LiverGroup.org
International Liver Surgery Outcomes Study

International Snapshot Study on the Outcomes of Liver surgery - *LiverGroup.org*

The LiverGroup.org Collaborative[1,2,3]

Affiliations/Sponsors

1. Department of HPB Surgery and Liver Transplantation, Royal Free Hospital NHS Foundation Trust, UCL Partners, London, UK
2. Department of Surgery, University Hospital Miguel Servet, University of Zaragoza, Spain
3. All affiliations of the LiverGroup.org Team Members

Trial registration: Awaiting submission at ClinicalTrials.gov

Protocol version: v1.3, 30 November 2018 (written by Erik Schadde, Dimitri Aristotle Raptis and Thomas Hanna), approved by the Chief Investigators and all Members of the Steering Committee, see below).

Funding: The sponsors are the Royal Free Hospital in London, UK and the University of Zaragoza in Spain. There are no industry funders allocated to this study.

Roles and responsibilities: The *headquarters* acting as the coordinating centre is located at the Royal Free Hospital in London, UK run by Dr. Dimitri Aristotle Raptis, Prof. Massimo Malagò and the Management Committee. The *Chief Investigators* of LiverGroup.org are Prof. Alejandro Serrablo from the University of Zaragoza, Spain and Prof. Massimo Malagò from the Royal Free Hospital, London, UK. The complete list of the LiverGroup.org Team is available at: https://livergroup.org/?q=team. The responsibilities of the members of the *Management Committee* are, among others facilitating the group's decision-making processes, distributing newsletters, announcements and invitation letters, safeguarding and applying regulations, arranging regular committee and general meetings of the group, recording decisions and tasks clearly, and providing support to the collaborators. The *Steering Committee* Members are: Christos Dervenis (Greece), Karl Jürgen Oldhafer (Germany), Marcel Autran Machado (Brazil), Martin Hertl (Chicago), Norihiro Kokudo (Japan), Pål-Dag Line (Norway) Roberto Hernandez-Alejandro (Canada), Stefan Breiteinstein (Switzerland), Thomas van Gulik (Netherlands), Yaman Tokat (Turkey) and (Ulf Peter Neumann (Germany). Their responsibilities include, among others overseeing and controlling the scientific part of the project and giving strategic direction and support to the members of the management committee. The Members of the Steering Committee have approved the study design and protocol of the LiverGroup.org Study. The *Country Leaders* are responsible for recruiting centers within their country/region. Additionally, *Auditors* (data monitors) will be assigned to monitor the adherence to the protocol as well as auditing the quality of data collection of the different participating centers.

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Summary

Introduction: Liver surgery was associated with at least 10% mortality in the 1970's. The safety of liver surgery has dramatically improved since with a mortality now of around 1-2%. Individual centres put the bar even higher and postulate that a perioperative mortality close to 0% should be the standard of major liver resection. Despite these claims, epidemiological studies paint a different picture again with a mortality rate of 6%.

Eligibility: Any surgeon performing liver resections is eligible to participate in LiverGroup.org. All consecutive cases must be included and there are no minimum patient numbers per centre. Liver transplantation is excluded.

Time period and team members: Each participant may form a team of 3 members in total. There will be 3 months of prospective patient enrolment and 3 months follow up within a 12-month frame (Jan – Dec 2019).

Inclusion criteria: All liver resections will be included:

- All indications (including benign and living donor resections), all co-morbidities
- Open, laparoscopic or robotic
- Single wedge resections to extended liver resections
- Single or two-stage hepatectomies
- Procedures with liver volume enhancement such as PVE, PVL, ALPPS.
- Resections involving cold perfusion (ex-situ and ante-situ)
- There are no exclusion criteria as related to indication, age or comorbidities.

Exclusion criteria:

- Liver transplantation
- CT-guided RFA, MWA, etc.
- Liver biopsies

Audit Standard: An audit of the consecutivity, intent-to-treat and completeness of data entered will be performed by random selection of at least 30% of the contributing surgeons. A member of LiverGroup.org will be assigned to audit one fellow surgeon of LiverGroup.org to perform a validation of the number of deaths and of the death dates.

Outcomes: the primary endpoint of the analysis will be 90-day mortality. Secondary endpoints will be liver failure, complications, and length of stay and incidence of re-hospitalisation.

Data ownership: The study sponsors, the Royal Free Hospital London and University of Zaragoza, will act as the custodians of the data. The steering and management committees together will decide after the publication of the main report about requests regarding secondary analysis and will consider all such requests based on quality and the validity of the proposed project and decide by majority decision.

Authorship: A single analysis and reporting without hierarchical authorship (no first author, no last author) is planned at the end of the study (a "pure" group author publication) to reflect the collaborative effort.

Register: Please register your interest for participation at:
https://LiverGroup.org/?q=register

Introduction

The safety of major liver surgery, defined as resection of four or more hepatic segments has improved significantly in recent decades with mortality rates improving from 10% in the 1970's[1] to 1-2% currently.[2-5] Some individual centres are now reporting perioperative mortality rates approaching 0%,[4,6] yet epidemiological studies suggest much higher mortality rates of up to 6%;[7] the reasons for this discrepancy are not completely understood.

Complexity and extent of liver surgery, patient selection and both centre and surgeon experience are all cited factors which may influence outcomes following major liver surgery. A large, single-centre analysis of outcomes following liver surgery found that the number of hepatic segments resected and operative blood loss were the only two predictors of both perioperative morbidity and mortality.[5] The authors suggest that whilst 'complex liver resections' defined as liver surgery with one or more major extrahepatic procedure, were associated with a higher mortality in conjunction with major hepatectomies, complexity had no impact on mortality when performed with minor hepatectomies, thus highlighting the importance of future liver remnant percentage (FLR) which has since been repeatedly demonstrated.[8,9] Induction of regeneration prior to resection using portal vein embolization, portal vein ligation or Associating Liver Partition and Portal vein ligation for Staged hepatectomy (ALPPS) are evolving strategies to mitigate the adverse outcomes associated with a major liver surgery. Such staged approaches to major liver resections are associated with a perioperative mortality of over 5% even in the most experienced centers[12-14] with the ALPPS procedure reported to have a mortality of 12% in voluntary registry studies.[15] Whether such strategies improve the safety of major liver surgery, or instead allow a more aggressive approach to resection of lesions previously deemed unresectable is contentious.

At the extreme end of complexity are ex-situ and ante-situ resections. The largest series of standardized in-situ hypothermic perfusion for patients with tumours involving the vena cava and the hepato-caval junction identified an overall mortality rate of 20%.[18]

An open debate and ultimately consensus amongst the HPB surgical community is required to address the delicate balance between improving mortality of liver surgery whilst developing approaches to treat the most challenging lesions. To inform this debate a robust prospective audit examining the current international experience and outcomes is required. Existing registry studies are based on national (French Liver surgery registry, Scandinavian liver surgery registry LiverMET Survey SweLiv[21], Italian laparoscopic liver surgery registry[22]) or

international collaborations (e.g. the ALPPS registry initiated in 2012, www.ALPPS.net[15]) are commendable attempts to provide valid data. They have however either not been international in scope, proprietary in character or have underestimated the true incidence of morbidity and mortality due to voluntary and selective reporting of patients or lack of monitoring of data entry. Large single centre studies both in Europe and the US with high quality retrospective databases have provided the most robust data,[3,5,6] but across a long enrolment periods and with a considerable era and centre bias. Furthermore, series from high volume, single centre, specialised units represents only the 'tip of the iceberg' of practice of liver resection worldwide.

The International Liver Surgery Outcomes Study – LiverGroup.org aims to measure the true worldwide practice of Liver surgery and associated outcomes by recruiting multiple international centres, committing to consecutive patient registration per surgeon and undergo rigorous data validation. It is hoped that these data will provide a more appropriate guide to inform surgeons and patients to assess which level of complexity should be routinely offered for high tumour burden and anatomically difficult scenarios.

Methods

Participants, interventions and outcomes

Study setting

This will be an International Liver Surgery Outcomes Study where all centres performing liver surgery world-wide will be able to participate. The current preliminary list of study sites is available at https://livergroup.org/?q=team.

Eligibility criteria

All patients undergoing liver resection by single surgeons at their respective centres are eligible for study inclusion. The *inclusion criteria* are patients 18 years of age or older, any indication for surgery, including benign and living donor resections, open, laparoscopic, hybrid or robotic approaches. Furthermore, any extent of liver resection is included, from single wedge resections to extended liver resections. Procedures with liver volume enhancement such as PVE, PVL, ALPPS, resections involving cold perfusion (ex-situ and ante-situ) are also included. The *exclusion criteria* are patients undergoing liver transplantation, liver biopsies or image-guided liver ablation alone.

Outcomes

The *primary objectives* of LiverGroup.org is to develop a non-proprietary international data set on the **morbidity** and **mortality** following liver resections among international surgeons. Morbidity will be recorded according to the Clavien-Dindo Classification of Surgical Complications, the FABIB Liver Surgery-Specific Classification and the novel Comprehensive Complication Index® (CCI®). Mortality will be captured until the 90th postoperative day.

The *secondary objective* is to identify independent risk factors for morbidity and mortality using multivariable regression models.

Participant timeline and study duration

The enrolment period will last 3 months and a minimum of 3 months period is required for follow-up of each patient. Surgeons may start enrolment at any time within the 12-month enrolment time frame: 1st of January 2019 until the 31st of December 2019. The Management Committee may decide to prolong the patient enrolment if deemed necessary.

Sample size

The study aims for the maximum number of patients it will be able to recruit and has no power calculation for specific outcomes. Assuming a 2.5% 90-day mortality rate, at least 2000 patients will have to be recruited to be able to perform a meaningful multivariate analysis on independent risk factors postoperative mortality

Recruitment

Surgeons joining LiverGroup.org are encouraged to propose a country or regional leader (north/south etc). This process will be guided by the management committee. The responsibilities of the *Regional* and *Country Leaders* representing each country in the world include, among others to recruit and co-ordinate collaborators in their own country or region as well as to provide additional scientific and administrative support to their collaborators. Additionally, personal contacts of the LiverGroup.org team will be used to recruit centres. Furthermore, the members of the Management Committee are seeking for endorsement of the International Hepato-Pancreato-Biliary Association (IHPBA), European-African Hepato-Pancreato-Biliary Association (E-AHPBA), the American Hepato-Pancreato-Biliary Association (AHPBA), and the Asian-Pacific Hepato-Pancreato-Biliary Association (A-PHPBA).

Data collection, management, and analysis

Study data

Data are “surgeon-based”, not “centre-based”. Surgeons participating in LiverGroup.org are only responsible for their own data. The data will indicate in an anoymized fashion that surgeons belong to a specific centre. Data will be entered using a personalized login assigned to surgeons, their assistants and in some centres, study nurses. The complete dataset of the electronic Case Report Form (CRF) are available at https://livergroup.org/?q=instructions.

Each CRF has a unique identifier. A participant may enter data for a colleague or partner under their login, as long as authorization has been granted by the user. If centres are not willing to disclose their identity to the management committee when asked to do so for the purpose of an audit, they are free to have their data excluded from the analysis. Such exclusion will be reported in the final report for transparency while assuring that the data are under control of the individual centre until the final analysis and audit is performed.

Data collection

Data will be entered directly onto the electronic CRF available at https://livergroup.org/?q=CRF which includes the unique identifier. Collaborators keep a paper key list connecting the unique database identifier with the patient name in a safe place locked away under their control and their responsibility. If the list gets lost and audit is impossible, the surgeons’ data will be excluded from the final analysis and reported in the final report. The LiverGroup.org management committee cannot identify an individual patient or surgeon or centre without contacting the local PI who entered the data and is in possession of the key to the data.

Data collection methods

The Management Committee currently consists of clinicians who will review data entered, monitor progress and maintain the platform and send reminders to the participants regarding completion of data or questions regarding clarifications. Any collaborator is welcome to join the Management Committee. This practice is introduced to avoid the proprietary use of the collected data by a few “founding members” or “coordinators” or members of an appointed “scientific committee”.

To avoid *selective reporting*, all consecutive patients undergoing liver resections by one individual surgeon over three months are included. In some patients the operation may not run the expected course, be aborted or changed in scope. Intraoperative findings may change the operative plan. These patients should also be recorded in the registry following the principle of intent-to treat to avoid incomplete reporting.

An audit of the consecutively, intent-to-treat, completeness of data entered will be performed by random selection of the contributing surgeons. A member of LiverGroup.org will be assigned to audit one fellow surgeon of LiverGroup.org to perform a validation of the number of and date of deaths. This randomly assigned peer-review by participating centres is entirely novel and has not been routinely performed in similar snapshot studies, to the best of our knowledge. In detail, e.g. a surgeon/monitor from site A will monitor site B while a surgeon/monitor from site B will monitor site C. The monitors themselves may want to carry the costs for the monitoring, but in case that is not possible, LiverGroup.org may help to provide funding from third parties.

As for the quality of the data collected, the electronic CRF is specially designed to force data entry for the important variables (e.g. comorbidities, procedure type, morbidity, mortality, etc.), has minimum and maximum allowed values to avoid typing errors for continuous variables, all categorical data are captured in the form of selection lists and there is a description for important variables within the CRF. Additionally, there are calculators available at LiverGroup.org (e.g. sFLR and conversion of lab values) to ensure uniform data capture. Furthermore, information regarding the Brisbane, Clavien-Dindo, FABIB, BCLC Staging, and Bismuth-Corlette classifications is also available at LiverGroup.org.

All participants will have the opportunity to read study documents available at LiverGroup.org including instructions as well as contact the Management Committee in case they have questions directly through the platform.

Data management

LiverGroup.org is a Clinical Trial Management System (CTMS) built on Drupal 7 that will act as the backbone of our study, by supporting administration, collaboration, communication and information sharing needs among members from several centres worldwide. Anonymised patient data will be stored in two separate secured sites with access given only to the relevant users. There will be regular backups. Furthermore, the CTMS is secured with a Hypertext Transfer Protocol Secure (HTTPS) in combination with a SSL/TLS protocol and an encrypted SQL database.[24]

The study sponsors, Royal Free Hospital London and University of Zaragoza, will act as the custodians of the data. The steering and management committees together will decide after the publication of the main report about requests regarding secondary analysis and will consider all such requests based on quality and the validity of the proposed project and decide by majority decision.

Statistical methods

The primary endpoint of the analysis will be the 90-day mortality; secondary endpoints will be liver failure by Clavien-Dindo score,[23] the FABIB classification, complications, length of stay and incidence of re-hospitalisation. Descriptive statistics will be performed. 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 test and the Pearson chi-square. Univariate analysis will be performed to test factors associated with post-operative complications and 90-day mortality. Multivariable regression models will be used to identify factors independently associated with these outcomes and to adjust for differences in confounders. 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 ideal cut-off points for continuous variables. All p values will be 2-sided and considered statistically significant if $p<0.05$. The 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).

Monitoring

The management committee will monitor the export database of all CRFs weekly. At least 30% of centre should have undergone on-site peer – monitoring as explained above prior to final analysis.

Safety

This trial involves no risk of bodily harm to patients or investigators. Therefore, adverse events will not be monitored or reported. Data confidentiality will be protected through local anonymization. Anonymization will be monitored and breaches of confidentiality reported. Individual participants are responsible toward their local authorities for breaches in confidentiality.

Ethics and dissemination

Research ethics approval

LiverGroup.org was recognised as an audit in the UK and does not require any ethics approval. The principal investigator in the UK must ensure the recording of data is carried out in accordance with the Research Governance Framework for Health and Social Care; Second Edition, 2005, and its subsequent amendments. The principle investigators in the respective countries must clarify the need for ethics and other regulatory approvals and ensure these are in place prior to data collection. The management committee will collect documentation of the necessary ethics and other regulatory approvals from the respective centres prior to providing electronic access to the CRF. Since this study is effectively a large-scale international clinical audit of anonymized data already recorded in the course of routine patients care, we expect that in most countries no

individual patient consent will be required (see above). For countries where individual consent is required, we will provide an informed consent form in English that may be adjusted to local requirements. Any not enrolled patient due to no patient consent will have to be recorded and reported in the final report. The English version of the patient information and consent form is available at https://livergroup.org/?q=instructions.

LiverGroup.org will support all surgeons with their respective institutional review boards/ethics committee applications. Individual modifications to the generic protocol may become necessary.

Declaration of interests

The are no financial and other competing interests of the principal investigators for the overall trial and each study site.

Access to data and dissemination policy

LiverGroup.org is a collaboration of all surgeons contributing data as equal partners. Each surgeon contributing data has access to analysis files of the entire database at any time point and the right to propose analyses and publish data as long as every surgeon contributing data are included as a group author in every publication and have an opportunity to review the data prior to submission. Each collaborator has access to their own data in a form of excel export file without requiring permission or approval by the LiverGroup.org management committee.

One single analysis without hierarchical authorship (no first author, no last author) is planned at the end of the study (a “pure” group author publication) to reflect the collaborative effort. Any member of the group is encouraged to step forward with secondary analyses on specific questions and will have full access to the data. There will be no need for approval of publication of data from The LiverGroup.org collaboration, but all group authors have the right to review the manuscripts and have to be given at least 1 week to be able to review the manuscripts.

References

1. Fortner JG, Kim DK, Maclean BJ, et al. Major hepatic resection for neoplasia: personal experience in 108 patients. Ann Surg 1978; 188:363-371.
2. Fortner JG, Blumgart LH. A historic perspective of liver surgery for tumors at the end of the millennium. J Am Coll Surg 2001; 193:210-222.
3. Belghiti J, Hiramatsu K, Benoist S, et al. Seven hundred forty-seven hepatectomies in the 1990s: an update to evaluate the actual risk of liver resection. J Am Coll Surg 2000; 191:38-46.
4. Fan ST, Lo CM, Liu CL, et al. Hepatectomy for hepatocellular carcinoma: toward zero hospital deaths. Ann Surg 1999; 229:322-330.
5. Jarnagin WR, Gonen M, Fong Y, et al. Improvement in perioperative outcome after hepatic resection: analysis of 1,803 consecutive cases over the past decade. Ann Surg 2002; 236:397-406; discussion 406-397.
6. Imamura H, Seyama Y, Kokudo N, et al. One thousand fifty-six hepatectomies without mortality in 8 years. Arch Surg 2003; 138:1198-1206; discussion 1206.
7. Asiyanbola B, Chang D, Gleisner AL, et al. Operative mortality after hepatic resection: are literature-based rates broadly applicable? J Gastrointest Surg 2008; 12:842-851.
8. Kishi Y, Abdalla EK, Chun YS, et al. Three hundred and one consecutive extended right hepatectomies: evaluation of outcome based on systematic liver volumetry. Ann Surg 2009; 250:540-548.
9. Lang H, Sotiropoulos GC, Brokalaki EI, et al. Left hepatic trisectionectomy for hepatobiliary malignancies. J Am Coll Surg 2006; 203:311-321.
10. Farges O, Belghiti J, Kianmanesh R, et al. Portal vein embolization before right hepatectomy: prospective clinical trial. Ann Surg 2003; 237:208-217.
11. Shindoh J, Tzeng CW, Aloia TA, et al. Optimal Future Liver Remnant in Patients Treated with Extensive Preoperative Chemotherapy for Colorectal Liver Metastases. Ann Surg Oncol 2013.
12. Wicherts DA, Miller R, de Haas RJ, et al. Long-term results of two-stage hepatectomy for irresectable colorectal cancer liver metastases. Ann Surg 2008; 248:994-1005.
13. Tsai S, Marques HP, de Jong MC, et al. Two-stage strategy for patients with extensive bilateral colorectal liver metastases. HPB (Oxford) 2010; 12:262-269.
14. Brouquet A, Abdalla EK, Kopetz S, et al. High survival rate after two-stage resection of advanced colorectal liver metastases: response-based selection and complete resection define outcome. J Clin Oncol 2011; 29:1083-1090.

15. Schadde E, Ardiles V, Robles-Campos R, et al. Early survival and safety of ALPPS: first report of the International ALPPS Registry. Ann Surg 2014; 260:829-836; discussion 836-828.
16. Dokmak S, Belghiti J. Which limits to the "ALPPS" approach? Ann Surg 2012; 256:e6; author reply e16-17.
17. Aloia TA, Vauthey JN. Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS): what is gained and what is lost? Ann Surg 2012; 256:e9; author reply e16-19.
18. Azoulay D, Lim C, Salloum C, et al. Complex Liver Resection Using Standard Total Vascular Exclusion, Venovenous Bypass, and In Situ Hypothermic Portal Perfusion: An Audit of 77 Consecutive Cases. Ann Surg 2015; 262:93-104.
19. Hernandez-Alejandro R, Bertens KA, Pineda-Solis K, et al. Can we improve the morbidity and mortality associated with the associating liver partition with portal vein ligation for staged hepatectomy (ALPPS) procedure in the management of colorectal liver metastases? Surgery 2015; 157:194-201.
20. Alvarez FA, Ardiles V, de Santibanes M, et al. Associating liver partition and portal vein ligation for staged hepatectomy offers high oncological feasibility with adequate patient safety: a prospective study at a single center. Ann Surg 2015; 261:723-732.
21. Emilsson L, Lindahl B, Koster M, et al. Review of 103 Swedish Healthcare Quality Registries. J Intern Med 2015; 277:94-136.
22. Aldrighetti L, Belli G, Boni L, et al. Italian experience in minimally invasive liver surgery: a national survey. Updates Surg 2015; 67:129-140.
23. Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg 2009; 250:187-196.
24. Raptis DA, Mettler T, Fischer MA, et al. Managing multicentre clinical trials with open source. Inform Health Soc Care. 2014 Mar;39(2):67-80.