Registry Protocol

International Living Donor Liver Transplantation Outcomes Registry – LDLTregistry.org

The LDLTregistry.org Collaborative

Summary

Background: Living donor liver transplantation (LDLT) was introduced in the early 90's to overcome an increasing shortage of available diseased donor organs for transplantation. LDLT remains the main source of grafts for liver transplantation in Asian countries, however, reports on donor morbidity and even mortality have hampered the uptake of the procedure in Western countries. Outcome data are available from developed countries, but outcomes in developing countries remain unknown. There is a need to collect data from all parts of the world, to create a single prospective registry and allow meaningful comparisons, as well as standardization of the procedure, across the globe.

Center eligibility: Any center worldwide involved in LDLT is eligible to participate in this registry. There are no minimum number of cases to be submitted or selection criteria for centers.

Team members: Each center may form a team of 3 members in total. Participants may include surgeons, anesthesiologists, hepatologists, critical care physicians and other members involved in LDLT. Auditors (data monitors) will be assigned to monitor the adherence to the registry protocol as well as auditing the quality of data collection of the participating centers.

Inclusion criteria: Cases must be prospectively registered. Both donors and recipients will be included in the registry, including adult and pediatric, two stage LDLT (e.g. Auxiliary, RAPID, APOLT, ASPIRE, RAVAS), as well as dual grafts.

Exclusion criteria: Domino grafts will be excluded.

Outcomes: Morbidity and mortality for both the donor and recipient until hospital discharge and up to 90 days postoperatively. Additional outcome data will be captured at 12 months follow up.

Data ownership: LDLTregistry.org will act as the custodian of the data. All participants will be able to access their own submitted data without the need for permission from the LDLTregistry.org Committees. The Chief Investigators, Scientific and Management committees together will decide about data sharing requests and will consider all such requests based on the quality and validity of the proposed project.

Data confidentiality: There will be no surgeon, or center related data reporting, all data will be fully anonymized.

Authorship: All LDLTregistry.org members, with submitted verified cases to the registry, will be PubMed cited as group authors in the main publications. Spin-off studies may include formal named authorship but must include the "LDLTregistry.org Collaborative" with group authorship for all participants.

International Audit Registration: RFH 513_21/22

In Partnership with: The International Liver Transplantation Society (ILTS)

Protocol

Introduction

Liver transplantation provides significant improvement in quality of life for patients with chronic liver disease, which has led to global implementation of transplantation programs over the last three decades (1-3). Refinement of organ and patient selection criteria, surgical expertise, and international collaborative efforts to enhance recovery after surgery have led to significant improvement in patient outcomes (4-6). Most comparative studies on liver transplantation are focused on deceased donor liver transplantation (DDLT) including livers donated after cardiac death (DCD) versus donated after brain death (DBD). Better outcomes are reported from DBD liver transplantation than DCD, as a result of the reduced warm ischemia time(7). Living donor liver transplantation (LDLT) may further improve outcomes by minimizing ischemia time and optimizing donor selection (8, 9).

LDLT was introduced in 1989 to overcome the disparity in organ demand and cadaveric donor supply (10, 11). Though initially implemented in a pediatric cohort (11), LDLT was increasingly embraced across the globe to address the shortage of organs for DDLT and hence improve survival prospects for patients on transplant waiting lists (12, 13). Particularly, LDLT is more commonly practiced in Asian countries due to religious beliefs, traditions and teachings surrounding organ donation after death, which have historically not been supported by religious leaders (14). Furthermore, high endemicity of hepatitis B and C viruses in Asia has led to the highest global rates of cirrhosis and hepatocellular carcinoma (HCC) in Asian countries. Indeed, it is anticipated that more than 80% of the global burden of HCC will be diagnosed in Asia in the next decade (15), which will further drive the organ demand.

Comparative studies of living donor liver transplantation (LDLT) with DCD and DBD transplants are relatively sparing; available evidence suggests similar graft survival rates but reports on donor morbidity and mortality have hindered its uptake in Western countries (16-18). In addition to recipient morbidity and mortality, a proportion of donors may experience severe and life-threatening complications including bile leak, sepsis, portal vein thrombosis; on top of a known mortality risk (19-21). On the other hand, the advent of new techniques, including minimally invasive approaches to donor hepatectomy, may have optimized donor outcomes but it is unknown how widely practiced nor disseminated these techniques have become (22). Regional efforts include the development of LDLT European Liver Transplant Registry (ELRT), in 2000 by the ELTR and The European Liver and Intestine Transplant Association (ELITA). This registry is updated every 6 months with data from October 1991 to December 2020, and demonstrates over **10,000 LDLT** with early outcome of donors and early and long-term outcome of recipients (23). Other known sources of registry data include the U.S. Scientific Registry of Transplant Recipients (SRTR) and Adult-to-adult Living Donor Liver Transplantation (A2ALL) (24, 25). Outcomes measured by SRTR include pre-transplant mortality rate, transplant rate and first-year graft survival (24). A2ALL outcomes include first-year graft survival, complication rates and predictors of graft failure. (26)
There is no evidence derived from randomised trials and current series are limited by risk of bias. Furthermore, series from high volume, single center, specialized units represent only the ‘tip of the iceberg’ of practice of LDLT worldwide (27-29). Assessing the peri-operative risks of LDLT through a prospective, granular, international registry will establish the true global morbidity and mortality for donors and recipients, as well as modifiable predictors of these outcomes, through an established model of international collaboration (30-33).

Objectives

The International Living Donor Liver Transplant Registry – LDLTregistry.org aims to measure the true worldwide practice of LDLT and associated outcomes by recruiting multiple international centers, committed to consecutive patient submission while undergoing rigorous data validation. The primary endpoint of the analysis study is 90-day morbidity and mortality for both recipient and donors. Secondary endpoints include identification of modifiable predictors of outcome. Additional outcome data will be captured at 12 months follow up. It is hoped that these data will provide a more appropriate guide to inform surgeons and patients to assess the true global morbidity and 90-day mortality of LDLT, without the impact of center bias. Additionally, this registry will aim to evaluate which surgical techniques are most used worldwide and their impact on short-term outcomes as well as the effect of perioperative measures used to prevent complications and to improve perioperative care after LDLT across the globe.

Methods

Study design

The proposed prospective registry provides the opportunity for international collaboration to gain a cross-sectional insight into the true worldwide morbidity and mortality after LDLT. Patient registries are powerful tools to observe the course of disease, understand variations in treatment and outcomes, examine factors that influence prognosis, describe care patterns, assess effectiveness, monitor safety and harm, measure quality of care, and assess costs.

Participants

There is no minimum threshold on the quantity of cases. All physicians across the world involved in LDLT are eligible to participate

Eligibility criteria

All donors and recipients involved in LDLT are eligible to participate. The inclusion criteria are single stage LDLT, two stage LDLT (e.g. Auxiliary, RAPID, APOLT, ASPIRE, RAVAS), dual grafts and recipients, as well as adult and pediatric patients undergoing LDLT for any indication. Domino grafts will be excluded. Each patient requires a minimum 90-day follow-up period after surgery and both the donor and recipient data must be fully completed for the follow up period to complete a valid submission to the registry. Additional outcome data will be captured at 12 months follow up.
All patients must be registered prospectively and no retrospective LDLT cases will be collected.

Variables, data sources and measurements

The Case Report Form (CRF) contains all the variables and their definitions, available at https://LDLTregistry.org/CRF. The electronic CRF is designed to mandate data entry for certain fields (e.g. morbidity, mortality, etc.) and has set maximum and minimum values for each to reduce human errors. These considerations aim to ensure the high quality of data collected. Discrete variables are recorded using dropdown selections for ease of use. Where relevant, descriptions of key data fields are provided. To convert between units and thus provide uniform collection of data, calculators are provided at LDLTregistry.org. Definitions and information concerning scores/classifications are also accessible at LDLTregistry.org. Basic hospital level data will be also captured.

Study size

The study aims for the maximum number of patients to recruit. The first report of initial registry outcomes will be published once the number of cases entered into the registry reaches at least 262. This calculation was based on a reported 30% 90-day complication rate of any severity, with 50% as a clinically relevant difference (i.e. 15%), 262 cases will need to be recruited for meaningful comparison of outcomes (alpha 0.05, power 80%). Outcome data will be published periodically thereafter.

Statistical methods

Descriptive and exploratory statistics will be performed by the R&D Team. Continuous variables will be compared with the student t-test, the Mann-Whitney U test and the Kruskal-Wallis H test or one-way ANOVA as appropriate. Differences among proportions derived from categorical data will be compared using the Fisher or the Pearson chi-square tests as appropriate. Univariate analysis will be performed to test factors associated with postoperative outcomes. Multivariable regression models will be used to identify factors independently associated with outcomes and to adjust for differences in confounders. The results of the multivariable analyses will be reported as adjusted odds ratios (OR) with 95% confidence intervals. ROC curves and the Youden's index will be used to identify optimal cut-off points for continuous variables. All p values will be 2-sided and considered statistically significant if $p<0.05$ in the univariate analysis and $p<0.10$ in the multivariate analysis. Missing data from not mandatory to submission fields will be clearly reported. Cases with incomplete data regarding morbidity or mortality will be excluded from the analysis and the number of those will be reported. Statistical analysis will be performed using R version 3.3.2 (R Core Team, GNU GPL v2 License), R Studio version 1.0.44 (RStudio, Inc. GNU Affero General Public License v3, Boston, MA, 2016) with the graphical user interface (GUI) rBiostatistics.com (rBiostatistics.com, London, UK, 2017).

Discussion

At present, many published LDLT cohorts originate from high-volume centers in developed countries (21-24) and therefore the true global morbidity and mortality are unknown, particularly in Eastern countries where the practice is more common, and the data less regularly reported. Current estimates of donor mortality suggest a risk of 0.15-0.50%, with morbidity of 0 to 100% (34-38); common complications include biliary leaks, infection, incisional hernias, and pleural effusions. Rates of severe complications, defined as those of Clavien-Dindo grade 3a and above, range from 3-40% (19, 29, 39, 40). The significant heterogeneity in morbidity and complications suggests a significant degree of variation in operative practice and highlights the urgent need for a prospective registry to identify modifiable predictors of outcome for LDLT. The need is compounded by underreporting of donor mortality in studies of LDLT, which tend to focus on the recipient outcomes alone and further complicates the matter of recording representative and accurate procedural data. The current best estimates for donor mortality are derived from high-output specialist center, cases which represent only a fraction of the true number of LDLT procedures being carried out worldwide in a vast range of settings, with a plethora of distinct techniques, skills and equipment (41).

In terms of recipients, LDLT was associated with lower mortality compared to DDLT, up to 5 years post-transplant in meta-analyses of adult and pediatric cohorts (42, 43) The authors also reported similar graft survival rates, shorter waiting time, lower MELD score at time of transplant and lower risk of rejection. In meta-regression, it was lower MELD at time of transplant that correlated with improved survival. However, biliary complications, were significantly more numerous in the LDLT group; rates of biliary complications in other series have been reported as 5-34%, with a corresponding failure to rescue of 19-57% (44-46). This is likely due to the technical aspects of the LDLT procedure; recognized risk factors include multiple bile duct anastomoses, MELD>35, post-operative bile leak, recurrent cholangitis and hospital acquired thrombosis (47). Whilst the meta-analyses are useful estimates of patient and graft survival, they only included trials with LDLT and DDLT cohorts, failing to account for single centres and thus the overall rates of morbidity and mortality that it presents are not representative. In single centre studies, the overall survival is improved with LDLT vs DDLT (48); studies reporting 90-day recipient mortality estimate the rate at 10-15%, (26, 37, 49, 50). Single-center case series have shown reduced mortality rates at one-year post-LDLT (7-10%) when compared to DDLT (11-16%) over the same period (50, 51). Whilst LDLT, in theory, confers several advantages over DDLT, the major caveat is the lack of reporting on donor morbidity in the aforementioned studies and this highlights the critical importance of establishing a prospective registry that can document recipient and donor outcomes.

In summary, the practice of LDLT is well established and likely to increase further in the coming decade (35). Modifiable factors that influence donor outcomes are not well documented and most studies fail to account for donor morbidity and mortality which limit their generalisability. Furthermore, with the practice of LDLT widespread throughout the East (52), most case series presented are produced by large centers in USA (19, 26, 37), Korea (27-29) and Japan (39, 46, 49) and are therefore not generalizable to the rest of the world or developing countries, performing these procedures with different levels of resources. Even accounting for this, the variation in morbidity and mortality estimates highlight the statistical and clinical heterogeneity that confounds the interpretation of current literature. To demonstrate the safety of LDLT for donors and recipients, an international collaborative registry will be established with the aim of identifying modifiable perioperative factors to improve morbidity and mortality for all.

Funding

The LDLTregistry.org is currently seeking for funding from various sources. Ideally, to comprehensively conduct the whole project and ensure success, the estimated cost is 150,000 USD for the first two years. However, the project can be conducted with less funds if this figure is not met.

Platform

The LDLTregistry.org platform is built on Drupal version 9, an open-source content management system written in PHP and distributed under the GNU General Public License. Two Apache servers (one used as a backup) physically based in the United States of America with a MySQL database are used. The most advanced firewalls are installed for monitoring and prevention of malware. The website and software

compatibility for different platforms, internet browsers, and devices were assessed using BrowserStack.com. The platform is “self-maintained” with automated updates.

Monitoring
The Management Committee are responsible for monitoring the CRF export database each month. All participating centers will undergo regular onsite peer-monitoring. **Auditors** (data monitors) from non-surgical disciplines will be assigned to ensure protocol adherence and to audit the quality of data collected at each center.

Safety
This study presents no physical risk to patients or researchers. Adverse events will thus not be recorded. Data confidentiality is ensured through local anonymization. Anonymization will be monitored, and any breaches reported. Individual participants will be accountable to their local authorities in the case of breaches in confidentiality.

Research ethics approval
The LDLT registry was registered as a prospective, international audit at the Royal Free Hospital, London, UK. The audit registration number is RFH513_21/22. LDLTregistry.org is an observational study without affecting the patient management. Data collection is fully anonymized without any patient identifiers. In many countries this study is considered as an audit (UK) or quality improvement program (USA), without necessitating a formal ethics approval. However, each country, state, region or institution may have different regulations for gaining ethics permission. The Management and Administration Committees of LDLTregistry.org will assist centers through any potential ethics approvals, if required. A Data Sharing Agreement (also known as Data Transfer Agreement, or Contract) is available at LDLTregistry.org and can be modified according to local regulations.

Access to data and dissemination policy
LDLTregistry.org is a collaboration between all data-contributing physicians as equal partners. The LDLTregistry.org Committees will act as the custodian of the data. Each data-contributing physician has access to analysis files of the entire database at any time point. Furthermore, they reserve the right to propose analyses and publish data provided every data-contributing physician is included as a group author in every publication and has an opportunity to review the data prior to submission. The LDLTregistry.org Committees will decide about data sharing requests and will consider all such requests based on the quality and validity of the proposed project. Each collaborator has access to their own data as an exported Excel file. They do not require permission or approval by the LDLTregistry.org Management Committee for this purpose.

Authorship
A single analysis without hierarchical authorship (no first author, no last author) is planned for the first report (a “pure” group author publication) to reflect the collaborative effort. All members of the group are encouraged to step forward with suggested secondary analyses on specific questions and will be granted full access to the acquired data once their proposal is approved by the Scientific Committee. There will be no need for approval of publishing data from the LDLTregistry.org collaborative.

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