 minute. This baseline is the study's uniform operational definition; the preceding 5 minutes of raw data will be retained for review [34]. Record onset, nadir MAP, duration, heart rate and rhythm, management, and recovery time. Insufficient signal or baseline makes PRS indeterminate. Arrhythmia, arrest, and clinically measured hyperkalemia will be separately recorded with potassium, reference upper limit, and sampling time; none alone substitutes for PRS, and no extra blood will be collected. PRS itself is not part of the 30-day postoperative primary composite.

3.5 Data Collection and Follow-up

3.5.1 Observation Schedule

Window	Clinical information and outcomes	Signals assessments and supplementary testing
Waiting-list or preoperative assessment	History organ function infection medication available donor and graft information	After consent assess cognition frailty daily living and quality of life

Window	Clinical information and outcomes	Signals assessments and supplementary testing
Within 30 days before surgery updated before surgery	Update status support clinical echocardiography routine laboratory results and interval to surgery	Latest valid cognition and function baseline; QoR-15 within 72 hours; sleep module PSQI and HADS within 7 days; document inability
Before induction to operating-room departure	Surgery anesthesia circulation respiratory management fluids transfusion ischemia bypass PRS	Continuous export of routine multimodal signals; no extra monitoring or electrodes
Postoperative days 0-7	Daily routine laboratory results SOFA components support medications infection organ events	Twice-daily sedation and delirium; day-3 QoR-15; daily symptoms and activities; existing exportable monitoring
Day 7 ±1 day	ICU and hospital outcomes organ recovery discharge destination	Key secondary QoR-15 and daily living; discharge assessment supplementary and does not replace day 7
Day 30 contact ±7 days	Verify death all complications and readmission through exact day 30; Clavien-Dindo and CCI if complete	QoR-15 daily living cognitive complaints DAH-30; module PSQI and HADS
Day 90 ±14 days	Survival graft readmission organ support	MoCA frailty daily living EQ-5D-5L DAH-90; module PSQI and HADS
Months 6 and 12 ±30 days	Survival graft status clinical complications readmission	Same-version cognition frailty daily living and quality of life

Each visit will record sources, including institutional or external records and recipient or proxy reports, evidence date, and verification status. Telephone reports suggesting objective events require medical documentation where possible. If unavailable, retain a self-report-only flag without automatically adjudicating a prespecified organ complication.

Contact windows schedule visits but do not change the day-30 outcome boundary. Interviews before day 30 or 90 require subsequent contact or authorized records after the observation period to complete mortality, complications, hospitalization, and home-status information before finalizing outcomes or DAH-30/90. Incomplete full-period verification is indeterminate. Actual dates of all tests and assessments will be retained. Telephone follow-up is permitted for authorized living-status and questionnaire assessments; telephone cognitive tools, abbreviated questions, and proxy answers will not be directly converted to in-person MoCA scores.

3.5.2 Multimodal and Care Records

Module	Core records	Technical and applicability limits
Procedures and treatment	Surgical phases actual medication transfusion fluids ventilation adjustments warming support emergencies	Distinguish event and entry time; retain precision dose and documented reasons
Circulation	ECG arterial pressure and waveforms heart rate SpO_2 pulse waveform clinically monitored CVP and cardiac output	No research arterial central venous or pulmonary artery catheters; save exportable waveforms
Respiration	Tidal volume rate minute ventilation FiO_2 PEEP airway pressure end-tidal CO_2 mode	Retain actual update frequency and mode changes; synchronously save available waveforms

Module	Core records	Technical and applicability limits
Temperature	Temperature site method warming	Separate sites and assess comparability; no additional invasive probes
EEG	Raw voltage leads reference sampling filters impedance or signal quality processed indices	Native rate target ≥128 Hz; flag lower capability and limit frequencies; no upsampling to fabricate high-frequency data
Clinical laboratories	Blood gases lactate electrolytes glucose blood count coagulation liver and kidney function available ammonia CRP PCT troponin BNP or NT-proBNP CK-MB	Actual clinical testing only; sample and result times units platform reference ranges
Cardiac investigations	Actual preoperative and postoperative LVEF structural and functional echocardiography ECG rhythm evidence	Date indication method; no added examinations; untested marked missing
Routine pathology	Existing donor-graft native-liver and post-transplant clinical biopsy reports	Separate source indication time; no requirement for all three and no added biopsy

Numerical streams will preferentially be exported every 1-5 seconds; equipment-limited data retain their actual frequency. Routine numerical charting targets intervals no longer than 1 minute as a data-quality goal. Approved passive interfaces will not control equipment or affect alarms or displays.

Each modality will retain device model, native capability, valid duration, and missingness reason. Patients missing a signal remain in clinical-outcome and other applicable analyses. No additional monitoring devices, electrodes, catheters, or invasive probes will be introduced, and collection will not delay treatment.

Cardiac fields. Retain the latest valid preoperative LVEF and all clinical repeats with date, interval from surgery, transthoracic or transesophageal approach, and reported method. Troponin records include high-sensitivity or conventional assay, T or I type, platform, unit, 99th-percentile upper reference limit, and sampling time. Raw hs-cTnT and hs-cTnI concentrations will not be pooled; normalization by reference limit does not make them fully equivalent. BNP and NT-proBNP remain separate. CK-MB is collected only if clinically available, without mandatory testing [12]. Routine laboratory extraction is not restricted by the residual-serum-only rule for supplementary research assays; existing results will be extracted without accepting extra research materials.

Pathology fields. Separately record donor graft, native liver, and post-transplant biopsy specimen type, collection and report dates, indication, diagnosis, existing steatosis or fibrosis grading, and immunohistochemistry, retaining score name and version. Original pathology numbers remain only in the controlled institutional mapping; analyses use research specimen IDs. No report, no collection, and no authorization are separate codes. Only actual clinical reports are extracted; no requirement exists for preoperative, intraoperative, and postoperative tissue or all three liver sources. Report extraction and residual-tissue assays are managed separately.

Preoperative and postoperative assessment sessions should generally remain within 30-40 minutes and may be divided. Clinical care takes priority when patients cannot cooperate. Reasons are recorded without assigning normal scores. Actual assessment method and time are retained. In-person assessments coincide with inpatient care or routine visits; no research-only attendance is required. When an in-person assessment cannot coincide with a visit within its window, record missingness and continue authorized telephone follow-up rather than substitute unvalidated telephone measurement.

The sleep and emotional module follows the same burden limits, preferentially uses existing visits, may be split within windows, and records actual duration. Module participants among the first 45 will assess added burden and feasibility. Severely ill patients will not be excluded to improve completion.

3.6 Outcomes and Operational Definitions

The primary outcome reflects early mortality and organ-event burden; organ-specific outcomes describe particular injuries. Day-7 QoR-15, DAH-30/90, and longitudinal function represent distinct aspects of recovery. These levels and each scale's measurement domain will be interpreted independently; no unvalidated overall recovery score will be constructed.

3.6.1 Primary Outcome

The primary outcome is all-cause mortality or at least one prespecified major organ complication within 30 days after transplant surgery starts. Components retain fixed windows: EAD, AKI, and delirium primarily within 7 days; other events through day 30. Multiple events during one operation count once at patient level, while all components remain fully recorded.

Component	Window	Adjudication requirements
All-cause mortality	Surgery start through day 30	Date and verifiable cause; includes intraoperative death
EAD or graft failure	EAD first 7 days; failure or retransplantation through day 30	Olthoff EAD definition; also record graft failure and retransplantation for failure
New or worsening moderate-to-severe AKI	First 7 days	Fixed KDIGO stage 2 or 3; pre-existing AKI must meet worsening rules
New delirium or definite acute neurological event	Delirium first 7 days; stroke or status epilepticus through day 30	Standardized reviewed delirium assessment; clinical diagnosis and appropriate investigations for stroke or status epilepticus
Clinically confirmed major cardiovascular event	Through day 30	Acute myocardial infarction arrest or new acute heart failure supported by clinical and objective evidence
Major pulmonary complication	Through day 30	ARDS meeting locked definition or unplanned intubation/reintubation for acute respiratory failure

Components differ in severity and prognostic importance. The binary patient-level composite is retained to describe overall early events, with component incidence, severity, and overlap reported separately. Clavien-Dindo grading and the Comprehensive Complication Index (CCI) will assess postoperative severity and cumulative burden. Sensitivity analyses will remove delirium and, separately, EAD defined solely by transaminase elevation, assessing their influence on results. These supplementary analyses do not replace the primary composite.

Hepatic outcomes. EAD is any of: total bilirubin ≥10 mg/dL (approximately 171 μmol/L) on postoperative day 7; INR ≥1.6 on day 7; or AST or ALT >2,000 IU/L during the first 7 days [9]. Day-7 tests will be assigned by postoperative calendar day with actual time retained. If repeated that day, use the prespecified result closest to 08:00; retain all original results. No research blood collection will replace a missing day-7 test, and results from other days will not directly substitute. A positive transaminase criterion establishes EAD; if this criterion is not met and day-7 data are insufficient, EAD is indeterminate. Death or retransplantation before day 7 enters the corresponding primary component and cannot be classified as event-free because laboratory data are missing.

Renal outcomes. The formal KDIGO 2012 definition and version will be locked [10]. AKI is a creatinine rise ≥0.3 mg/dL within 48 hours, an increase to ≥1.5 times baseline within 7 days, or urine output <0.5 mL/kg/h for ≥6 hours. Stage 2 is creatinine 2.0-2.9 times baseline or urine output <0.5 mL/kg/h for ≥12 hours. Stage 3 is creatinine ≥3 times baseline, an acute rise to ≥4.0 mg/dL, initiation of renal replacement

for AKI, urine output <0.3 mL/kg/h for ≥24 hours, or anuria for ≥12 hours. Use the higher creatinine or urine stage; creatinine ≥4.0 mg/dL must occur in an acute-change context. Urine output uses a fixed preoperative reference weight, documenting weight selection in marked ascites. Inadequate continuous urine data will be flagged, and creatinine-only findings also reported.

Baseline renal function will preferentially use median creatinine during stable illness 7-90 days before transplantation; the latest 7-day changes determine preoperative AKI. Without a stable historical value, use the latest within 24 hours before induction, flagging baseline uncertainty. Creatinine will not be back-calculated assuming normal function. Preoperative stage 1 progressing to 2 or 3 and stage 2 progressing to 3 count as worsening. Existing stage 3 or acute renal replacement does not become a new event merely by remaining stage 3; treatment persistence and recovery are reported separately. Maintenance-dialysis patients are excluded from the new-AKI denominator but remain in other analyses. As of September 21, 2026, the KDIGO website still listed the 2026 AKI/AKD public-review draft and indicated that publication was being prepared after feedback. This protocol locks the formal 2012 criteria and does not mix draft definitions [11].

Brain-function outcomes. Preoperative encephalopathy, delirium, and cognition will be recorded. During the first 7 inpatient postoperative days, trained staff assess RASS morning and evening, followed by CAM-ICU; general wards use uniformly trained CAM. RASS −4 or −5 indicates coma or deep sedation and nonassessability, not a negative delirium assessment. Otherwise, assessment follows tool applicability [13]. Positive assessments receive independent review. In patients with preoperative delirium, persistent positivity is persistence, not a new event. New delirium requires renewed positivity after at least 24 hours with two consecutive assessable negative results. If preoperative hepatic encephalopathy prevents reliable mental-status classification, new delirium is indeterminate. Patients discharged before day 7 retain inpatient assessments and verified subsequent medical events; telephone interviews do not replace standardized delirium diagnosis, and missed assessment opportunities are flagged.

Cardiovascular outcomes. Myocardial infarction will use the 2018 Fourth Universal Definition, requiring troponin dynamics and evidence of ischemia. At least one troponin above the assay's 99th-percentile upper reference limit indicates myocardial injury; a rise/fall prompts assessment of acute injury. Elevation alone does not establish infarction [12]. No additional troponin, ECG, or echocardiography will be ordered. Absence of testing cannot establish absence of myocardial injury. Primary cardiovascular outcomes are limited to clinically confirmable events. A clinically major cardiovascular event may be classified absent after hospitalization, discharge, reattendance, and follow-up records for the window have been verified, no qualifying event or unresolved suspicious symptom, sign, or care clue is present, and an independent adjudicator has reviewed the case. Lack of systematic troponin testing alone does not make clinical-event status indeterminate, but cannot exclude subclinical injury. Suspected events with insufficient diagnostic information or missing key clinical/follow-up records are indeterminate. Acute heart failure requires new signs or symptoms and objective support; positive fluid balance, vasoactive use, or a single LVEF alone is insufficient.

Pulmonary outcomes. ARDS uses the 2024 Global Definition. Retain onset, bilateral imaging, oxygenation, respiratory support and settings, and exclude predominantly cardiogenic edema. Criteria require onset within 1 week of a known insult or new/worsening respiratory symptoms, bilateral imaging abnormalities, and hypoxemia not primarily explained by cardiac factors. Oxygenation is PaO_2/FiO_2 ≤300 mmHg or SpO_2/FiO_2 ≤315 when SpO_2 ≤97%, together with appropriate respiratory-support conditions. Nonintubated patients require documentation of high-flow nasal oxygen ≥30 L/min or qualifying noninvasive support; invasively ventilated patients require parameters including PEEP ≥5 cmH_2O. Berlin-defined results may also be calculated where needed [14]. Planned intubation for repeat surgery does not count as reintubation for respiratory failure.

Pre-existing abnormalities in other organs count only when explicit new-onset or worsening rules are met. Each outcome is coded absent, present, not applicable, or indeterminate. Absence requires the relevant observation and verification; missing diagnostic codes or no examination alone are insufficient. EAD, AKI,

and delirium follow their respective laboratory, urine-output, and assessment rules; major clinical cardiovascular events follow the verification rules above. Not applicable is restricted to prespecified baseline conditions and is not a substitute for missingness. Any confirmed component makes the composite positive. The composite is negative only if no event is confirmed and every applicable component is ascertainably absent. If any applicable component lacks required key information, the composite is indeterminate, with the event and reason specified. No extra examination or sampling will complete outcomes.

3.6.2 Secondary Outcomes

Occurrence, timing, stage, and severity of all primary components will be recorded, along with stage-1 AKI, lactate and routine organ-function changes, renal replacement, infection, reoperation, rejection, vascular and biliary complications, ICU readmission, and hospital readmission.

Infection and organ function. Record site, suspected or confirmed status, onset and diagnosis times, microbiology, imaging, anti-infective treatment, and clinical basis. An isolated CRP or PCT elevation does not confirm infection. Traditional SOFA components and worst values will be extracted for the preoperative 24 hours and fixed daily 24-hour inpatient windows during the first 7 postoperative days, using the version in Sepsis-3. Retain effects of organ support and sedation; missing components are missing, not zero. Suspected infections after day 7 will use existing SOFA components and support records before infection and around onset, retaining times. Clinically recorded APACHE II may be retained as an ICU extension with version and time; no new universal assessment is required.

Sepsis requires suspected/confirmed infection and an acute SOFA increase ≥ 2 attributable to infection under Sepsis-3. Baseline uses the nearest ascertainable pre-infection organ state. Cirrhosis and other pre-existing abnormalities preclude assuming baseline zero. Unclear baseline or inadequate infection attribution is indeterminate; postoperative abnormalities require clinical evaluation of attribution. Septic shock additionally requires vasoactive drugs to maintain MAP ≥ 65 mmHg and lactate >2 mmol/L despite adequate volume resuscitation, assessed in context [31]. Infection, sepsis, and septic shock are secondary outcomes through day 30; later events are separately recorded.

Complication severity and cumulative burden. All actual postoperative complications within 30 days after surgery starts will retain type, time, treatment, and outcome and receive Clavien-Dindo grading. Report the highest patient grade and proportion with grade $\geq$III [32]. Planned routine ICU admission, prophylaxis, and treatment intrinsic to transplantation do not themselves establish a complication grade. With complete full-period event and treatment records, calculate the formal CCI (0-100): zero for no complication and 100 for death. Include all qualifying complications using the formal weighted algorithm, not only primary composite events or direct addition of grades [33]. A continuous course or treatment escalation updates the same event and highest grade rather than generating duplicates. Incomplete verification makes CCI indeterminate.

Secondary cardiovascular measures. Record clinically supported myocardial injury and new or clearly worsened arrhythmias through day 30, including atrial fibrillation, atrial tachycardia, and other rhythms, with ECG/monitor evidence, start/end, duration, hemodynamic impact, and treatment. Pre-existing persistent arrhythmia is not new. Changes in LVEF, troponin, BNP, or NT-proBNP will be analyzed only with clinically obtained comparable repeats. No extra testing will replace missing data, and proportions in tested patients will not be extrapolated directly to the cohort.

Record durations of mechanical ventilation, vasoactive use, and renal replacement, and ICU and hospital stay. Day-28 invasive-ventilation-free days are days alive and free of invasive ventilation; death within 28 days scores zero. Separately report mortality and ventilation duration among survivors to reduce distortion of support and recovery measures by early death.

Patient survival, graft status, retransplantation, and readmission will be recorded at days 30 and 90 and months 6 and 12. Cognition, frailty, daily living, and quality of life will be assessed at day 90 and months 6

and 12. The core cognitive measure is a uniform Chinese MoCA total and change from baseline, interpreted with education, language, sensory limitations, and current illness. Formal perioperative neurocognitive-disorder diagnosis requires appropriate neuropsychological testing, subjective change, and functional-impact information; MoCA decline alone is insufficient [15].

Frailty will use the Liver Frailty Index when safe cooperation is possible, retaining raw grip strength, chair stands, and balance, with specific noncompletion reasons [23]. Approved-version procedures will be followed. Clinical staff must confirm stability, activity permission, and willingness before testing; safety and stopping rules are below. Tests withheld for safety are not assigned normal values. Completed items retain raw results, with scoring determined by version rules. Daily living uses uniform Barthel and Lawton instrumental activities of daily living scales; quality of life uses an authorized Chinese EQ-5D-5L. Early recovery uses an authorized Chinese QoR-15, with day-7 total the key secondary patient-reported outcome, plus preoperative and day-3/day-30 changes [5,6]. Versions, permissions, and assessor training will be standardized. Proxy and patient reports will be flagged and analyzed separately.

3.6.3 Patient Reported Outcomes and Functional Recovery

QoR-15 scoring. Use a validated authorized Chinese version with formal scoring: 15 items, total 0-150, higher scores indicating better recovery. Domains include comfort, physical independence, emotional state, psychological support, and pain [5,6]. Responses reflect the patient's actual preceding 24 hours; retain item responses and total. Trained researchers may read original items and record the patient's own answers without rewriting or substituting clinical impressions. Validation in general Chinese surgical populations does not establish measurement performance in liver transplantation; completion, score distribution, internal consistency, and floor/ceiling effects will also be reported.

Timing and main comparisons. Assess within 72 hours preoperatively and on day 3 ±1, day 7 ±1, and day 30 ±7. Baseline must precede sedation and require reliable response. Day-7 total is the key secondary outcome; day-3/day-30 totals, changes, and repeated trajectories are other secondary measures. Early discharge does not remove fixed-window authorized interviews; record method. Discharge-day scores supplement rather than replace day 7. Emergency recipients without baseline retain postoperative absolute scores without baseline changes.

Nonassessability and missing items. Coma, deep sedation, current delirium, or unreliable expression will be recorded. QoR-15 will not be assigned zero or normal scores or directly completed by relatives. Scores after death are undefined and not numerically imputed. Reassessment is allowed after improvement within the window; out-of-window results are flagged. Missing items will be clarified within the window where possible. If incomplete, retain raw responses and follow formal version rules for total scoring; no unvalidated mean imputation or prorating. Report death, nonassessability, refusal, and completion at each point.

Days at home at 30 and 90 days. DAH-30/90 equals the observation period minus initial hospitalization, readmissions, and inpatient rehabilitation or nursing-facility days, counting overlapping dates once. Calendar-date intervals include admission and exclude discharge dates, clipped to the continuous 30- or 90-day period starting on the surgery date. Ordinary homes and nonmedical temporary accommodation count as home; institution type and discharge destination are recorded separately. Death within the corresponding period scores zero, with mortality, institutional stays, and readmission separately reported. Missing hospitalization or destination data make home status uncertain. DAH-90 captures longer recovery beyond initial admission and does not replace cognition or independent-living assessment [7].

Symptoms and mobility. During the first 7 inpatient days, record daily self-reported rest and activity pain NRS (0-10), preceding-24-hour nausea (none/mild/moderate/severe), vomiting episodes, and rescue analgesics and antiemetics when assessable. Record actual first standing out of bed, first walking ≥10 m, and assistance required. Activity must follow clinical rehabilitation; support will not be withdrawn early or

intensity increased for research. Inability to assess symptoms and failure to reach mobility milestones are separate. Analyses account for death and illness limitations.

Roles of measures. QoR-15 assesses early subjective recovery. EQ-5D-5L, Barthel, Lawton IADL, LFI, and MoCA respectively add quality of life, daily living, frailty, and cognition under the existing schedule. PSQI and HADS serve the prespecified module below and will not be merged with other scales into one recovery score.

Sleep and emotional recovery module. This prespecified extension will launch when staff, authorized versions, and follow-up resources are ready. Its start date will be explicit; thereafter eligible parent-cohort recipients will be consecutively invited regardless of operation time, severity, or follow-up convenience. Participation does not affect parent-cohort eligibility. Chinese-validated, authorized PSQI and HADS versions, scoring, and interview methods will be locked before launch.

Assess within 7 preoperative days, on day 30 ±7, and day 90 ±14. Baseline must precede sedation and require reliable answers; no retrospective postoperative completion of preoperative scales. Record date, inpatient/home status, prior sleep or mood disorders, relevant treatment, and link existing sedation, analgesia, and immunosuppression. Out-of-window results are flagged; discharge assessment does not replace fixed windows.

PSQI retains items, seven component scores, and total 0-21 under formal rules; higher scores indicate worse self-reported sleep over the preceding month [28]. Day 30 generally covers inpatient and post-discharge experiences; day 90 primarily reflects its preceding month, not the entire 90 days. HADS-A and HADS-D are separate 0-21 scores, higher indicating more anxiety or depressive symptoms over the preceding week [29,30]. Continuous scores and baseline changes are primary; screening cutoffs do not directly diagnose insomnia, anxiety disorder, or depressive disorder.

Report PSQI, HADS-A, and HADS-D at each time and change from valid baseline. Without baseline, retain postoperative status without calculating change. Suspend self-assessment during delirium, coma, deep sedation, or unreliable expression and document reasons. No relative substitution, zero assignment, or post-death score is allowed. Trained staff may read formal items and record the patient's answers. Missing items follow version rules without unvalidated completion; recall periods remain consistent. Report death, surviving but unassessable, refusal, loss, and completion at each time, and assess population differences from the parent cohort and feasibility.

3.7 Supplementary Testing of Residual Clinical Serum and Tissue

Only residual serum and tissue already collected for care, no longer needed after routine testing, diagnosis, necessary review, and retention, and confirmed by laboratory/pathology staff as available for research will be accepted. Materials will be received at formal handover, never recovered after entry into medical-waste disposal.

No added punctures, tubes, volume, or frequency are allowed. No extra sampling at specified reperfusion windows or changes in clinical timing will be requested. Native-liver, donor-graft, or transplanted-liver tissue must already have been clinically collected with genuine residual material. Blocks, slides, or tissue still requiring clinical retention cannot be declared waste by researchers. Donor tissue requires source verification and donor-side authorization; recipient consent does not replace it.

Testing is restricted to non-genetic protein quantification or histology related to protocol questions. An independently approved list may specify serum-compatible candidate markers of neural injury, inflammation, or endothelial responses, and histology or immunohistochemistry on suitable tissue. Only separately approved assays are permitted; genetic sequencing, single-cell research, or comprehensive multiomics require separate approval. No research materials will be accepted without an approved list.

Each assay list must specify the question, marker, material source, method, minimum quantity, quality conditions, maximum temporary storage, and final disposal. Only actual residual serum amounts are used;

no required pairing or target number. Storage for approved assays should generally not exceed 6 months after receipt, followed by approved disposal after testing and necessary review. Shorter clinical-department requirements prevail. Materials will not become unapproved future-research reserves.

Assays requiring plasma, whole blood, or additional fixed-time blood collection are outside this supplementary scope. Arginine-related metabolites, enzyme activity, or unlisted assays are not automatically included. Research needs at 1, 6, or 24 hours cannot change clinical blood draws. Serum methods require prior suitability confirmation and review of purpose and method. Every approved substudy assay uses dedicated traceable records linked to study IDs, retaining methods, batches, and results even if absent from the core case-report form.

Record actual clinical sampling, receipt and processing times, source, indication, storage, freeze-thaw cycles, hemolysis or other quality issues, batches, and final disposition. No material, insufficient amount, poor quality, and no authorization are separate codes; no replacement collection or normal-value assignment. Cases and controls will be balanced across batches where feasible; laboratory staff will be blinded to outcomes.

3.8 Sample Size

3.8.1 Precision Based Design for the Primary Outcome Proportion

The study primarily establishes a single-center prospective cohort, systematically collecting perioperative care, multiorgan outcomes, and long-term recovery rather than performing a confirmatory test of a specified exposure. The parent-cohort sample size therefore primarily reflects precision in estimating the 30-day primary composite proportion. Specific exposure and recovery analyses require separate information assessments. Approximately 100 adult transplants annually yield about 500 procedures over 5 years. Given this population, use conservative $p = 0.50$, a two-sided 95% confidence level, and absolute margin $d = 0.05$.

$$\textbf{Evaluable sample size } n = 1.96^2 \times p \times (1 - p) / d^2$$

Substitution gives 384.16, rounded up to 385. Allowing 10% incomplete primary-outcome ascertainment requires 385 / 0.90 = 427.78, rounded up to 428 enrollments. The target is 450 first-time isolated liver recipients, yielding approximately 405 evaluable primary outcomes. Ten percent is a planning allowance, not an observed loss-to-follow-up rate.

This calculation concerns the overall proportion among this center's recipients. Final reporting will include proportions and confidence intervals, using recipient-level resampling where appropriate. Generalizability from this single center to other centers or the national population is limited.

3.8.2 Procedure Volume and Enrollment Target

Approximately 500 procedures may be screened over 5 years. Reaching 450 requires around 90% to enter the main cohort after first-isolated-transplant and valid-consent criteria, a feasibility assumption to be assessed using consecutive screening. Screening follows actual procedure order to avoid selection.

If only 80% are eligible and consenting, approximately 400 would enroll and 360 would be evaluable at 90% ascertainment. At $p = 0.50$, the approximate 95% interval half-width is 5.17 percentage points. Actual precision will be reported. Independent sample size counts recipients, not repeat transplant events or signal segments. Extended enrollment or additional centers require separate assessment and amendment.

Evaluable primary outcomes	Approximate half-width at p = 0.30	Approximate half-width at p = 0.50
360	4.73 percentage points	5.17 percentage points
385	4.58 percentage points	4.99 percentage points

Evaluable primary outcomes	Approximate half-width at p = 0.30	Approximate half-width at p = 0.50
405	4.46 percentage points	4.87 percentage points
450	4.23 percentage points	4.62 percentage points

These normal approximations are for planning; actual proportion intervals use Wilson's method. Screening volume, consent, primary-outcome assessability, and multimodal-feature availability are calculated separately. Expected procedures, evaluable primary outcomes, and each substudy's analysis population are distinct.

3.8.3 Limits for Association Studies and Prediction Models

Parent-cohort precision does not establish power for every association. Each substudy will calculate sample size from exposure distribution, anticipated effect, outcome proportion, missingness, and adjustment needs. Without reliable effect sizes, analyses will emphasize estimates and confidence intervals and be designated exploratory.

The 450 target is based on precision of the 30-day clinical outcome while collecting early and long-term recovery. Power for QoR-15 group differences requires its own measurement-distribution assessment. A substudy making QoR-15 primary must consider standard deviation, completion, repeated-measure correlation, and a prespecified minimum relevant difference. Thresholds from other surgical populations will not be treated as transplant-validated cutoffs.

The sleep and emotional substudy requires a separate rationale based on the prespecified PSQI, HADS-A, or HADS-D outcome and time, score variation, within-person correlation, coverage, and attrition. The parent target does not mean all 450 can complete the module or guarantee power for every sleep and mood hypothesis.

Prediction-model sample size follows Riley et al., considering total size, event proportion, candidate parameters, anticipated Cox-Snell R^2, and shrinkage, rather than the 10-events-per-variable heuristic alone [16,17]. As a complexity example, assume Cox-Snell $R^2 = 0.15$, target shrinkage $S = 0.90$, and $P = 6$ candidate parameters. The overfitting-control criterion alone gives:

$$\textbf{Required } n = P / [(S - 1) \times \ln(1 - R^2/S)] = 330 \textbf{ after rounding up}$$

Under the same assumptions, $P = 7$ requires 384 and $P = 8$ requires 439. If $R^2 = 0.10$, $P = 6$ requires 510, beyond expected effective size. These are planning assumptions, not observed performance; additional criteria for overall risk estimation and optimism control must also be met.

Among 405 evaluable recipients, event proportions of 20%, 30%, or 50% yield approximately 81, 122, or 203 events. Multimodal models are further limited by signal availability. Initial models therefore target approximately six effective parameters, counting categorical terms, nonlinear terms, and interactions. Complexity increases only with full sample-size support. Individual modalities may be added separately to a common clinical model with question-specific prespecified features. After the first 45, overall event rates and signal availability inform feasible complexity. Inadequate information restricts work to low-dimensional prespecified associations, existing-model validation, or description. Arbitrary splitting and repeated selection will not inflate complexity. Independent models for rare organ events depend on actual event counts.

3.9 Statistical Analysis

3.9.1 Principles and Analysis Populations

Before primary-outcome analysis, lock the statistical plan, exposure representation, and feature-extraction version. The main clinical analysis includes all enrolled eligible first-time isolated liver recipients who actually undergo surgery; extended-registry recipients are separate. Modality and scale analysis sets depend on assessability, with differences from the full cohort and missingness explained. Supplementary assays use actual evaluable participants only.

Analyses address, in order, distributions of events and recovery; associations of care exposures and physiology; relationships between early events and later function; and incremental prediction from prespecified dynamic information. Models use question-relevant data without requiring every exposure and modality. Completeness of EEG or any single measure does not define the full cohort.

Continuous variables are summarized as mean and standard deviation or median and interquartile range according to distribution; categorical variables as counts, proportions, and denominators. Main effects include 95% confidence intervals and applicable center, period, and assessability conditions. Clinical knowledge and temporal position determine adjustment, not univariable P-value screening.

3.9.2 Primary and Organ Specific Outcomes

Report the 30-day composite proportion and interval with component and overlap counts. Indeterminate cases receive counts, reasons, and boundary analyses assuming all had events or none had events. With adequate auxiliary clinical information and defensible missingness assumptions, multiple imputation will provide the primary estimate alongside observed-case analyses.

PRS, infection/sepsis, arrhythmia, Clavien-Dindo, and CCI remain secondary without changing the composite. Report grade distribution and grade ≥III; present CCI continuously with an evaluable denominator. Cardiac biomarkers and repeated LVEF will be described by actual time and comparable methods. Adjusted analyses require adequate coverage and covariates; tested and untested patients will be compared. No testing is not a negative result, and indication-related selection bias will be explained.

Organ-specific analyses use the corresponding at-risk population and baseline. Death precluding an organ event is a competing event for cumulative incidence. Death is already part of the composite and is not its competing event. Because some components are only ascertainable by day, the primary analysis is a 30-day binary result. Time-to-event models are reserved for outcomes with sufficiently reliable onset times.

3.9.3 Associations of Care Exposures and Physiology With Organ Outcomes

Questions and temporal order. Surgery/ischemia, fluids/transfusion, vasoactive drugs, anesthesia/analgesia, and respiratory/temperature substudies will separately prespecify questions, variables, outcomes, and risk windows. Dose, duration, and phase will be interpreted with pretreatment status. Outcome-risk windows must follow exposure windows; prior events cannot be new outcomes of later treatment. Whole-operation cumulative exposures address postoperative events; intraoperative events require temporally appropriate exposure windows.

Shared physiology. The five prespecified low-dimensional features will each be modeled against the primary outcome without privileging a modality. Depending on frequency and assumptions, logistic or appropriate robust Poisson regression will report odds or risk ratios with 95% intervals and clinically interpretable absolute risk differences from standardized predictions. Continuous exposures remain continuous; nonlinear relationships require sufficient information and prior specification.

Baseline risk and indications. Candidate adjustment includes age, liver severity, target-organ baseline, and necessary graft and surgical data, using a parsimonious set appropriate to exposure timing. Transfusion analyses consider preceding bleeding and illness; vasoactive analyses preceding circulation;

sedation/anesthesia analyses prior encephalopathy and indications. Unmeasured indications will be acknowledged as residual confounding. Dose or support associations do not directly demonstrate treatment harm.

Different aims require separate models. Overall care-exposure associations use adjustment based on the target effect and temporal order, avoiding inappropriate adjustment for post-exposure physiology or injury. Incremental physiological information analyses include prior treatment variables according to the prespecified aim. Each substudy lists variables and reasons, distinguishing confounders, mediators, and post-outcome variables.

Repeated observations. Categorical, nonlinear, and interaction terms count toward parameter totals. Multiple times or segments within patients require mixed-effects models or suitable correlation structures and do not increase independent sample size.

Information and causal interpretation. Exposure substudies separately justify effect range, evaluable numbers, and adjustment; limited information reduces complexity or limits reporting to description. Causal analysis of time-varying treatment requires separate prespecification of time intervals, indications, estimands, and assumptions. Marginal structural models or other methods may be used when supported, checking weights and overlap. Ordinary regression in the parent protocol will be described as association.

3.9.4 Risk Prediction and Validation

Prediction and association research are reported separately. The principal prediction time is surgery end. Only previously available information predicts postoperative events not yet occurring; intraoperative events are excluded as new events at this time. Separate 6-hour or 24-hour dynamic prediction redefines the still-at-risk population and predicts only later new events, avoiding use of post-outcome tests or treatment as predictors.

Establish a clinical baseline model, then add prespecified multimodal features in the same evaluable population. Prioritize age, liver severity, and target-organ baseline. Limit parameters by actual information, preferentially using penalized regression and low-dimensional interpretable features. Deep learning and automated high-dimensional research are extensions requiring independent sample-size justification, not mandatory outputs.

Patient-level bootstrap internal validation will generally use 500 replicates. Missing-data processing, standardization, feature selection, and tuning occur within each training sample. All times, waveform segments, and assays from one recipient remain in the same dataset to prevent leakage.

External applicability requires future independent validation. If insufficient events prevent stable development, report only feasible internal validation and uncertainty.

Assess discrimination, calibration intercept and slope, calibration curves, Brier score, and decision-curve net benefit across prespecified clinical thresholds. Compare metrics before and after multimodal additions with confidence intervals. Models without independent validation will not guide treatment; improved prediction is not equivalent to clinical benefit. Reporting follows TRIPOD+AI [18].

3.9.5 Organ Events Recovery Missingness and Supplementary Assays

Early recovery. Analyze QoR-15 continuously, with day-7 total key secondary; report distributions and completion at each time. Repeated-measures models treat time categorically and account for within-patient correlation, adjusting for valid baseline when available. Marked skewness or ceiling effects warrant robust or quantile methods. No outcome-driven optimal poor-recovery cutoff will be chosen.

Events and recovery. For any QoR-15 or function assessment, analyses of prior events and subsequent recovery include only preceding events, retaining actual intervals. Day-7 associations with recovery at day 90 or later require an explicit landmark population and prior-event status. Events after day 7 but within the

30-day composite cannot be preceding predictors of day-7 QoR-15. All analyses report deaths, nonassessable patients, and surviving evaluable patients.

Days at home. Report DAH-30/90 distributions and zero proportions; two-part models may analyze zero versus positive values and positive days separately. Death and full-period institutional stays are shown separately. Complications and DAH within the same period represent concurrent associations, recognizing hospitalization as part of DAH. Landmark prediction of later home status redefines the outcome window after the landmark and is reported separately from full DAH-30/90.

Long-term function. Repeated-measures models for frailty, living abilities, cognition, and quality of life consider baseline, time, age, education, and relevant context. Improvement, stability, and decline are all possible. Without valid baseline, subsequent status is reported without change. In-person versus telephone and patient versus proxy measurements remain flagged; unvalidated measures are not directly pooled. Pain, nausea/vomiting, and mobility milestones support secondary description or prespecified associations and enter substudy multiplicity plans.

Sleep and emotional recovery. Analyze PSQI, HADS-A, and HADS-D separately as continuous scores, with preoperative, day-30/day-90 distributions and changes. When information permits, use categorical time, patient random intercepts, and baseline scores, with question-specific adjustment. Only preceding organ events support subsequent recovery analyses; events and scores within the same recall period are concurrent. PSQI and HADS recall windows are explicitly different. Plans prespecify main comparisons and control multiplicity across scores, times, and exposures. Limited information warrants effect estimates and intervals; independent modeling depends on actual information.

Death and nonassessability. Death, coma/deep sedation, illness preventing assessment, refusal, technical failure, and loss are coded separately. QoR-15, PSQI, HADS, cognitive, and functional scores after death are undefined and not ordinarily numerically imputed. Longitudinal results jointly report survival, survivors' trajectories, and assessability. Selective survivor attrition may use inverse-probability weighting under appropriate assumptions with missingness sensitivity analyses.

Missing data. Clinical covariates may use multiple imputation under acceptable missingness assumptions, including outcomes and auxiliary variables, generally with at least 20 imputations adjusted for missingness. Prediction-validation imputation rules are developed only within corresponding training data. Long waveform gaps will not be reconstructed as real signals. Equipment-related absence of an entire modality requires coverage reporting and appropriate restricted analyses, not statistical imputation replacing actual measurement.

Supplementary assays. Compare baseline and outcomes in tested versus untested participants, considering collection indications, timing, transfusion and dilution, clearance, processing, and batch. Selection-probability weighting requires adequate covariates and assumptions; residual selection bias remains explicit. No paired analysis without paired material; native and donor livers are not pre/post samples of one organ.

3.9.6 Multiplicity and Sensitivity Analyses

The primary proportion is reported as an estimate with precision. The five prespecified physiological-feature associations form one testing family, with Holm control of two-sided familywise error at 0.05. Exposure substudies prespecify their own hypotheses and families, apply appropriate correction, and distinguish primary from exploratory tests.

Organ-specific, phase, subgroup, and extended-feature analyses are secondary or exploratory. Larger-scale feature screening uses Benjamini-Hochberg false-discovery control with effect sizes and uncertainty. Each recovery measure has an explicit role to prevent selective reporting across scales, times, or thresholds.

Prespecified sensitivity analyses include alternative MAP thresholds, high-quality signals only, alternative organ baselines, different composite components, boundary handling of indeterminate primary outcomes,

and results by donor type and preoperative support. Recovery analyses assess nonassessability and selective attrition. Subgroup differences rely on interactions and intervals, not significance in one group and nonsignificance in another. For indeterminate 30-day outcomes, report proportion, reasons, and baseline differences and perform appropriate analyses according to data and missingness. Medical-record-confirmed and self-report-only events are counted separately; unverified diagnoses are not adjudicated endpoints.

3.10 Data Management Quality Control and Safety Oversight

3.10.1 Data Management and Quality Control

Structure and traceability. Use uniform electronic case-report forms and a dictionary, with separate linked tables for recipients, transplant episodes, grafts, repeated tests, treatment events, outcomes, scales, signals, and supplementary assays. Name/contact/hospital-number mappings remain in a controlled institutional environment; analysis databases use coded IDs.

Time synchronization. Use an institution-approved time source and record device offsets. Check differences before and after surgery; synchronize network-capable devices when permitted. Retain original timestamps, corrections, and rationale. Operational targets are ≤1-second offsets for automated data and ≤1-minute errors for key manual events. Otherwise flag precision and restrict second-level coupling or short-window analysis. Analytical resolution cannot exceed source precision.

Raw-signal protection. Retain original files, device model, firmware, sampling, leads, filters, quality, and checksums. Raw data remain read-only; cleaning and feature files are separate and versioned. Device trends do not replace waveforms. Long gaps remain flagged and are not smoothed or interpolated into measured signals.

Training and adjudication. Before launch, train eligibility, events, RASS, CAM-ICU/CAM, and functional assessment using standardized cases and paired-assessor agreement practice; retrain new staff. Investigator 5 manages adjudication. Difficult events receive independent review by investigator 5 and an investigator from 2-4 who did not treat that case; the principal investigator resolves disagreement. Adjudicators do not extract the corresponding research signal features and remain blinded to them and assay results.

The sleep module adds training on versions, item reading, recall periods, and missing items. Before launch, standardized cases verify donor/graft classification, ischemia, PRS, infection attribution, and Clavien-Dindo. CCI and scales use checked fixed algorithms with original events, items, and calculation versions retained.

Entry and checking. Validate units, ranges, chronology, duplicate enrollment, pre/postoperative placement, and outcome logic. Perform full source verification for primary outcomes, death, retransplantation, and key surgical times, plus random review of at least 10% of cases each quarter. Outliers trigger verification, not automatic deletion of real extreme values. Changes retain operator, time, and reason.

Comparability. Retain laboratory platforms and ranges, use consistent dose units, and document native sampling. Equipment changes remain metadata; restrict to comparable devices or periods when necessary. Statisticians periodically summarize coverage and missingness, applying prespecified scope criteria.

For cardiac testing, report clinical coverage and comparable repeated-testing proportions separately. For the sleep module, report eligible, consenting, deceased, surviving assessable, and actual completers by enrollment date and time. Distinguish patients before module launch from enrolled participants lost later. Changes in platforms, versions, or administration retain boundaries and are not automatically pooled.

Permissions and security. Use role-based authorization, encrypted transfer, access logs, and backups. Analysis data should generally remain in an institution-approved environment within China. Share coded data only within institutional, contractual, and ethics authorization. Retention follows institutional policy,

consent, and applicable requirements, with approved disposal afterward. Reidentifiable coded data will not be called anonymized.

3.10.2 Safety Reporting and Adverse Events

The study allocates no treatment and adds no biological collection, monitoring equipment, or electrodes. Routine-monitoring use and safety remain with clinicians. Data interfaces must meet equipment and information-security rules without affecting displays, alarms, or operation. Questionnaires may cause fatigue or emotional discomfort; grip, chair-stand, and balance testing may cause fatigue, pain, or instability. Trained staff will perform standardized physical tests only after clinicians confirm stability, permitted activity, and patient willingness, with necessary protection. Acute deterioration, activity restriction, or unreliable cooperation warrants deferral and documentation. Dizziness, dyspnea, pain, marked fatigue, loss of balance, or a request to stop requires immediate termination and clinically appropriate management. Tests remain within allowed activity; no training or rehabilitation changes are made to improve scores. First standing and walking milestones are observed during natural clinical rehabilitation; no added walking test. Stopping one test does not end other follow-up.

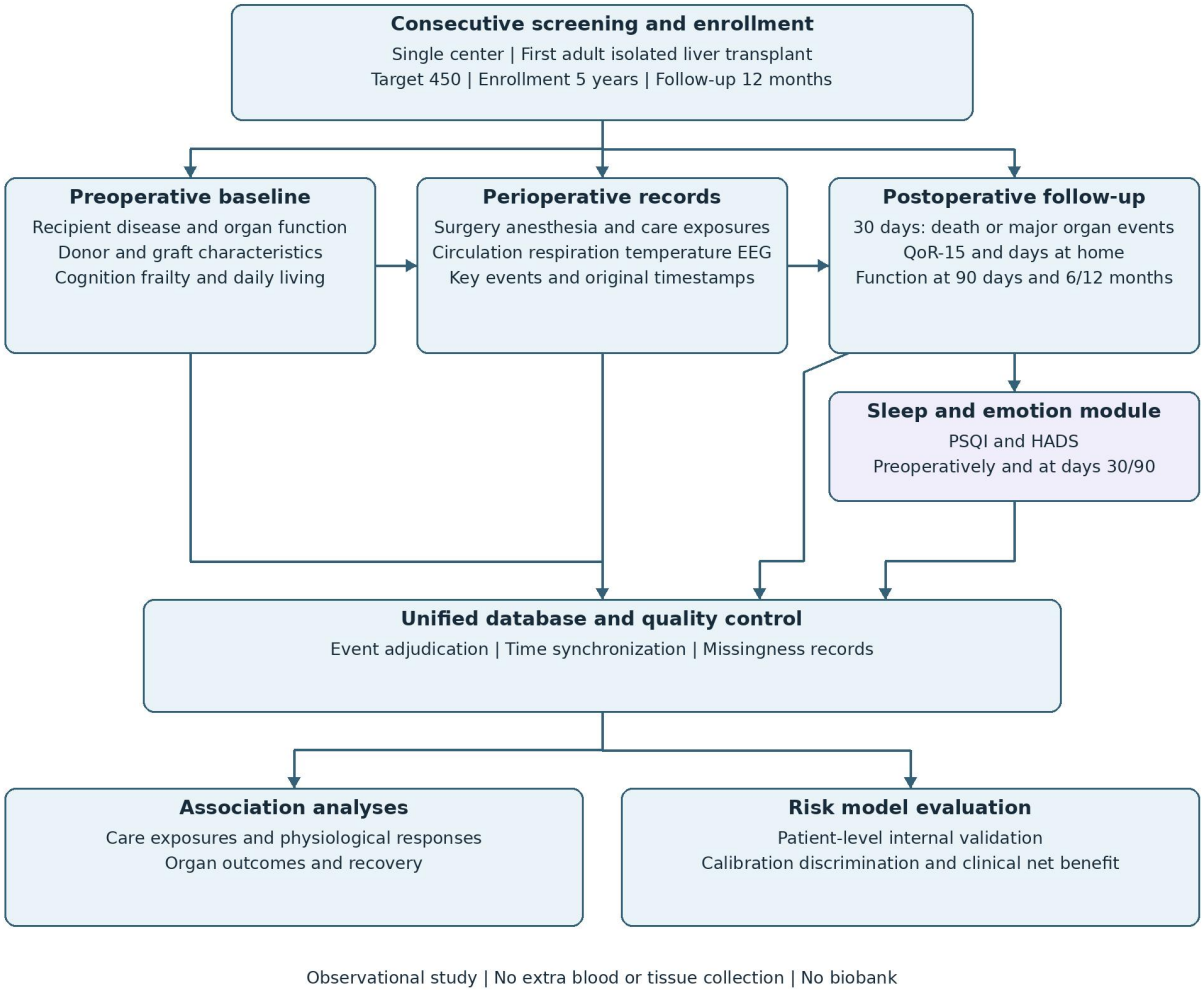
All study-related adverse events retain onset, manifestations, severity, duration, management, outcome, and relatedness. Death, life threat, hospitalization or prolongation, and persistent impairment are assessed as serious events under institutional rules. Disease and surgical complications enter outcome records in full, with independent assessment of research relatedness. Common transplant complications will not be omitted; attribution depends on procedures and evidence.

For serious events, unanticipated problems, or personal-information incidents, first provide clinical rescue or limit harm. Notify the principal investigator immediately on awareness; target internal initial reporting within 24 hours. Ethics and institutional deadlines follow local rules, with ongoing updates. Relevant assessments, collection equipment, or assays may be paused and resumed after review.

Research signal features, model outputs, and residual-material results are for analysis only, without treatment allocation, adjustment, or research alerts. Potentially urgent abnormalities discovered during routine-data collection require prompt notice to the responsible clinician and verification through normal care. Clinical management takes priority over blinding. Unvalidated candidate biomarkers will not guide diagnosis or treatment.

Pause or stop sleep/mood interviews causing marked distress. Scores alone do not establish psychiatric diagnoses or treatment decisions. Clinically concerning symptoms will be referred through existing care pathways, respecting privacy and consent.

4. Study Workflow



Screening and baseline. Consecutively screen adult recipients at this center, targeting 450 first-time isolated liver transplant recipients over 5 years with 12-month follow-up each. Obtain consent and recipient, donor, and graft data; assess preoperative organ function, cognition, frailty, daily living, and recovery quality. The sleep/emotion extension completes PSQI and HADS within 7 days before surgery.

Perioperative recording. Collect surgery, anesthesia, and other care exposures while synchronously retaining circulatory, respiratory, temperature, and EEG data. Preserve key event, medication, and test times; assess phase-specific physiological changes and adjudicate PRS around first reperfusion.

Early outcomes and recovery. Adjudicate major organ events in prespecified windows, verify death and all postoperative complications through day 30, apply Clavien-Dindo, and calculate CCI when complete. Assess QoR-15 and DAH-30 as scheduled; repeat the sleep/emotion module at day 30.

Longitudinal follow-up. Assess survival, graft, and function on day 90 and at months 6 and 12. Calculate DAH-90 and complete the sleep/emotion module on day 90. Record death, nonassessability, refusal, and loss separately.

Analysis and validation. Standardize definitions, timing, and adjudication; analyze care exposures and physiological changes in relation to organ outcomes and early events in relation to later recovery. Prediction studies use patient-level internal validation.

Supplementary assays. Use only authorized residual serum and tissue intended for disposal, retaining collection, processing, and assay information. No additional blood or tissue is collected, complete pairing is not required, and no biobank is established.

5. Timeline and Expected Outputs

5.1 Expected Outputs

Establish a prospective single-center adult liver transplant cohort with standardized care, outcome, and functional follow-up data. Outputs include associations of care exposures and physiology with injury, links between early events and later recovery, recovery patterns across baseline risk groups, and risk validation supported by available information, informing validation of specific management strategies.

5.1.1 Scientific Evaluation Measures

Care exposures and organ outcomes. Report effect estimates, 95% confidence intervals, and absolute risk differences for prespecified exposures and physiological features in relation to the primary and organ-specific outcomes, specifying populations, windows, and adjustment. Primary and component proportions are shared descriptive outputs.

Patient recovery. Report day-7 QoR-15 and trajectories, DAH-30/90, organ support, mobility, long-term function, cognition, and quality of life. Assess early-event associations with later recovery alongside death, nonassessability, and completion.

The sleep/emotion module reports day-30/day-90 PSQI, HADS-A, and HADS-D and baseline changes, plus coverage, duration, feasibility, and differences from the parent cohort. Complete complication data support Clavien-Dindo and CCI; clinical cardiac testing supports injury, arrhythmia, and function-change reporting.

Risk information and model performance. When information permits, compare calibration, discrimination, Brier score, and decision-curve net benefit before and after physiological features, with validation methods and intervals. Present actual validation uncertainty.

Completion depends on standardized collection, traceable follow-up, and analyses proportionate to information, not positive associations, a particular AUC, or proof of treatment benefit. Negative and imprecise results will be reported accurately.

5.2 Schedule and Operational Evaluation

5.2.1 Timeline

Before initiation. Complete institutional and ethics review, collaboration and responsibilities, training, dictionary and electronic forms, and verification of signal interfaces, synchronization, and follow-up.

Initiation. Use the first 45 cases to assess recording, transfer, and measurement feasibility; improve operations based on completeness, reliability, and overall event frequency. Cases meeting formal criteria with identical primary-outcome definitions enter the final cohort.

Consecutive enrollment. Enroll for 5 years from the first participant. Approximately 100 adult procedures annually yield about 500 screened, targeting 450 main-cohort recipients. Continue quarterly quality review and individual follow-up.

Follow-up completion and analysis. Follow every recipient for 12 months; the last visit is expected around 6 years after first enrollment. Analyze primary and substudy outcomes once data mature and plans are locked, then complete cleaning, reporting, and the final study summary.

5.2.2 Cohort Operational Indicators

Indicator	Definition	Operational target

Indicator	Definition	Operational target
Consecutive-screening coverage	Procedures with screening status recorded / all adult liver transplants in the same period	≥95%
Primary-outcome ascertainment	Recipients with determinable 30-day composite / enrolled recipients undergoing surgery	≥90%
Core-field completeness	Required fields completed or with valid missingness reason / all required fields	≥95%; separately report actual measurement rate
Key-event time completeness	Key events with time obtained and precision stated / expected events	≥95%
Within-patient valid signal coverage	Artifact-free valid duration / planned recording duration	Target ≥80% for each core modality; report separately
Raw EEG availability in brain-function module	Cases with analysis-ready raw EEG / enrolled surgical cases	Target ≥85%; module-specific and not a sole parent-cohort completion threshold
Delirium-status recording	Completed assessments or explicit nonassessability reasons / scheduled inpatient opportunities	≥90%; separately report completion among assessable opportunities
Outcome agreement	Agreement and kappa in repeat adjudication	Target $\kappa \geq 0.80$; consider event-rate effects on kappa
12-month survival ascertainment	Known survival / recipients entering the window	≥90%
12-month functional completion	Survivors completing assessment / all survivors reaching the window	Target ≥85%; separately show nonassessability and refusal
Additional research biological sampling	Blood volume and tissue procedures added for research	0 mL and 0 procedures

These proposed targets will be assessed in the first 45 participants and used to improve execution. Actual availability and missingness will be reported by modality, scale, and field while preserving the common clinical-outcome denominator. Unmet targets require investigation, not exclusion of difficult cases to improve rates. Assay volume and material-pairing rates are not primary completion indicators.

6. Medical Ethics and Risk Analysis

This is a single-center prospective observational clinical cohort. It allocates no treatment, changes no routine monitoring, investigations, or rehabilitation, and adds no blood or tissue collection. Activities comprise clinical and routine-monitoring data use, questionnaires, functional assessment, follow-up, and authorized residual-material assays. Active assessments record status and outcomes rather than seek to alter physiological, psychological, or behavioral states. Institutional initiation, ethics review, and required registration remain mandatory; observational status or residual materials do not independently exempt review. Questionnaire and physical-assessment risk must be evaluated for the actual population, procedures, and protections, with institutional confirmation that the study meets observational-research requirements. Added examinations, laboratory tests, or diagnostics exceeding minimal risk may not proceed under this protocol; classification and scientific/ethics review must be reconsidered [24,25].

Consent separately explains use of clinical data and routine signals, questionnaires and function, follow-up contact, and residual-material assays. Residual-material authorization is optional, and refusal does not affect cohort enrollment. Impaired capacity due to encephalopathy or sedation requires approved proxy

consent and renewed explanation and appropriate consent after recovery. Emergency conditions do not authorize investigator-declared waiver; unapproved deferred-consent or waiver procedures are prohibited.

Participation, questionnaire content, visit frequency, and burden of the sleep/emotion module are separately explained in consent. Recipients may decline the module or skip questions while continuing other observations. Responses are sensitive health data and are not disclosed without authorization to relatives or unrelated persons.

Avoiding extra blood and tissue reduces invasive risk but does not remove review or consent duties. Clinical laboratory and pathology diagnosis takes priority. Source, availability, purpose, temporary storage, and disposal must remain authorized. Native liver, donor tissue, and post-transplant tissue are separately labeled; unclear-source or inadequately authorized material is not used.

Health information is sensitive personal information. Apply data minimization, purpose limitation, and tiered access, with clear withdrawal, contact, and processing arrangements. Relevant institutional offices determine procedures for tissue and potentially applicable human genetic resources activities. This protocol includes no provision of materials or identifiable personal data overseas. Residual-material use follows requirements applicable to the actual activity.

Funding follows the institution-approved budget. Research assessments, follow-up, management, and approved residual-material assays are included, without recipient charges or additional financial burden from participation. Funding or existing resources must be secured before each activity; unsupported activities will not start. Routine care costs follow existing rules. Follow-up combines routine care and approved remote contact; no research-only hospital visit is required. Direct health benefit is not guaranteed. Participation does not affect organ allocation, surgical timing, treatment, or rehabilitation. Residual materials are not an open-ended long-term reserve. Future uses beyond approved aims, methods, or authorization require renewed review.

Principal investigator signature: _____

September 22, 2026