BMJ Open

Evaluation of Transhepatic Flow Changes in Major Hepatectomy (THEFLOW): study protocol for a single center, non-interventional cohort study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-029618
Article Type:	Protocol
Date Submitted by the Author:	01-Feb-2019
Complete List of Authors:	Golriz, Mohammad ; University of Heidelberg, General, Visceral, and Transplantation Surgery Lemekhova, Anastasia; University of Heidelberg, General, Visceral, and Transplantation Surgery Khajeh, Elias ; University of Heidelberg, General, Visceral, and Transplantation Surgery Ghamarnejad, Omid ; University of Heidelberg, General, Visceral, and Transplantation Surgery Al-Saeedi, Mohammed ; University of Heidelberg, General, Visceral, and Transplantation Surgery Strobel, Oliver ; University of Heidelberg, General, Visceral, and Transplantation Surgery Thilo, Hackert; University of Heidelberg, Department of Surgery Müller-Stich, Beat ; University of Heidelberg, General, Visceral, and Transplantation Surgery Schneider, Martin ; University of Heidelberg, General, Visceral, and Transplantation Surgery Berchtold, Christoph ; University of Heidelberg, General, Visceral, and Transplantation Surgery Tinoush, Parham; University Hospital Heidelberg, Department of Diagnostic and Interventional Radiology Mayer, Philipp; University Hospital Heidelberg, Diagnostic and Interventional Radiology Chang, De-Hua; University Hospital Heidelberg, Diagnostic and Interventional Radiology Weiss, KarlHeinz; University of Heidelberg, Gastroenterology and Hepatology Hoffmann, Katrin ; University of Heidelberg, General, Visceral, and Transplantation Surgery Mehrabi, Arianeb; University of Heidelberg, General, Visceral, and Transplantation Surgery
Keywords:	Liver resection, Liver failure, Small for size, Transhepatic flow, Transhepatic pressure
Note: The following files were submitted by the author for peer review, but cannot be converted to PDF. You must view these files (e.g. movies) online.	

SPIRIT Checklist.doc

Evaluation of Transhepatic Flow Changes in Major Hepatectomy (THEFLOW): study protocol for a single center, non-interventional cohort study

Mohammad Golriz[1,2,3,*], Anastasia Lemekhova[1,2,3,*], Elias Khajeh[1,2], Omid Ghamarnejad[1,2], Mohammed Al-Saeedi[1], Oliver Strobel[1,3], Thilo Hackert[1,3], Beat Müller-Stich[1], Martin Schneider[1,3], Christoph Berchtold[1], Parham Tinoush[4], Philipp Mayer[4], De-Hua Chang[3,4], Karl Heinz Weiss[3,5], Katrin Hoffmann[1,2,3], Arianeb Mehrabi[1,2,3]

[1]Department of General, Visceral, and Transplantation Surgery, University of Heidelberg, Heidelberg, Germany

[2]Division of Liver Surgery at Department of General, Visceral, and Transplantation Surgery, University of Heidelberg, Heidelberg, Germany

[3]Liver Cancer Center Heidelberg (LCCH), Heidelberg, Germany

[4]Department of Diagnostic and Interventional Radiology, University Hospital Heidelberg, Heidelberg, Germany

[5]Department of Gastroenterology and Hepatology, University of Heidelberg, Heidelberg, Germany

* Both authors contributed equally to this work

Correspondence to:

Prof. Dr. med. A. Mehrabi, FICS, FEBS, FACS

Head of the Division of Liver Surgery and Visceral Transplantation

Department of General, Visceral, and Transplantation Surgery

University of Heidelberg

Im Neuenheimer Feld 110

69120 Heidelberg, Germany

Tel: 0049 – 6221 - 5636223

Fax: 0049 – 6221 - 567470

E-Mail: arianeb.mehrabi@med.uni-heidelberg.de

Abstract

Introduction

Liver resection is the only curative treatment for primary and secondary hepatic tumors. Improvements in perioperative preparation of patients and new surgical developments have made complex liver resections possible. However, small for size and flow syndrome (SFSF) is still a challenging issue, rendering patients inoperable and causing postoperative morbidity and mortality. Although the role of transhepatic flow in the postoperative outcome has been shown in small partial liver transplantation and experimental studies of SFSF, this has never been studied in the clinical setting following liver resection. The aim of this study is to systematically evaluate transhepatic flow changes following major liver resection and its correlation with postoperative outcomes.

Methods and analysis

The THEFLOW study is a single center, non-interventional cohort study. All patients undergoing major hepatectomy (defined as hemihepatectomy or extended hepatectomy based on the Brisbane classification) are screened for eligibility. The portal venous flow, hepatic artery flow, and portal venous pressure are measured before and after each resection. All patients are followed-up for 3 months after the operation. During each evaluation, standard clinical data, PHLF, and overall morbidity and mortality will be recorded.

Discussion

Findings of THEFLOW study will show the correlation between transhepatic flow and pressure and postoperative outcomes following major liver resection. A cut off level for portal vein flow

and pressure as a risk factor for SFSF may also be defined. Moreover, we will compare the role of portal vein flow and pressure in a small remnant liver between patients with and without adjuvant chemotherapy.

Ethics and dissemination:

This protocol study received approval from the Ethics Committee of the University of Heidelberg (registration number: S576/2017). The results of this study will be published in a peer-reviewed journal, and will also be presented at medical meetings.

Trial registration number: NCT03762876.

Strengths and limitations of this study

- The THEFLOW study will be the first prospective clinical study to systematically evaluate the role of transhepatic flow changes in prediction of SFSF after major hepatectomy
- A limitation of this study is, that a postoperative monitoring of the portal vein pressure is not possible
- The comprehensive findings of this study may show that the postoperative outcomes of patients with a high risk of SFSF can be improved by adjusting the surgical strategy and by providing more intensive perioperative care

Introduction

Liver resection is the only curative treatment for many primary and secondary hepatic tumors [1-3]. Improvements in patient selection criteria, surgical methods, and postoperative care have made major liver resections (hemihepatectomy or extended hepatectomy) more feasible and safer [4-8]. However, posthepatectomy liver failure (PHLF) or the risk of developing PHLF because of small remnant liver (as small for size syndrome) still need novel predictive factors [9 10] and remain challenging because they can render the patient inoperable or cause postoperative mortality and morbidity [11 12]. The current preventive and therapeutic efforts, which focus only on the remnant liver volume (e.g., two-staged hepatectomy, portal vein embolization, or associating liver partition and portal vein ligation for staged hepatectomy [ALPPS]) have improved the results, but they are still not effective enough [13-16]. Therefore, there are still many patients, who either are not operated because of the high risk of PHLF or suffer from PHLF following major hepatectomy.

Findings from partial liver transplantation have revealed that the role of transhepatic flow parallel to the size of the remnant liver [17 18]; therefore, the syndrome was discussed to be called as small for size and flow syndrome (SFSF) [19-21]. In an experimental setting, the portal vein flow (PVF) and the portal vein pressure (PVP) increase significantly for the remnant liver volume following major liver resection [22]. This increase has important pathophysiologic consequences, causing cellular necrosis and SFSF [8 23-25]. Troisi et al. suggested an upper limit of 250 ml/min/100g PVF to prevent SFSF after living donor liver transplantation [19 26]. Although transhepatic flow plays a role in partial liver transplantation [27] and in experimental liver resection [22], this has never been shown systematically following liver resection in the clinical setting.

The aim of this study is to systematically evaluate transhepatic flow changes following major liver resection to predict and prevent SFSF.

Methods and analysis

Study Settings

The THEFLOW study is a single center, non-interventional cohort study. The study aims to enroll 50 patients undergoing major liver resection (i.e., a hemihepatectomy or an extended hemihepatectomy) with or without prior chemotherapy. This study is taking place at the Division of Liver Surgery in the Department of General, Visceral, and Transplantation Surgery of the University of Heidelberg. It was initiated on 25 March 2018 and is expected to progress for two years. The study protocol was registered at ClinicalTrials.gov (registration number: NCT03762876).

Patient recruitment

The study plan was approved by the Ethics Committee of the Medical Faculty of Heidelberg (S576/2017). As shown in the study flow chart (Figure 1), all patients who undergo major hepatectomy (defined as hemihepatectomy or extended hepatectomy according to the Brisbane nomenclature) [28] are currently being screened for eligibility. Eligible patients that provide informed consent will be treated and followed up according to routine procedures at the Department of General, Visceral, and Transplantation Surgery in Heidelberg University Hospital. Transhepatic flow and pressure parameters, i.e., portal venous flow, hepatic artery flow (HAF) and portal venous pressure (PVP), will be measured in study participants before and after resection, meanwhile the standard surgical procedure is not altered. We will look for anatomical variations, stenosis of the celiac trunk or superior mesentery artery, as these factors affect the physiological flow of the liver artery and portal vein. Eligibility will be determined based on informed consent status, age, planned surgery, and comorbidities (Table 1). Furthermore, total

liver volume will be calculated based on preoperative imaging. It is important to note that central tumors may compress the vessels, precluding measurement of physiological flow or pressure. Patients with such tumors will be excluded from the study.

Table 1. Inclusion and exclusion criteria of the THEFLOW study

Inclusion criteria	Exclusion criteria
Aged above 18 years	Previous surgery of the hepatoduodenal ligament
Undergoing major hepatectomy	Status after transjugular intrahepatic portosystemic shunt
Patient consent	Portal vein thrombosis
	Portal vein hypertension
	Vascular malformation
	Cirrhosis
	Metabolic liver diseases
	Cardiac failure
	Pulmonary hypertension
	Not able to give consent

Outcome measures

After enrolment, demographic and baseline data (Table 2) of included patients will be recorded. Participants will be monitored intraoperatively, on postoperative days (PODs) 1, 2, 3, and at discharge. After discharge, patients will be visited on POD 90. As shown in Table 3, all intraoperative findings, postoperative complications, and laboratory parameters will be recorded intraoperatively, during hospital stay, and on POD 90. To enhance participant retention and to

avoid loss to follow-up, we will contact patients during the follow-up period to remind them of scheduled visits and to arrange appointments.

Table 2. Demographic and baseline data

Gender (f/m)
Age (years)
Height (cm)
Weight (kg)
Medications
Previous surgeries
Indication for surgery
Anatomical variations of the abdominal arteries
Total liver volume as measured on preoperative CT scan
Calculated future liver volume based on preoperative CT scan
Liver stiffness (measured by fibroscan)
Comorbidities:
Cardiac
Pulmonary
Renal
Autoimmune
Infectious

Table 3. THEFLOW study design according to the SPIRIT checklist

	Study period						
	Enrolment	Operation	Post operation				
TIME POINT	*Admission day*	*Operation day*	*POD 1*	*POD 2*	*POD 3*	*Discharge*	*POD 90*
Enrolment:							
Eligibility screen	X						
Informed consent	X						
Baseline assessments[a]	X						
Assessments:							
Flows (PVF, HAF), pressures (PVP, CVP, and MAP), and vital signs		X					
Type of resection and transection technique		X					
Intraoperative complications		X					
Estimated blood loss		X					
Operating time		X					
Liver stiffness	X					X	X
CT volumetric assessment	X					X	X
Length of hospital stay			X	X	X	X	
Drainage losses			X	X	X	X	
Laboratory findings[b]	X	X	X	X	X	X	X

Postoperative complications			X	X	X	X	X
PHLF			X	X	X	X	X
Mortality		X	X	X	X	X	X

POD, postoperative day; PVF, portal vein flow; PVP, portal vein pressure; HAF, hepatic artery flow; CVP, central vein pressure; MAP, mean arterial pressure; PHLF, posthepatectomy liver failure.

[a]Baseline assessments are shown in Table 2; [b]Laboratory findings are shown in Table 5

Primary endpoint

PVF will be measured before and following the liver resection. To assess the predictive role of PVF in SFSF, changes in PVF will be evaluated and stratified based on remnant liver volume (Table 4).

Secondary endpoint

Intraoperative outcomes, including vital signs, central vein pressure, mean arterial pressure, type of resection, transection technique, intraoperative complications, HAF, PVP, estimated blood loss, and operating time, will be reported. To calculate the variation of the transhepatic flow to the remnant liver volume, we will measure the removed liver volume during surgery and use CT volumetric assessment to quantify the liver volume before and 3 months after surgery. Additionally, liver stiffness will be evaluated using fibroscan before surgery, at discharge, and 3 months after surgery. Laboratory results (Table 5), length of hospital stay, postoperative complications, PHLF, and all-cause mortality will also be reported until POD 90 (Table 3 and 4).

Table 4. Primary and secondary endpoints of the THEFLOW study

Endpoints	Definitions
Primary endpoint	
Portal vein flow (PVF)	PVF (ml/min)
Secondary endpoints	
Portal vein pressure (PVP)	PVP (mmHg)
Hepatic artery flow (HAF)	HAF (ml/min)
Central vein pressure (CVP)	CVP (mmHg)
Mean arterial pressure (MAP)	MAP (mmHg)
Heart rate	Heart rate (beats per minute)
Positive end-expiratory pressure (PEEP)	PEEP (cmH_2O)
Type of resection and transection technique	Type of resection and transection technique will be documented during the surgery
Intraoperative complications	Any complication occurring during the operation
Estimated blood loss	The entire blood loss (ml) from skin incision to skin closure
Operating time	Time (min) from skin incision to closure of the skin incision
Length of hospital stay	Time (days) from the day of the operation until the day of discharge
Liver stiffness	Will be reported according to the fibroscan results
CT volumetric assessment	Total liver volume, future liver remnant volume, and liver volume 3 months after surgery will be evaluated (cm^3)
Drainage losses	The amount (ml) and content of drainage will be evaluated during hospitalization
Laboratory findings	Presented in Table 5
Postoperative complications	Each complication will be reported and graded according to the Clavien-Dindo classification [29]
Posthepatectomy liver failure (PHLF)	PHLF rate will be determined based on the ISGLS criteria [30]
Mortality	Death due to any cause at any time during the follow-up period

Table 5. Details of laboratory parameters

Laboratory findings	**Parameters**
Cholestasis parameters	Alkalinephosphatase (U/l) and gamma-glutamyltransferase (U/l)
Excretion parameters	Bilirubin (mg/dl)
Hepatocellular integrity	Glutamate-oxalacetate-transaminase (U/l), and glutamate-pyruvate-transaminase (U/l)
Synthesis parameters	Albumin (g/l) and INR
Tumor markers	Alpha fetoprotein (ng/mL), carcinoembryonic antigen (µg/l), and carbohydrate antigen 19-9 (U/ml)
Infection parameters	Leukocytes (/nl), c-reactive protein (mg/l), and procalcitonin (ng/ml)
Cardiovascular parameters	Blood pressure, pulse, hemoglobin (g/dl), and hematocrit (l/l)
Electrolytes	Sodium (mmol/l), potassium (mmol/l), and calcium (mmol/l)
Kidney function	Creatinine (mg/dl) and glomerular filtration rate
Pancreatic enzymes	Amylase (U/l) (pancreatic) and lipase (U/l)

Modification of the protocol

Protocol amendments will be considered by the principal investigator. All protocol amendments will be submitted to the Ethics Committee for approval. No patients will be recruited until the modifications are accepted.

Methods for minimizing bias

To avoid selection bias and to ensure homogeneity of patients, all patients admitted to Heidelberg University Hospital that are scheduled to undergo major liver resection will be screened for eligibility. Every patient who meets the inclusion criteria and does not meet the exclusion criteria will be informed of the study and included if he/she gives consent to participate (Table 1). Data will be analyzed after all data have been collected. Furthermore, selective reporting will be avoided by submitting the study protocol prior to data collection including all information concerning study endpoints and statistical analysis. Any financial relationship and any conflict of interest that may arise will also be declared.

Ethical and legal aspects and termination criteria

Patients will be informed verbally and in writing about the nature and scope of the planned study and participation in the study will be voluntary. The names of the patients and all other confidential information will be subject to medical confidentiality and the provisions of the Federal Data Protection Act (BDSG). In accordance with the European General Data Protection Regulations (EU-DSGVO), all patient data will be collected anonymously. For statistical analysis, patient data will only be transferred in anonymized form. Third parties will not have access to original patient records.

Consent to participate may be withdrawn at any time, without giving reasons and without affecting further medical care. Upon withdrawal from the study, the patient's data will be irreversibly deleted unless they agree to materials and data already collected being used anonymously in evaluation.

Data management

All data will be collected and recorded in case report forms (CRFs) by an investigator before transfer to the data management center. To ensure accurate data collection, the CRF will be completed by an investigator who did not evaluate the patient after each patient visit. All demographic and baseline clinical data, as well as primary and secondary outcome measures, will be recorded in the CRF. All data will be checked, and any missing data will be obtained from the trial database or from participants. To ensure patient confidentiality, the CRF for each patient will be given an anonymous allocation number. We will ask for permission to continue follow-up and data collection in the event of withdrawal from the study. The principal investigator will review and sign all completed CRFs.

Statistical design and analysis

Sample size

This is an explorative study; therefore, a formal sample size was not calculated. Transhepatic flow changes will be measured in 50 patients, which is considered sufficient.

Statistical analysis

Data distribution will be evaluated using the one-sample Kolmogorov-Smirnov test. Paired t test or Wilcoxon signed-rank test will be used to compare continuous variables. Continuous variables will be compared between two groups using Student's t test or Mann-Whitney U test. The association of categorical variables will be evaluated by chi-square or Fisher's exact test as appropriate. To assess the predictive role of transhepatic flow changes, multivariate regression analysis will be performed. The significance level will be set at $\alpha \leq 0.05$, representing 95% confidence interval.

Ethics and dissemination:

This protocol study received approval from the Ethics Committee of the University of Heidelberg (registration number: S576/2017). All patients receive clarifications regarding the objectives and procedures, and written informed consent is obtained from those who agree to participate. The results of this study will be published in a peer-reviewed journal, and will also be presented at medical meetings.

Discussion

Despite numerous new surgical achievements, SFSF remains a challenging risk for patients who have to undergo major liver resection [19]. Patients with marginal remnant liver volume are particularly at risk and as a result, these patients are often considered inoperable or develop postoperative SFSF. To overcome this problem and prevent PHLF, efforts have been made to give the remnant liver time to regenerate after resection, such as in two-staged hepatectomy, portal vein embolization, and ALPPS [31] [32]. However, despite promising primary results,

complications remain high and dropouts due to inadequate liver regeneration is often, meaning many patients cannot be operated on further [32]. During the last years, findings from partial liver transplantation [33] have highlighted the important role of transhepatic flow in major liver resection [19]. This important role was confirmed by experimental studies[22]. In our previous experimental study, major liver resection increased the PVF and PVP for the remnant liver volume [22]. This was particularly significant after extended liver resection. The high PVF and PVP put too much pressure on the parenchyma, causing sinus endothelial damage through high shear stress. This leads to hemorrhage, cellular damage, and production of reactive oxygen species [34], meaning the remnant liver volume fails to function properly.

Although there are many clinical transplantation studies and experimental studies, to the best of our knowledge, there is still no clinical study evaluating transhepatic flow changes and their association with PHLF following major liver resection. Moreover, transhepatic flow and pressure variation have not been compared between the normal liver and a liver after chemotherapy. The THEFLOW study will be the first study to systematically evaluate transhepatic hemodynamic changes in normal and post-chemotherapy livers following major hepatectomy. Furthermore, the correlation of the transhepatic flow changes with postoperative outcomes will be evaluated. Findings of the THEFLOW study will define cut off values for the PVF and PVP that can predict the risk of SFSF in patients undergoing major hepatectomy. Patients with marginal remnant liver volume and/or a hemodynamic risk of SFSF may benefit from a different surgical strategy, e.g., adjustment from a one-step to a two-step concept.

In summary, the association between transhepatic flow changes and SFSF after major hepatectomy has not been well investigated. The THEFLOW study will be the first prospective clinical study to systematically evaluate the role of transhepatic flow changes in prediction of SFSF after major hepatectomy. The comprehensive findings of this study may show that the postoperative outcomes of patients with a high risk of SFSF can be improved by adjusting the surgical strategy and by providing more intensive perioperative care.

Trials status

The THEFLOW study is currently recruiting participants.

Acknowledgements

Not applicable.

Contributions

AM, MG, and AN developed the original concept of the trial. AM, MG, AN, EK, and OG developed the design and methodology. MG, EK, and OG performed the statistical assessments and developed the analysis plan. MG, AN, EK, OG, MAS, and PT contributed to drafting the protocol of the paper and the article. MAS, OS, TH, BMS, MS, CB, PM, DHC, KHW, KH, and AM contributed to the revision of the final report. All authors read and approved the final manuscript.

Funding

This research received no specific funding from the public, commercial, or not-for-profit sectors.

Competing interests

The authors declare that they have no competing interests.

Patients Consent

Written informed consent for publication of clinical images will be obtained from the patients.

Ethics approval

This protocol study received approval from the Ethics Committee of the University of Heidelberg (registration number: S576/2017).

Provenance and peer review

Not commissioned; externally peer reviewed.

References

1. El-Serag HB, Marrero JA, Rudolph L, et al. Diagnosis and treatment of hepatocellular carcinoma. *Gastroenterology* 2008;134(6):1752-63. doi: 10.1053/j.gastro.2008.02.090
2. Manfredi S, Lepage C, Hatem C, et al. Epidemiology and management of liver metastases from colorectal cancer. *Ann Surg* 2006;244(2):254-9. doi: 10.1097/01.sla.0000217629.94941.cf
3. Poon RT, Fan ST, Lo CM, et al. Improving survival results after resection of hepatocellular carcinoma: a prospective study of 377 patients over 10 years. *Ann Surg* 2001;234(1):63-70.
4. Abdalla EK, Barnett CC, Doherty D, et al. Extended hepatectomy in patients with hepatobiliary malignancies with and without preoperative portal vein embolization. *Arch Surg* 2002;137(6):675-80; discussion 80-1.
5. 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(1):38-46.
6. Rahbari NN, Elbers H, Koch M, et al. Randomized clinical trial of stapler versus clamp-crushing transection in elective liver resection. *Br j Surg* 2014;101(3):200-7. doi: 10.1002/bjs.9387 [published Online First: 2014/01/10]

7. Fritzmann J, Kirchberg J, Sturm D, et al. Randomized clinical trial of stapler hepatectomy versus LigaSure transection in elective hepatic resection. *Br j Surg* 2018;105(9):1119-27. doi: 10.1002/bjs.10902 [published Online First: 2018/08/03]
8. Rahbari NN, Koch M, Zimmermann JB, et al. Infrahepatic inferior vena cava clamping for reduction of central venous pressure and blood loss during hepatic resection: a randomized controlled trial. *Ann Surg* 2011;253(6):1102-10. doi: 10.1097/SLA.0b013e318214bee5 [published Online First: 2011/03/18]
9. Mehrabi A, Golriz M, Khajeh E, et al. Meta-analysis of the prognostic role of perioperative platelet count in posthepatectomy liver failure and mortality. *Br j Surg* 2018;105(10):1254-61. doi: 10.1002/bjs.10906 [published Online First: 2018/07/13]
10. Golriz M, Ghamarnejad O, Khajeh E, et al. Preoperative Thrombocytopenia May Predict Poor Surgical Outcome after Extended Hepatectomy. *Can J Gastroenterol Hepatol* 2018;2018:1275720. doi: 10.1155/2018/1275720 [published Online First: 2018/12/06]
11. Shoup M, Gonen M, D'Angelica M, et al. Volumetric analysis predicts hepatic dysfunction in patients undergoing major liver resection. *J Gastrointest Surg* 2003;7(3):325-30.
12. Ren Z, Xu Y, Zhu S. Indocyanine green retention test avoiding liver failure after hepatectomy for hepatolithiasis. *Hepatogastroenterology* 2012;59(115):782-4. doi: 10.5754/hge11453
13. Schadde E, Raptis DA, Schnitzbauer AA, et al. Prediction of Mortality After ALPPS Stage-1: An Analysis of 320 Patients From the International ALPPS Registry. *Ann Surg* 2015;262(5):780-5; discussion 85-6. doi: 10.1097/sla.0000000000001450 [published Online First: 2015/11/20]
14. Wanis KN, Buac S, Linecker M, et al. Patient Survival After Simultaneous ALPPS and Colorectal Resection. *World J Surg* 2017;41(4):1119-25. doi: 10.1007/s00268-016-3818-1 [published Online First: 2016/11/12]
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(5):829-36; discussion 36-8. doi: 10.1097/sla.0000000000000947 [published Online First: 2014/11/08]
16. Kremer M, Manzini G, Hristov B, et al. Impact of Neoadjuvant Chemotherapy on Hypertrophy of the Future Liver Remnant after Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy. *J Am Coll Surg* 2015;221(3):717-28.e1. doi: 10.1016/j.jamcollsurg.2015.05.017 [published Online First: 2015/08/02]
17. Asencio JM, Vaquero J, Olmedilla L, et al. "Small-for-flow" syndrome: shifting the "size" paradigm. *Med Hypotheses* 2013;80(5):573-7. doi: 10.1016/j.mehy.2013.01.028
18. Vasavada BB, Chen CL, Zakaria M. Portal flow is the main predictor of early graft dysfunction regardless of the GRWR status in living donor liver transplantation - a retrospective analysis of 134 patients. *Int J Surg* 2014;12(2):177-80. doi: 10.1016/j.ijsu.2013.12.006
19. Golriz M, Majlesara A, El Sakka S, et al. Small for Size and Flow (SFSF) syndrome: An alternative description for posthepatectomy liver failure. *Clin Res Hepatol Gastroenterol* 2015 doi: 10.1016/j.clinre.2015.06.024
20. Guglielmi A, Ruzzenente A, Conci S, et al. How much remnant is enough in liver resection? *Dig Surg* 2012;29(1):6-17. doi: 10.1159/000335713
21. Golriz M, Ashrafi M, Khajeh E, et al. Establishing a Porcine Model of Small for Size Syndrome following Liver Resection. *Can J Gastroenterol Hepatol* 2017;2017:5127178. doi: 10.1155/2017/5127178 [published Online First: 2017/09/28]

22. Golriz M, El Sakka S, Majlesara A, et al. Hepatic Hemodynamic Changes Following Stepwise Liver Resection. *J Gastrointest Surg* 2016;20(3):587-94. doi: 10.1007/s11605-015-3021-y [published Online First: 2015/11/18]
23. Kelly DM, Demetris AJ, Fung JJ, et al. Porcine partial liver transplantation: a novel model of the "small-for-size" liver graft. *Liver Transpl* 2004;10(2):253-63. doi: 10.1002/lt.20073 [published Online First: 2004/02/06]
24. Man K, Fan ST, Lo CM, et al. Graft injury in relation to graft size in right lobe live donor liver transplantation: a study of hepatic sinusoidal injury in correlation with portal hemodynamics and intragraft gene expression. *Ann Surg* 2003;237(2):256-64. doi: 10.1097/01.SLA.0000048976.11824.67 [published Online First: 2003/02/01]
25. Nagino M, Ando M, Kamiya J, et al. Liver regeneration after major hepatectomy for biliary cancer. *Br j Surg* 2001;88(8):1084-91. doi: 10.1046/j.0007-1323.2001.01832.x [published Online First: 2001/08/08]
26. Troisi R, de Hemptinne B. Clinical relevance of adapting portal vein flow in living donor liver transplantation in adult patients. *Liver Transpl* 2003;9(9):S36-41. doi: 10.1053/jlts.2003.50200
27. Troisi RI, Berardi G, Tomassini F, et al. Graft inflow modulation in adult-to-adult living donor liver transplantation: A systematic review. *Transplant Rev (Orlando)* 2017;31(2):127-35. doi: 10.1016/j.trre.2016.11.002 [published Online First: 2016/12/19]
28. Pang YY. The Brisbane 2000 terminology of liver anatomy and resections. HPB 2000; 2:333-39. *HPB : the official journal of the International Hepato Pancreato Biliary Association* 2002;4(2):99; author reply 99-100. doi: 10.1080/136518202760378489 [published Online First: 2008/03/12]
29. Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien-Dindo classification of surgical complications: five-year experience. *Ann Surg* 2009;250(2):187-96. doi: 10.1097/SLA.0b013e3181b13ca2 [published Online First: 2009/07/30]
30. Rahbari NN, Garden OJ, Padbury R, et al. Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS). *Surgery* 2011;149(5):713-24. doi: 10.1016/j.surg.2010.10.001 [published Online First: 2011/01/18]
31. Vivarelli M, Vincenzi P, Montalti R, et al. ALPPS Procedure for Extended Liver Resections: A Single Centre Experience and a Systematic Review. *PloS one* 2015;10(12):e0144019. doi: 10.1371/journal.pone.0144019 [published Online First: 2015/12/25]
32. Schnitzbauer AA. A Comparison of Pitfalls after ALPPS Stage 1 or Portal Vein Embolization in Small-for-Size Setting Hepatectomies. *Visc Med* 2017;33(6):435-41. doi: 10.1159/000480100 [published Online First: 2018/01/19]
33. Troisi R, Ricciardi S, Smeets P, et al. Effects of hemi-portocaval shunts for inflow modulation on the outcome of small-for-size grafts in living donor liver transplantation. *Am J Transplant* 2005;5(6):1397-404. doi: 10.1111/j.1600-6143.2005.00850.x [published Online First: 2005/05/13]
34. Serenari M, Cescon M, Cucchetti A, et al. Liver function impairment in liver transplantation and after extended hepatectomy. *World J Gastroenterol* 2013;19(44):7922-9. doi: 10.3748/wjg.v19.i44.7922 [published Online First: 2013/12/07]

Figure legends

Fig. 1. Study design flow chart.

*Preoperative assessments: Baseline data (e.g., date of birth, gender, weight [kg], height [cm], diagnosis, prior treatment [chemotherapy], comorbidities, spleen size), total and future liver volume (measured by CT volumetry), and liver stiffness (measured by fibroscan). PVF, portal vein flow; PVP, portal vein pressure; HAF, hepatic artery flow; CVP, central vein pressure; MAP, mean arterial pressure; HR, heart rate; PEEP, positive end-expiratory pressure; PHLF, posthepatectomy liver failure.

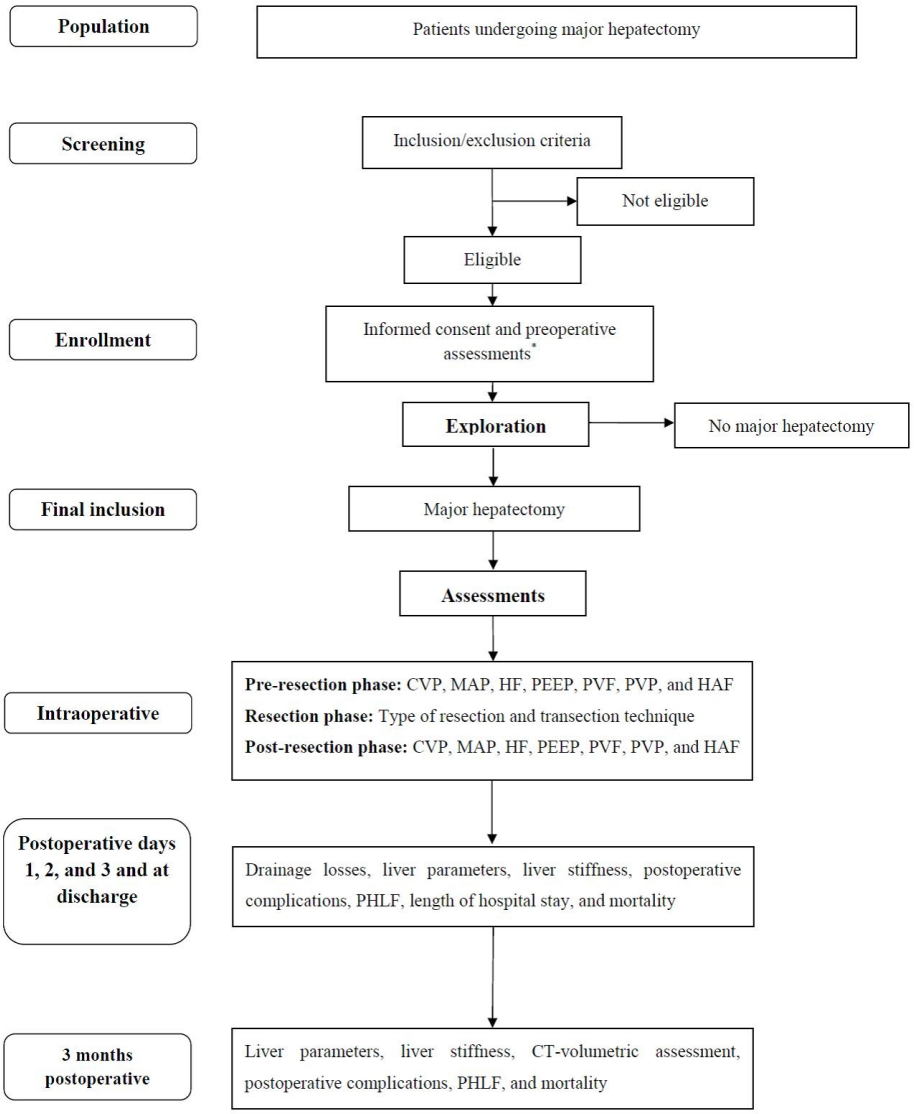

Fig. 1. Study design flow chart.
*Preoperative assessments: Baseline data (e.g., date of birth, gender, weight [kg], height [cm], diagnosis, prior treatment [chemotherapy], comorbidities, spleen size), total and future liver volume (measured by CT volumetry), and liver stiffness (measured by fibroscan). PVF, portal vein flow; PVP, portal vein pressure; HAF, hepatic artery flow; CVP, central vein pressure; MAP, mean arterial pressure; HR, heart rate; PEEP, positive end-expiratory pressure; PHLF, posthepatectomy liver failure.

346x442mm (96 x 96 DPI)

BMJ Open

Evaluation of Transhepatic Flow Changes in Major Hepatectomy (THEFLOW): study protocol for a single center, non-interventional cohort study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-029618.R1
Article Type:	Protocol
Date Submitted by the Author:	08-Jul-2019
Complete List of Authors:	Golriz, Mohammad ; University of Heidelberg, General, Visceral, and Transplantation Surgery Lemekhova, Anastasia; University of Heidelberg, General, Visceral, and Transplantation Surgery Khajeh, Elias ; University of Heidelberg, General, Visceral, and Transplantation Surgery Ghamarnejad, Omid ; University of Heidelberg, General, Visceral, and Transplantation Surgery Al-Saeedi, Mohammed ; University of Heidelberg, General, Visceral, and Transplantation Surgery Strobel, Oliver ; University of Heidelberg, General, Visceral, and Transplantation Surgery Thilo, Hackert; University of Heidelberg, Department of Surgery Müller-Stich, Beat ; University of Heidelberg, General, Visceral, and Transplantation Surgery Schneider, Martin ; University of Heidelberg, General, Visceral, and Transplantation Surgery Berchtold, Christoph ; University of Heidelberg, General, Visceral, and Transplantation Surgery Tinoush, Parham; University Hospital Heidelberg, Department of Diagnostic and Interventional Radiology Mayer, Philipp; University Hospital Heidelberg, Diagnostic and Interventional Radiology Chang, De-Hua; University Hospital Heidelberg, Diagnostic and Interventional Radiology Weiss, KarlHeinz; University of Heidelberg, Gastroenterology and Hepatology Hoffmann, Katrin ; University of Heidelberg, General, Visceral, and Transplantation Surgery Mehrabi, Arianeb; University of Heidelberg, General, Visceral, and Transplantation Surgery
Primary Subject Heading:	Gastroenterology and hepatology
Secondary Subject Heading:	Surgery
Keywords:	Liver resection, Liver failure, Small for size, Transhepatic flow, Transhepatic pressure

Evaluation of Transhepatic Flow Changes in Major Hepatectomy (THEFLOW): study protocol for a single center, non-interventional cohort study

Mohammad Golriz[1,2,3,*], Anastasia Lemekhova[1,2,3,*], Elias Khajeh[1,2], Omid Ghamarnejad[1,2], Mohammed Al-Saeedi[1], Oliver Strobel[1,3], Thilo Hackert[1,3], Beat Müller-Stich[1], Martin Schneider[1,3], Christoph Berchtold[1], Parham Tinoush[4], Philipp Mayer[4], De-Hua Chang[3,4], Karl Heinz Weiss[3,5], Katrin Hoffmann[1,2,3], Arianeb Mehrabi[1,2,3]

[1]Department of General, Visceral, and Transplantation Surgery, University of Heidelberg, Heidelberg, Germany

[2]Division of Liver Surgery at Department of General, Visceral, and Transplantation Surgery, University of Heidelberg, Heidelberg, Germany

[3]Liver Cancer Center Heidelberg (LCCH), Heidelberg, Germany

[4]Department of Diagnostic and Interventional Radiology, University Hospital Heidelberg, Heidelberg, Germany

[5]Department of Gastroenterology and Hepatology, University of Heidelberg, Heidelberg, Germany

* Both authors contributed equally to this work

Correspondence to:

Prof. Dr. med. A. Mehrabi, FICS, FEBS, FACS

Head of the Division of Liver Surgery and Visceral Transplantation

Department of General, Visceral, and Transplantation Surgery

University of Heidelberg

Im Neuenheimer Feld 110

69120 Heidelberg, Germany

Tel: 0049 – 6221 - 5636223

Fax: 0049 – 6221 - 567470

E-Mail: arianeb.mehrabi@med.uni-heidelberg.de

Abstract

Introduction

Liver resection is the only curative treatment for primary and secondary hepatic tumors. Improvements in perioperative preparation of patients and new surgical developments have made complex liver resections possible. However, small for size and flow syndrome (SFSF) is still a challenging issue, rendering patients inoperable and causing postoperative morbidity and mortality. Although the role of transhepatic flow in the postoperative outcome has been shown in small partial liver transplantation and experimental studies of SFSF, this has never been studied in the clinical setting following liver resection. The aim of this study is to systematically evaluate transhepatic flow changes following major liver resection and its correlation with postoperative outcomes.

Methods and analysis

The THEFLOW study is a single center, non-interventional cohort study. All patients undergoing major hepatectomy (defined as hemihepatectomy or extended hepatectomy based on the Brisbane classification) are screened for eligibility. The portal venous flow, hepatic artery flow, and portal venous pressure are measured before and after each resection. All patients are followed-up for 3 months after the operation. During each evaluation, standard clinical data, PHLF, and overall morbidity and mortality will be recorded.

Discussion

Findings of THEFLOW study will show the correlation between transhepatic flow and pressure and postoperative outcomes following major liver resection. A cut off level for portal vein flow

and pressure as a risk factor for SFSF may also be defined. Moreover, we will compare the role of portal vein flow and pressure in a small remnant liver between patients with and without adjuvant chemotherapy.

Ethics and dissemination:

This protocol study received approval from the Ethics Committee of the University of Heidelberg (registration number: S576/2017). The results of this study will be published in a peer-reviewed journal, and will also be presented at medical meetings.

Trial registration number: NCT03762876.

Strengths and limitations of this study

- The THEFLOW study will be the first prospective clinical study to systematically evaluate the role of transhepatic flow changes in prediction of SFSF after major hepatectomy
- A limitation of this study is, that a postoperative monitoring of the portal vein pressure is not possible
- The comprehensive findings of this study may show that the postoperative outcomes of patients with a high risk of SFSF can be improved by adjusting the surgical strategy and by providing more intensive perioperative care

Introduction

Liver resection is the only curative treatment for many primary and secondary hepatic tumors [1-3]. Improvements in patient selection criteria, surgical methods, and postoperative care have made major liver resections (hemihepatectomy or extended hepatectomy) more feasible and safer [4-8]. However, posthepatectomy liver failure (PHLF) or the risk of developing PHLF because of small remnant liver (as small for size syndrome) still need novel predictive factors [9 10] and remain challenging because they can render the patient inoperable or cause postoperative mortality and morbidity [11 12]. The current preventive and therapeutic efforts, which focus only on the remnant liver volume (e.g., two-staged hepatectomy, portal vein embolization, or associating liver partition and portal vein ligation for staged hepatectomy [ALPPS]) have improved the results, but they are still not effective enough [13-16]. Therefore, there are still many patients, who either are not operated because of the high risk of PHLF or suffer from PHLF following major hepatectomy.

Findings from partial liver transplantation have revealed that the role of transhepatic flow parallel to the size of the remnant liver [17 18]; therefore, the syndrome was discussed to be called as small for size and flow syndrome (SFSF) [19-21]. In an experimental setting, the portal vein flow (PVF) and the portal vein pressure (PVP) increase significantly for the remnant liver volume following major liver resection [22]. This increase has important pathophysiologic consequences, causing cellular necrosis and SFSF [8 23-25]. Troisi et al. suggested an upper limit of 250 ml/min/100g PVF to prevent SFSF after living donor liver transplantation [19 26]. Although transhepatic flow plays a role in partial liver transplantation [27] and in experimental liver resection [22], this has never been shown systematically following liver resection in the clinical setting.

The primary aim of this study is to systematically evaluate the amount of changes in transhepatic flow following major liver resection. Furthermore, association of transhepatic flow with postoperative outcomes such as SFSF will be investigated.

Methods and analysis

Study Settings

The THEFLOW study is a single center, non-interventional cohort study. The study aims to enroll 50 patients undergoing major liver resection (i.e., a hemihepatectomy or an extended hemihepatectomy) with or without prior chemotherapy. This study is taking place at the division of liver surgery in the Department of General, Visceral, and Transplantation Surgery of the University of Heidelberg. Our center is a referral hepatopancreatobiliary center that is highly specialized in treatment of patients with advanced hepatobiliary cancer. It was initiated on 25 March 2018 and is expected to progress for two years. The study protocol was registered at ClinicalTrials.gov (registration number: NCT03762876).

Patient recruitment

The study plan was approved by the Ethics Committee of the Medical Faculty of Heidelberg (S576/2017). As shown in the study flow chart (Figure 1), all patients who undergo major hepatectomy (defined as hemihepatectomy or extended hepatectomy according to the Brisbane nomenclature) [28] are currently being screened for eligibility. Eligible patients that provide informed consent will be treated and followed up according to routine procedures at the Department of General, Visceral, and Transplantation Surgery in Heidelberg University Hospital. Transhepatic flow and pressure parameters, i.e., portal venous flow, hepatic artery flow (HAF) and portal venous pressure (PVP), will be measured in study participants before and after resection, meanwhile the standard surgical procedure is not altered. We will look for anatomical variations, stenosis of the celiac trunk or superior mesentery artery, as these factors affect the physiological flow of the liver artery and portal vein. Eligibility will be determined based on

informed consent status, age, planned surgery, and comorbidities (Table 1). Furthermore, total liver volume will be calculated based on preoperative imaging. It is important to note that central tumors may compress the vessels, precluding measurement of physiological flow or pressure. Patients with such tumors will be excluded from the study.

Table 1. Inclusion and exclusion criteria of the THEFLOW study

Inclusion criteria	**Exclusion criteria**
Aged above 18 years	Previous surgery of the hepatoduodenal ligament
Undergoing major hepatectomy	Status after transjugular intrahepatic portosystemic shunt
Patient consent	Portal vein thrombosis
	Portal vein hypertension
	Vascular malformation
	Cirrhosis
	Metabolic liver diseases
	Cardiac failure
	Pulmonary hypertension
	Not able to give consent

Outcome measures

After enrolment, demographic and baseline data (Table 2) of included patients will be recorded. Participants will be monitored intraoperatively, on postoperative days (PODs) 1, 2, 3, and at discharge. After discharge, patients will be visited on POD 90. As shown in Table 3, all intraoperative findings, postoperative complications, and laboratory parameters will be recorded

intraoperatively, during hospital stay, and on POD 90. To enhance participant retention and to avoid loss to follow-up, we will contact patients during the follow-up period to remind them of scheduled visits and to arrange appointments.

Table 2. Demographic and baseline data

Gender (f/m)
Age (years)
Height (cm)
Weight (kg)
Medications
Previous surgeries
Indication for surgery
Anatomical variations of the abdominal arteries
Total liver volume as measured on preoperative CT scan
Calculated future liver volume based on preoperative CT scan
Liver stiffness (measured by fibroscan)
Comorbidities:
Cardiac
Pulmonary
Renal
Autoimmune
Infectious

Table 3. THEFLOW study design according to the SPIRIT checklist

	Study period						
	Enrolment	Operation	Post operation				
TIME POINT	*Admission day*	*Operation day*	*POD 1*	*POD 2*	*POD 3*	*Discharge*	*POD 90*
Enrolment:							
Eligibility screen	X						
Informed consent	X						
Baseline assessments	X						
Assessments:							
Flows (PVF, HAF), pressures (PVP, CVP, and MAP), and vital signs		X					
Type of resection and transection technique		X					
Intraoperative complications		X					
Estimated blood loss		X					
Operating time		X					
Liver stiffness	X					X	X
CT volumetric assessment	X					X	X
Length of hospital stay			X	X	X	X	
Drainage losses			X	X	X	X	
Laboratory findings	X	X	X	X	X	X	X

Postoperative complications			X	X	X	X	X
PHLF			X	X	X	X	X
Mortality		X	X	X	X	X	X

POD, postoperative day; PVF, portal vein flow; PVP, portal vein pressure; HAF, hepatic artery flow; CVP, central vein pressure; MAP, mean arterial pressure; PHLF, posthepatectomy liver failure.

Primary endpoint

PVF will be measured before and following the liver resection. To assess the predictive role of PVF in SFSF, changes in PVF will be evaluated and stratified based on remnant liver volume (Table 4).

Secondary endpoint

Intraoperative outcomes, including vital signs, central vein pressure, mean arterial pressure, type of resection, transection technique, intraoperative complications, HAF, PVP, estimated blood loss, and operating time, will be reported. To calculate the variation of the transhepatic flow to the remnant liver volume, we will measure the removed liver volume during surgery and use CT volumetric assessment to quantify the liver volume before and 3 months after surgery. Additionally, liver stiffness will be evaluated using fibroscan before surgery, at discharge, and 3 months after surgery. Laboratory results (Table 5), length of hospital stay, postoperative complications, PHLF, and all-cause mortality will also be reported until POD 90 (Table 3 and 4).

Table 4. Primary and secondary endpoints of the THEFLOW study

Endpoints	Definitions
Primary endpoint	
Portal vein flow (PVF)	PVF (ml/min)
Secondary endpoints	
Portal vein pressure (PVP)	PVP (mmHg)
Hepatic artery flow (HAF)	HAF (ml/min)
Central vein pressure (CVP)	CVP (mmHg)
Mean arterial pressure (MAP)	MAP (mmHg)
Heart rate	Heart rate (beats per minute)
Positive end-expiratory pressure (PEEP)	PEEP (cmH_2O)
Type of resection and transection technique	Type of resection and transection technique will be documented during the surgery
Intraoperative complications	Any complication occurring during the operation
Estimated blood loss	The entire blood loss (ml) from skin incision to skin closure
Operating time	Time (min) from skin incision to closure of the skin incision
Length of hospital stay	Time (days) from the day of the operation until the day of discharge
Liver stiffness	Will be reported according to the fibroscan results
CT volumetric assessment	Total liver volume, future liver remnant volume, and liver volume 3 months after surgery will be evaluated (cm^3)
Drainage losses	The amount (ml) and content of drainage will be evaluated during hospitalization
Laboratory findings	Presented in Table 5
Postoperative complications	Each complication will be reported and graded according to the Clavien-Dindo classification [29]
Posthepatectomy liver failure (PHLF)	PHLF rate will be determined based on the ISGLS criteria [30]
Mortality	Death due to any cause at any time during the follow-up period

Table 5. Details of laboratory parameters

Laboratory findings	**Parameters**
Cholestasis parameters	Alkalinephosphatase (U/l) and gamma-glutamyltransferase (U/l)
Excretion parameters	Bilirubin (mg/dl)
Hepatocellular integrity	Glutamate-oxalacetate-transaminase (U/l), and glutamate-pyruvate-transaminase (U/l)
Synthesis parameters	Albumin (g/l) and INR
Tumor markers	Alpha fetoprotein (ng/mL), carcinoembryonic antigen (µg/l), and carbohydrate antigen 19-9 (U/ml)
Infection parameters	Leukocytes (/nl), c-reactive protein (mg/l), and procalcitonin (ng/ml)
Cardiovascular parameters	Blood pressure, pulse, hemoglobin (g/dl), and hematocrit (l/l)
Electrolytes	Sodium (mmol/l), potassium (mmol/l), and calcium (mmol/l)
Kidney function	Creatinine (mg/dl) and glomerular filtration rate
Pancreatic enzymes	Amylase (U/l) (pancreatic) and lipase (U/l)

Modification of the protocol

Protocol amendments will be considered by the principal investigator. All protocol amendments will be submitted to the Ethics Committee for approval. No patients will be recruited until the modifications are accepted.

Methods for minimizing bias

To avoid selection bias and to ensure homogeneity of patients, all patients admitted to Heidelberg University Hospital that are scheduled to undergo major liver resection will be screened for eligibility. Every patient who meets the inclusion criteria and does not meet the exclusion criteria will be informed of the study and included if he/she gives consent to participate (Table 1). Data will be analyzed after all data have been collected. Furthermore, selective reporting will be avoided by submitting the study protocol prior to data collection including all information concerning study endpoints and statistical analysis. Any financial relationship and any conflict of interest that may arise will also be declared.

Ethical and legal aspects and termination criteria

Patients will be informed verbally and in writing about the nature and scope of the planned study and participation in the study will be voluntary. The names of the patients and all other confidential information will be subject to medical confidentiality and the provisions of the Federal Data Protection Act (BDSG). In accordance with the European General Data Protection Regulations (EU-DSGVO), all patient data will be collected anonymously. For statistical analysis, patient data will only be transferred in anonymized form. Third parties will not have access to original patient records.

Consent to participate may be withdrawn at any time, without giving reasons and without affecting further medical care. Upon withdrawal from the study, the patient's data will be irreversibly deleted unless they agree to materials and data already collected being used anonymously in evaluation.

Data management

All data will be collected and recorded in case report forms (CRFs) by an investigator before transfer to the data management center. To ensure accurate data collection, the CRF will be completed by an investigator who did not evaluate the patient after each patient visit. All demographic and baseline clinical data, as well as primary and secondary outcome measures, will be recorded in the CRF. All data will be checked, and any missing data will be obtained from the trial database or from participants. To ensure patient confidentiality, the CRF for each patient will be given an anonymous allocation number. We will ask for permission to continue follow-up and data collection in the event of withdrawal from the study. The principal investigator will review and sign all completed CRFs.

Statistical design and analysis

Sample size

This is an explorative study; therefore, a formal sample size was not calculated. Transhepatic flow changes will be measured in 50 patients, which is considered sufficient.

Statistical analysis

Wilcoxon signed-rank test will be used to compare paired variables (i.e. PVF, PVP, HAF, CVP, MAP, and heart rate) before and after liver resection. Continuous variables will be compared between two groups using Mann-Whitney U test. The association of categorical variables will be evaluated by Fisher's exact test. To assess the predictive role of transhepatic flow changes, multivariate logistic regression analyses with forward stepwise selection will be performed. Variables with a *p* value <0.1 from the univariate analysis will be included in the multivariate logistic regression analysis. The significance level will be set at $\alpha \leq 0.05$, representing 95% confidence interval.

Ethics and dissemination:

This protocol study received approval from the Ethics Committee of the University of Heidelberg (registration number: S576/2017). All patients receive clarifications regarding the objectives and procedures, and written informed consent is obtained from those who agree to participate. The results of this study will be published in a peer-reviewed journal, and will also be presented at medical meetings.

Discussion

Despite numerous new surgical achievements, SFSF remains a challenging risk for patients who have to undergo major liver resection [19]. Patients with marginal remnant liver volume are particularly at risk and as a result, these patients are often considered inoperable or develop postoperative SFSF. To overcome this problem and prevent PHLF, efforts have been made to give the remnant liver time to regenerate after resection, such as in two-staged hepatectomy,

portal vein embolization, and ALPPS [31] [32]. However, despite promising primary results, complications remain high and dropouts due to inadequate liver regeneration is often, meaning many patients cannot be operated on further [32]. During the last years, findings from partial liver transplantation [33] have highlighted the important role of transhepatic flow in major liver resection [19]. This important role was confirmed by experimental studies[22]. In our previous experimental study, major liver resection increased the PVF and PVP for the remnant liver volume [22]. This was particularly significant after extended liver resection. The high PVF and PVP put too much pressure on the parenchyma, causing sinus endothelial damage through high shear stress. This leads to hemorrhage, cellular damage, and production of reactive oxygen species [34], meaning the remnant liver volume fails to function properly.

Although there are many clinical transplantation studies and experimental studies, to the best of our knowledge, there is still no clinical study evaluating transhepatic flow changes and their association with PHLF following major liver resection. Moreover, transhepatic flow and pressure variation have not been compared between the normal liver and a liver after chemotherapy. The THEFLOW study will be the first study to systematically evaluate transhepatic hemodynamic changes in normal and post-chemotherapy livers following major hepatectomy. Furthermore, the correlation of the transhepatic flow changes with postoperative outcomes will be evaluated. Findings of the THEFLOW study will define cut off values for the PVF and PVP that can predict the risk of SFSF in patients undergoing major hepatectomy. Patients with marginal remnant liver volume and/or a hemodynamic risk of SFSF may benefit from a different surgical strategy, e.g., adjustment from a one-step to a two-step concept.

In summary, the association between transhepatic flow changes and SFSF after major hepatectomy has not been well investigated. The THEFLOW study will be the first prospective clinical study to systematically evaluate the role of transhepatic flow changes in prediction of SFSF after major hepatectomy. The comprehensive findings of this study may show that the postoperative outcomes of patients with a high risk of SFSF can be improved by adjusting the surgical strategy and by providing more intensive perioperative care.

Trials status

The THEFLOW study is currently recruiting participants.

Acknowledgements

Not applicable.

Contributions

AM, MG, AL, and MAS developed the original concept of the trial. AM, MG, AL, MAS, OS, EK, and OG developed the design and methodology. MG, AL, TH, BMS, EK, and OG performed the statistical assessments and developed the analysis plan. MG, AL, EK, OG, MAS, CB, and PT contributed to drafting the protocol of the paper and the article. MAS, OS, TH, BMS, MS, CB, PM, DHC, KHW, KH, and AM contributed to the revision of the final report. All authors read and approved the final manuscript.

Funding

This research received no specific funding from the public, commercial, or not-for-profit sectors.

Competing interests

The authors declare that they have no competing interests.

Patients Consent

Written informed consent for publication of clinical images will be obtained from the patients.

Ethics approval

This protocol study received approval from the Ethics Committee of the University of Heidelberg (registration number: S576/2017).

Provenance and peer review

Not commissioned; externally peer reviewed.

References

1. El-Serag HB, Marrero JA, Rudolph L, et al. Diagnosis and treatment of hepatocellular carcinoma. *Gastroenterology* 2008;134(6):1752-63. doi: 10.1053/j.gastro.2008.02.090
2. Manfredi S, Lepage C, Hatem C, et al. Epidemiology and management of liver metastases from colorectal cancer. *Ann Surg* 2006;244(2):254-9. doi: 10.1097/01.sla.0000217629.94941.cf
3. Poon RT, Fan ST, Lo CM, et al. Improving survival results after resection of hepatocellular carcinoma: a prospective study of 377 patients over 10 years. *Ann Surg* 2001;234(1):63-70.
4. Abdalla EK, Barnett CC, Doherty D, et al. Extended hepatectomy in patients with hepatobiliary malignancies with and without preoperative portal vein embolization. *Arch Surg* 2002;137(6):675-80; discussion 80-1.
5. 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(1):38-46.
6. Rahbari NN, Elbers H, Koch M, et al. Randomized clinical trial of stapler versus clamp-crushing transection in elective liver resection. *Br j Surg* 2014;101(3):200-7. doi: 10.1002/bjs.9387 [published Online First: 2014/01/10]

7. Fritzmann J, Kirchberg J, Sturm D, et al. Randomized clinical trial of stapler hepatectomy versus LigaSure transection in elective hepatic resection. *Br j Surg* 2018;105(9):1119-27. doi: 10.1002/bjs.10902 [published Online First: 2018/08/03]
8. Rahbari NN, Koch M, Zimmermann JB, et al. Infrahepatic inferior vena cava clamping for reduction of central venous pressure and blood loss during hepatic resection: a randomized controlled trial. *Ann Surg* 2011;253(6):1102-10. doi: 10.1097/SLA.0b013e318214bee5 [published Online First: 2011/03/18]
9. Mehrabi A, Golriz M, Khajeh E, et al. Meta-analysis of the prognostic role of perioperative platelet count in posthepatectomy liver failure and mortality. *Br j Surg* 2018;105(10):1254-61. doi: 10.1002/bjs.10906 [published Online First: 2018/07/13]
10. Golriz M, Ghamarnejad O, Khajeh E, et al. Preoperative Thrombocytopenia May Predict Poor Surgical Outcome after Extended Hepatectomy. *Can J Gastroenterol Hepatol* 2018;2018:1275720. doi: 10.1155/2018/1275720 [published Online First: 2018/12/06]
11. Shoup M, Gonen M, D'Angelica M, et al. Volumetric analysis predicts hepatic dysfunction in patients undergoing major liver resection. *J Gastrointest Surg* 2003;7(3):325-30.
12. Ren Z, Xu Y, Zhu S. Indocyanine green retention test avoiding liver failure after hepatectomy for hepatolithiasis. *Hepatogastroenterology* 2012;59(115):782-4. doi: 10.5754/hge11453
13. Schadde E, Raptis DA, Schnitzbauer AA, et al. Prediction of Mortality After ALPPS Stage-1: An Analysis of 320 Patients From the International ALPPS Registry. *Ann Surg* 2015;262(5):780-5; discussion 85-6. doi: 10.1097/sla.0000000000001450 [published Online First: 2015/11/20]
14. Wanis KN, Buac S, Linecker M, et al. Patient Survival After Simultaneous ALPPS and Colorectal Resection. *World J Surg* 2017;41(4):1119-25. doi: 10.1007/s00268-016-3818-1 [published Online First: 2016/11/12]
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(5):829-36; discussion 36-8. doi: 10.1097/sla.0000000000000947 [published Online First: 2014/11/08]
16. Kremer M, Manzini G, Hristov B, et al. Impact of Neoadjuvant Chemotherapy on Hypertrophy of the Future Liver Remnant after Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy. *J Am Coll Surg* 2015;221(3):717-28.e1. doi: 10.1016/j.jamcollsurg.2015.05.017 [published Online First: 2015/08/02]
17. Asencio JM, Vaquero J, Olmedilla L, et al. "Small-for-flow" syndrome: shifting the "size" paradigm. *Med Hypotheses* 2013;80(5):573-7. doi: 10.1016/j.mehy.2013.01.028
18. Vasavada BB, Chen CL, Zakaria M. Portal flow is the main predictor of early graft dysfunction regardless of the GRWR status in living donor liver transplantation - a retrospective analysis of 134 patients. *Int J Surg* 2014;12(2):177-80. doi: 10.1016/j.ijsu.2013.12.006
19. Golriz M, Majlesara A, El Sakka S, et al. Small for Size and Flow (SFSF) syndrome: An alternative description for posthepatectomy liver failure. *Clin Res Hepatol Gastroenterol* 2015 doi: 10.1016/j.clinre.2015.06.024
20. Guglielmi A, Ruzzenente A, Conci S, et al. How much remnant is enough in liver resection? *Dig Surg* 2012;29(1):6-17. doi: 10.1159/000335713
21. Golriz M, Ashrafi M, Khajeh E, et al. Establishing a Porcine Model of Small for Size Syndrome following Liver Resection. *Can J Gastroenterol Hepatol* 2017;2017:5127178. doi: 10.1155/2017/5127178 [published Online First: 2017/09/28]

22. Golriz M, El Sakka S, Majlesara A, et al. Hepatic Hemodynamic Changes Following Stepwise Liver Resection. *J Gastrointest Surg* 2016;20(3):587-94. doi: 10.1007/s11605-015-3021-y [published Online First: 2015/11/18]
23. Kelly DM, Demetris AJ, Fung JJ, et al. Porcine partial liver transplantation: a novel model of the "small-for-size" liver graft. *Liver Transpl* 2004;10(2):253-63. doi: 10.1002/lt.20073 [published Online First: 2004/02/06]
24. Man K, Fan ST, Lo CM, et al. Graft injury in relation to graft size in right lobe live donor liver transplantation: a study of hepatic sinusoidal injury in correlation with portal hemodynamics and intragraft gene expression. *Ann Surg* 2003;237(2):256-64. doi: 10.1097/01.SLA.0000048976.11824.67 [published Online First: 2003/02/01]
25. Nagino M, Ando M, Kamiya J, et al. Liver regeneration after major hepatectomy for biliary cancer. *Br j Surg* 2001;88(8):1084-91. doi: 10.1046/j.0007-1323.2001.01832.x [published Online First: 2001/08/08]
26. Troisi R, de Hemptinne B. Clinical relevance of adapting portal vein flow in living donor liver transplantation in adult patients. *Liver Transpl* 2003;9(9):S36-41. doi: 10.1053/jlts.2003.50200
27. Troisi RI, Berardi G, Tomassini F, et al. Graft inflow modulation in adult-to-adult living donor liver transplantation: A systematic review. *Transplant Rev (Orlando)* 2017;31(2):127-35. doi: 10.1016/j.trre.2016.11.002 [published Online First: 2016/12/19]
28. Pang YY. The Brisbane 2000 terminology of liver anatomy and resections. HPB 2000; 2:333-39. *HPB : the official journal of the International Hepato Pancreato Biliary Association* 2002;4(2):99; author reply 99-100. doi: 10.1080/136518202760378489 [published Online First: 2008/03/12]
29. Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien-Dindo classification of surgical complications: five-year experience. *Ann Surg* 2009;250(2):187-96. doi: 10.1097/SLA.0b013e3181b13ca2 [published Online First: 2009/07/30]
30. Rahbari NN, Garden OJ, Padbury R, et al. Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS). *Surgery* 2011;149(5):713-24. doi: 10.1016/j.surg.2010.10.001 [published Online First: 2011/01/18]
31. Vivarelli M, Vincenzi P, Montalti R, et al. ALPPS Procedure for Extended Liver Resections: A Single Centre Experience and a Systematic Review. *PloS one* 2015;10(12):e0144019. doi: 10.1371/journal.pone.0144019 [published Online First: 2015/12/25]
32. Schnitzbauer AA. A Comparison of Pitfalls after ALPPS Stage 1 or Portal Vein Embolization in Small-for-Size Setting Hepatectomies. *Visc Med* 2017;33(6):435-41. doi: 10.1159/000480100 [published Online First: 2018/01/19]
33. Troisi R, Ricciardi S, Smeets P, et al. Effects of hemi-portocaval shunts for inflow modulation on the outcome of small-for-size grafts in living donor liver transplantation. *Am J Transplant* 2005;5(6):1397-404. doi: 10.1111/j.1600-6143.2005.00850.x [published Online First: 2005/05/13]
34. Serenari M, Cescon M, Cucchetti A, et al. Liver function impairment in liver transplantation and after extended hepatectomy. *World J Gastroenterol* 2013;19(44):7922-9. doi: 10.3748/wjg.v19.i44.7922 [published Online First: 2013/12/07]

Figure legends

Fig. 1. Study design flow chart.

*Preoperative assessments: Baseline data (e.g., date of birth, gender, weight [kg], height [cm], diagnosis, prior treatment [chemotherapy], comorbidities, spleen size), total and future liver volume (measured by CT volumetry), and liver stiffness (measured by fibroscan). PVF, portal vein flow; PVP, portal vein pressure; HAF, hepatic artery flow; CVP, central vein pressure; MAP, mean arterial pressure; HR, heart rate; PEEP, positive end-expiratory pressure; PHLF, posthepatectomy liver failure.

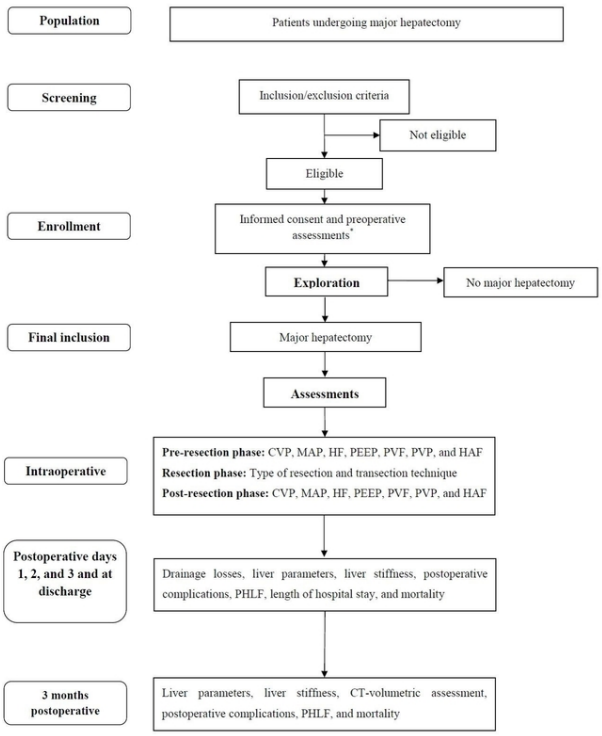

Fig. 1. Study design flow chart.
*Preoperative assessments: Baseline data (e.g., date of birth, gender, weight [kg], height [cm], diagnosis, prior treatment [chemotherapy], comorbidities, spleen size), total and future liver volume (measured by CT volumetry), and liver stiffness (measured by fibroscan). PVF, portal vein flow; PVP, portal vein pressure; HAF, hepatic artery flow; CVP, central vein pressure; MAP, mean arterial pressure; HR, heart rate; PEEP, positive end-expiratory pressure; PHLF, posthepatectomy liver failure.

90x90mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4, 7
	2b	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	3	Date and version identifier	7
Funding	4	Sources and types of financial, material, and other support	20
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 20
	5b	Name and contact information for the trial sponsor	NA
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	NA
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	9, 15

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5, 6
	6b	Explanation for choice of comparators	5, 6
Objectives	7	Specific objectives or hypotheses	6, 17
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6, 7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7, 8, Table 1
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	NA
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	NA
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	NA
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9, 15, 16, Table 2
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figures 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11, 12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	10, 11
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10, 11
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10, 11
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8, 10, 11
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	8

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12, 13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	NA
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	11
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	10
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	9, 10
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	7
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	NA

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7, 17, 18
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	18
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	11
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17, 18
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	11
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	9, 10
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	NA
	31b	Authorship eligibility guidelines and any intended use of professional writers	17, 18
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Additional file 3
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Evaluation of the role of transhepatic flow in postoperative outcomes following major hepatectomy (THEFLOW): study protocol for a single center, non-interventional cohort study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-029618.R2
Article Type:	Protocol
Date Submitted by the Author:	02-Sep-2019
Complete List of Authors:	Golriz, Mohammad ; University of Heidelberg, General, Visceral, and Transplantation Surgery; Liver Cancer Center Heidelberg (LCCH) Lemekhova, Anastasia; University of Heidelberg, General, Visceral, and Transplantation Surgery; Liver Cancer Center Heidelberg (LCCH) Khajeh, Elias ; University of Heidelberg, General, Visceral, and Transplantation Surgery Ghamarnejad, Omid ; University of Heidelberg, General, Visceral, and Transplantation Surgery Al-Saeedi, Mohammed ; University of Heidelberg, General, Visceral, and Transplantation Surgery Strobel, Oliver ; University of Heidelberg, General, Visceral, and Transplantation Surgery; Liver Cancer Center Heidelberg (LCCH) Thilo, Hackert; University of Heidelberg, Department of General, Visceral, and Transplantation Surgery; Liver Cancer Center Heidelberg (LCCH) Müller-Stich, Beat ; University of Heidelberg, General, Visceral, and Transplantation Surgery Schneider, Martin ; University of Heidelberg, General, Visceral, and Transplantation Surgery; Liver Cancer Center Heidelberg (LCCH) Berchtold, Christoph ; University of Heidelberg, General, Visceral, and Transplantation Surgery Tinoush, Parham; University Hospital Heidelberg, Department of Diagnostic and Interventional Radiology Mayer, Philipp; University Hospital Heidelberg, Diagnostic and Interventional Radiology Chang, De-Hua; University Hospital Heidelberg, Diagnostic and Interventional Radiology; Liver Cancer Center Heidelberg (LCCH) Weiss, KarlHeinz; University of Heidelberg, Gastroenterology and Hepatology; Liver Cancer Center Heidelberg (LCCH) Hoffmann, Katrin ; University of Heidelberg, General, Visceral, and Transplantation Surgery; Liver Cancer Center Heidelberg (LCCH) Mehrabi, Arianeb; University of Heidelberg, General, Visceral, and Transplantation Surgery; Liver Cancer Center Heidelberg (LCCH)
Primary Subject Heading:	Surgery
Secondary Subject Heading:	Surgery, Gastroenterology and hepatology
Keywords:	Transhepatic flow, Major hepatectomy, CHEMOTHERAPY, small for size

	and flow syndrome

Evaluation of the role of transhepatic flow in postoperative outcomes following major hepatectomy (THEFLOW): study protocol for a single center, non-interventional cohort study

Mohammad Golriz[1,2,3,*], Anastasia Lemekhova[1,2,3,*], Elias Khajeh[1,2], Omid Ghamarnejad[1,2], Mohammed Al-Saeedi[1], Oliver Strobel[1,3], Thilo Hackert[1,3], Beat Müller-Stich[1], Martin Schneider[1,3], Christoph Berchtold[1], Parham Tinoush[4], Philipp Mayer[4], De-Hua Chang[3,4], Karl Heinz Weiss[3,5], Katrin Hoffmann[1,2,3], Arianeb Mehrabi[1,2,3]

[1]Department of General, Visceral, and Transplantation Surgery, University of Heidelberg, Heidelberg, Germany

[2]Division of Liver Surgery at Department of General, Visceral, and Transplantation Surgery, University of Heidelberg, Heidelberg, Germany

[3]Liver Cancer Center Heidelberg (LCCH), Heidelberg, Germany

[4]Department of Diagnostic and Interventional Radiology, University Hospital Heidelberg, Heidelberg, Germany

[5]Department of Gastroenterology and Hepatology, University of Heidelberg, Heidelberg, Germany

* Both authors contributed equally to this work

Correspondence to:

Prof. Dr. med. A. Mehrabi, FICS, FEBS, FACS

Head of the Division of Liver Surgery and Visceral Transplantation

Department of General, Visceral, and Transplantation Surgery

University of Heidelberg

Im Neuenheimer Feld 110

69120 Heidelberg, Germany

Tel: 0049 – 6221 - 5636223

Fax: 0049 – 6221 - 567470

E-Mail: arianeb.mehrabi@med.uni-heidelberg.de

Word count: 1909

Abstract

Introduction

Liver resection is the only curative treatment for primary and secondary hepatic tumors. Improvements in perioperative preparation of patients and new surgical developments have made complex liver resections possible. However, small for size and flow syndrome (SFSF) is still a challenging issue, rendering patients inoperable and causing postoperative morbidity and mortality. Although the role of transhepatic flow in the postoperative outcome has been shown in small partial liver transplantation and experimental studies of SFSF, this has never been studied in the clinical setting following liver resection. The aim of this study is to systematically evaluate transhepatic flow changes following major liver resection and its correlation with postoperative outcomes.

Methods and analysis

The THEFLOW study is a single center, non-interventional cohort study, and aims to enroll 50 patients undergoing major hepatectomy (defined as hemihepatectomy or extended hepatectomy based on the Brisbane classification) with or without prior chemotherapy. The portal venous flow, hepatic artery flow, and portal venous pressure are measured before and after each resection. All patients are followed-up for 3 months after the operation. During each evaluation, standard clinical data, PHLF, and overall morbidity and mortality will be recorded. THEFLOW Study was initiated on 25 March 2018 and is expected to progress for two years.

Ethics and dissemination

This protocol study received approval from the Ethics Committee of the University of Heidelberg (registration number: S576/2017). The results of this study will be published in a peer-reviewed journal, and will also be presented at medical meetings.

Trial registration number: NCT03762876.

Keywords: Transhepatic flow; Major hepatectomy; Chemotherapy; small for size and flow syndrome.

Strengths and limitations of this study

- The THEFLOW study is a single center, non-interventional cohort study.
- The THEFLOW study will be the first prospective clinical study to systematically evaluate the association between transhepatic flow changes and posthepatectomy results.
- Transhepatic hemodynamic changes following liver resection will be assessed in livers with and without prior chemotherapy.
- A limitation of this study is, that a postoperative monitoring of the portal vein pressure is not possible.
- Findings of this study may help to improve the postoperative outcomes of patients with a high risk of SFSF.

Introduction

Liver resection is the only curative treatment for many primary and secondary hepatic tumors.[1-3] Improvements in patient selection criteria, surgical methods, and postoperative care have made major liver resections (hemihepatectomy or extended hepatectomy) more feasible and safer.[4-8] However, posthepatectomy liver failure (PHLF) or the risk of developing PHLF because of small remnant liver (as small for size syndrome) still need novel predictive factors[9 10] and remain challenging because they can render the patient inoperable or cause postoperative mortality and morbidity.[11 12] The current preventive and therapeutic efforts, which focus only on the remnant liver volume (e.g., two-staged hepatectomy, portal vein embolization, or associating liver partition and portal vein ligation for staged hepatectomy [ALPPS]) have improved the results, but they are still not effective enough.[13-16] Therefore, there are still many patients, who either are not operated because of the high risk of PHLF or suffer from PHLF following major hepatectomy.

Findings from partial liver transplantation have revealed that the role of transhepatic flow parallel to the size of the remnant liver;[17 18] therefore, the syndrome was discussed to be called as small for size and flow syndrome (SFSF).[19-21] In an experimental setting, the portal vein flow (PVF) and the portal vein pressure (PVP) increase significantly for the remnant liver volume following major liver resection.[22] This increase has important pathophysiologic consequences, causing cellular necrosis and SFSF.[8 23-25] Troisi et al. suggested an upper limit of 250 ml/min/100g PVF to prevent SFSF after living donor liver transplantation.[19 26] Although transhepatic flow plays a role in partial liver transplantation[27] and in experimental liver resection,[22] this has never been shown systematically following liver resection in the clinical setting.

The primary aim of this study is to systematically evaluate the amount of changes in transhepatic flow following major liver resection. Furthermore, association of transhepatic flow with postoperative outcomes such as SFSF will be investigated.

Methods and analysis

Study Settings

The THEFLOW study is a single center, non-interventional cohort study. The study aims to enroll 50 patients undergoing major liver resection (i.e., a hemihepatectomy or an extended hemihepatectomy) with or without prior chemotherapy. This study is taking place at the division of liver surgery in the Department of General, Visceral, and Transplantation Surgery of the University of Heidelberg. Our center is a referral hepatopancreatobiliary center that is highly specialized in treatment of patients with advanced hepatobiliary cancer. It was initiated on 25 March 2018 and is expected to progress for two years. The study protocol was registered at ClinicalTrials.gov (registration number: NCT03762876).

Patient recruitment

The study plan was approved by the Ethics Committee of the Medical Faculty of Heidelberg (S576/2017). As shown in the study flow chart (Figure 1), all patients who undergo major hepatectomy (defined as hemihepatectomy or extended hepatectomy according to the Brisbane nomenclature)[28] are currently being screened for eligibility. Eligible patients that provide informed consent will be treated and followed up according to routine procedures at the Department of General, Visceral, and Transplantation Surgery in Heidelberg University Hospital. Transhepatic flow and pressure parameters, i.e., portal venous flow, hepatic artery flow (HAF) and portal venous pressure (PVP), will be measured in study participants before and after resection, meanwhile the standard surgical procedure is not altered. We will look for anatomical variations, stenosis of the celiac trunk or superior mesentery artery, as these factors affect the physiological flow of the liver artery and portal vein. Eligibility will be determined based on

informed consent status, age, planned surgery, and comorbidities (Table 1). Furthermore, total liver volume will be calculated based on preoperative imaging. It is important to note that central tumors may compress the vessels, precluding measurement of physiological flow or pressure. Patients with such tumors will be excluded from the study.

Table 1. Inclusion and exclusion criteria of the THEFLOW study

Inclusion criteria	**Exclusion criteria**
Aged above 18 years	Previous surgery of the hepatoduodenal ligament
Undergoing major hepatectomy	Status after transjugular intrahepatic portosystemic shunt
Patient consent	Portal vein thrombosis
	Portal vein hypertension
	Vascular malformation
	Cirrhosis
	Metabolic liver diseases
	Cardiac failure
	Pulmonary hypertension
	Not able to give consent

Outcome measures

After enrolment, demographic and baseline data (Table 2) of included patients will be recorded. Participants will be monitored intraoperatively, on postoperative days (PODs) 1, 2, 3, and at discharge. After discharge, patients will be visited on POD 90. As shown in Table 3, all intraoperative findings, postoperative complications, and laboratory parameters will be recorded

intraoperatively, during hospital stay, and on POD 90. To enhance participant retention and to avoid loss to follow-up, we will contact patients during the follow-up period to remind them of scheduled visits and to arrange appointments.

Table 2. Demographic and baseline data

Gender (f/m)
Age (years)
Height (cm)
Weight (kg)
Medications
Previous surgeries
Indication for surgery
Anatomical variations of the abdominal arteries
Total liver volume as measured on preoperative CT scan
Calculated future liver volume based on preoperative CT scan
Liver stiffness (measured by fibroscan)
Comorbidities:
Cardiac
Pulmonary
Renal
Autoimmune
Infectious

Table 3. THEFLOW study design according to the SPIRIT checklist

	Study period						
	Enrolment	Operation	Post operation				
TIME POINT	*Admission day*	*Operation day*	*POD 1*	*POD 2*	*POD 3*	*Discharge*	*POD 90*
Enrolment:							
Eligibility screen	X						
Informed consent	X						
Baseline assessments	X						
Assessments:							
Flows (PVF, HAF), pressures (PVP, CVP, and MAP), and vital signs		X					
Type of resection and transection technique		X					
Intraoperative complications		X					
Estimated blood loss		X					
Operating time		X					
Liver stiffness	X					X	X
CT volumetric assessment	X					X	X
Length of hospital stay			X	X	X	X	
Drainage losses			X	X	X	X	
Laboratory findings	X	X	X	X	X	X	X

Postoperative complications			X	X	X	X	X
PHLF			X	X	X	X	X
Mortality		X	X	X	X	X	X

POD, postoperative day; PVF, portal vein flow; PVP, portal vein pressure; HAF, hepatic artery flow; CVP, central vein pressure; MAP, mean arterial pressure; PHLF, posthepatectomy liver failure.

Primary endpoint

PVF will be measured before and following the liver resection. To assess the predictive role of PVF in SFSF, changes in PVF will be evaluated and stratified based on remnant liver volume (Table 4).

Secondary endpoint

Intraoperative outcomes, including vital signs, central vein pressure, mean arterial pressure, type of resection, transection technique, intraoperative complications, HAF, PVP, estimated blood loss, and operating time, will be reported. To calculate the variation of the transhepatic flow to the remnant liver volume, we will measure the removed liver volume during surgery and use CT volumetric assessment to quantify the liver volume before and 3 months after surgery. Additionally, liver stiffness will be evaluated using fibroscan before surgery, at discharge, and 3 months after surgery. Laboratory results (Table 5), length of hospital stay, postoperative complications, PHLF, and all-cause mortality will also be reported until POD 90 (Table 3 and 4).

Table 4. Primary and secondary endpoints of the THEFLOW study

Endpoints	Definitions
Primary endpoint	
Portal vein flow (PVF)	PVF (ml/min)
Secondary endpoints	
Portal vein pressure (PVP)	PVP (mmHg)
Hepatic artery flow (HAF)	HAF (ml/min)
Central vein pressure (CVP)	CVP (mmHg)
Mean arterial pressure (MAP)	MAP (mmHg)
Heart rate	Heart rate (beats per minute)
Positive end-expiratory pressure (PEEP)	PEEP (cmH_2O)
Type of resection and transection technique	Type of resection and transection technique will be documented during the surgery
Intraoperative complications	Any complication occurring during the operation
Estimated blood loss	The entire blood loss (ml) from skin incision to skin closure
Operating time	Time (min) from skin incision to closure of the skin incision
Length of hospital stay	Time (days) from the day of the operation until the day of discharge
Liver stiffness	Will be reported according to the fibroscan results
CT volumetric assessment	Total liver volume, future liver remnant volume, and liver volume 3 months after surgery will be evaluated (cm^3)
Drainage losses	The amount (ml) and content of drainage will be evaluated during hospitalization
Laboratory findings	Presented in Table 5
Postoperative complications	Each complication will be reported and graded according to the Clavien-Dindo classification[29]
Posthepatectomy liver failure (PHLF)	PHLF rate will be determined based on the ISGLS criteria[30]
Mortality	Death due to any cause at any time during the follow-up period

Table 5. Details of laboratory parameters

Laboratory findings	Parameters
Cholestasis parameters	Alkalinephosphatase (U/l) and gamma-glutamyltransferase (U/l)
Excretion parameters	Bilirubin (mg/dl)
Hepatocellular integrity	Glutamate-oxalacetate-transaminase (U/l), and glutamate-pyruvate-transaminase (U/l)
Synthesis parameters	Albumin (g/l) and INR
Tumor markers	Alpha fetoprotein (ng/mL), carcinoembryonic antigen (µg/l), and carbohydrate antigen 19-9 (U/ml)
Infection parameters	Leukocytes (/nl), c-reactive protein (mg/l), and procalcitonin (ng/ml)
Cardiovascular parameters	Blood pressure, pulse, hemoglobin (g/dl), and hematocrit (l/l)
Electrolytes	Sodium (mmol/l), potassium (mmol/l), and calcium (mmol/l)
Kidney function	Creatinine (mg/dl) and glomerular filtration rate
Pancreatic enzymes	Amylase (U/l) (pancreatic) and lipase (U/l)

Patient and public involvement

The patients and public were not involved in the planning of this study.

Modification of the protocol

Protocol amendments will be considered by the principal investigator. All protocol amendments will be submitted to the Ethics Committee for approval. No patients will be recruited until the modifications are accepted.

Methods for minimizing bias

To avoid selection bias and to ensure homogeneity of patients, all patients admitted to Heidelberg University Hospital that are scheduled to undergo major liver resection will be screened for eligibility. Every patient who meets the inclusion criteria and does not meet the exclusion criteria will be informed of the study and included if he/she gives consent to participate (Table 1). Data will be analyzed after all data have been collected. Furthermore, selective reporting will be avoided by submitting the study protocol prior to data collection including all information concerning study endpoints and statistical analysis. Any financial relationship and any conflict of interest that may arise will also be declared.

Ethical and legal aspects and termination criteria

Patients will be informed verbally and in writing about the nature and scope of the planned study and participation in the study will be voluntary. The names of the patients and all other confidential information will be subject to medical confidentiality and the provisions of the Federal Data Protection Act (BDSG). In accordance with the European General Data Protection Regulations (EU-DSGVO), all patient data will be collected anonymously. For statistical analysis, patient data will only be transferred in anonymized form. Third parties will not have access to original patient records.

Consent to participate may be withdrawn at any time, without giving reasons and without affecting further medical care. Upon withdrawal from the study, the patient's data will be irreversibly deleted unless they agree to materials and data already collected being used anonymously in evaluation.

Data management

All data will be collected and recorded in case report forms (CRFs) by an investigator before transfer to the data management center. To ensure accurate data collection, the CRF will be completed by an investigator who did not evaluate the patient after each patient visit. All demographic and baseline clinical data, as well as primary and secondary outcome measures, will be recorded in the CRF. All data will be checked, and any missing data will be obtained from the trial database or from participants. To ensure patient confidentiality, the CRF for each patient will be given an anonymous allocation number. We will ask for permission to continue follow-up and data collection in the event of withdrawal from the study. The principal investigator will review and sign all completed CRFs.

Statistical design and analysis

Sample size

This is an explorative study; therefore, a formal sample size was not calculated. Transhepatic flow changes will be measured in 50 patients, which is considered sufficient.

Statistical analysis

Wilcoxon signed-rank test will be used to compare paired variables (i.e. PVF, PVP, HAF, CVP, MAP, and heart rate) before and after liver resection. Continuous variables will be compared between two groups using Mann-Whitney U test. The association of categorical variables will be evaluated by Fisher's exact test. To assess the predictive role of transhepatic flow changes, multivariate logistic regression analyses with forward stepwise selection will be performed.

Variables with a *p* value <0.1 from the univariate analysis will be included in the multivariate logistic regression analysis. The significance level will be set at $\alpha \leq 0.05$, representing 95% confidence interval.

Ethics and dissemination:

This protocol study received approval from the Ethics Committee of the University of Heidelberg (registration number: S576/2017). All patients receive clarifications regarding the objectives and procedures, and written informed consent is obtained from those who agree to participate. The results of this study will be published in a peer-reviewed journal, and will also be presented at medical meetings.

Discussion

Despite numerous new surgical achievements, SFSF remains a challenging risk for patients who have to undergo major liver resection.[19] Patients with marginal remnant liver volume are particularly at risk and as a result, these patients are often considered inoperable or develop postoperative SFSF. To overcome this problem and prevent PHLF, efforts have been made to give the remnant liver time to regenerate after resection, such as in two-staged hepatectomy, portal vein embolization, and ALPPS.[31] [32] However, despite promising primary results, complications remain high and dropouts due to inadequate liver regeneration is often, meaning many patients cannot be operated on further.[32] During the last years, findings from partial liver transplantation[33] have highlighted the important role of transhepatic flow in major liver resection.[19] This important role was confirmed by experimental studies.[22] In our previous experimental study, major liver resection increased the PVF and PVP for the remnant liver volume.[22] This was particularly significant after extended liver resection. The high PVF and PVP put too much pressure on the parenchyma, causing sinus endothelial damage through high shear stress. This leads to hemorrhage, cellular damage, and production of reactive oxygen species,[34] meaning the remnant liver volume fails to function properly.

Although there are many clinical transplantation studies and experimental studies, to the best of our knowledge, there is still no clinical study evaluating transhepatic flow changes and their association with PHLF following major liver resection. Moreover, transhepatic flow and pressure variation have not been compared between the normal liver and a liver after chemotherapy. The THEFLOW study will be the first study to systematically evaluate transhepatic hemodynamic changes in normal and post-chemotherapy livers following major hepatectomy. Furthermore, the

correlation of the transhepatic flow changes with postoperative outcomes will be evaluated. Findings of the THEFLOW study will define cut off values for the PVF and PVP that can predict the risk of SFSF in patients undergoing major hepatectomy. Patients with marginal remnant liver volume and/or a hemodynamic risk of SFSF may benefit from a different surgical strategy, e.g., adjustment from a one-step to a two-step concept.

In summary, the association between transhepatic flow changes and SFSF after major hepatectomy has not been well investigated. The THEFLOW study will be the first prospective clinical study to systematically evaluate the role of transhepatic flow changes in prediction of SFSF after major hepatectomy. The comprehensive findings of this study may show that the postoperative outcomes of patients with a high risk of SFSF can be improved by adjusting the surgical strategy and by providing more intensive perioperative care.

Trials status

The THEFLOW study is currently recruiting participants.

Acknowledgements

Not applicable.

Contributions

AM, MG, and AL developed the original concept of the trial. AM, MG, AL, MAS, and OS developed the design and methodology. MG, AL, EK, and OG performed the statistical assessments and developed the analysis plan. MG, AL, EK, OG, MAS, CB, PT, and PM contributed to drafting the protocol of the paper and the article. OS, TH, BMS, MS, CB, PM, DHC, KHW, KH, and AM contributed to the revision of the final report. All authors read and approved the final manuscript.

Funding

This research received no specific funding from the public, commercial, or not-for-profit sectors.

Competing interests

The authors declare that they have no competing interests.

Patients Consent

Written informed consent for publication of clinical images will be obtained from the patients.

Ethics approval

This protocol study received approval from the Ethics Committee of the University of Heidelberg (registration number: S576/2017).

Provenance and peer review

Not commissioned; externally peer reviewed.

References

1. El-Serag HB, Marrero JA, Rudolph L, et al. Diagnosis and treatment of hepatocellular carcinoma. *Gastroenterology*2008;134(6):1752-63. doi: 10.1053/j.gastro.2008.02.090
2. Manfredi S, Lepage C, Hatem C, et al. Epidemiology and management of liver metastases from colorectal cancer. *Ann Surg*2006;244(2):254-9. doi: 10.1097/01.sla.0000217629.94941.cf
3. Poon RT, Fan ST, Lo CM, et al. Improving survival results after resection of hepatocellular carcinoma: a prospective study of 377 patients over 10 years. *Ann Surg*2001;234(1):63-70.
4. Abdalla EK, Barnett CC, Doherty D, et al. Extended hepatectomy in patients with hepatobiliary malignancies with and without preoperative portal vein embolization. *Arch Surg*2002;137(6):675-80; discussion 80-1.
5. 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(1):38-46.
6. Rahbari NN, Elbers H, Koch M, et al. Randomized clinical trial of stapler versus clamp-crushing transection in elective liver resection. *Br j Surg*2014;101(3):200-7. doi: 10.1002/bjs.9387 [published Online First: 2014/01/10]
7. Fritzmann J, Kirchberg J, Sturm D, et al. Randomized clinical trial of stapler hepatectomy versus LigaSure transection in elective hepatic resection. *Br j Surg*2018;105(9):1119-27. doi: 10.1002/bjs.10902 [published Online First: 2018/08/03]
8. Rahbari NN, Koch M, Zimmermann JB, et al. Infrahepatic inferior vena cava clamping for reduction of central venous pressure and blood loss during hepatic resection: a randomized controlled trial. *Ann Surg*2011;253(6):1102-10. doi: 10.1097/SLA.0b013e318214bee5 [published Online First: 2011/03/18]
9. Mehrabi A, Golriz M, Khajeh E, et al. Meta-analysis of the prognostic role of perioperative platelet count in posthepatectomy liver failure and mortality. *Br j Surg*2018;105(10):1254-61. doi: 10.1002/bjs.10906 [published Online First: 2018/07/13]
10. Golriz M, Ghamarnejad O, Khajeh E, et al. Preoperative Thrombocytopenia May Predict Poor Surgical Outcome after Extended Hepatectomy. *Can J Gastroenterol Hepatol*2018;2018:1275720. doi: 10.1155/2018/1275720 [published Online First: 2018/12/06]
11. Shoup M, Gonen M, D'Angelica M, et al. Volumetric analysis predicts hepatic dysfunction in patients undergoing major liver resection. *J Gastrointest Surg*2003;7(3):325-30.
12. Ren Z, Xu Y, Zhu S. Indocyanine green retention test avoiding liver failure after hepatectomy for hepatolithiasis. *Hepatogastroenterology*2012;59(115):782-4. doi: 10.5754/hge11453
13. Schadde E, Raptis DA, Schnitzbauer AA, et al. Prediction of Mortality After ALPPS Stage-1: An Analysis of 320 Patients From the International ALPPS Registry. *Ann Surg*2015;262(5):780-5; discussion 85-6. doi: 10.1097/sla.0000000000001450 [published Online First: 2015/11/20]
14. Wanis KN, Buac S, Linecker M, et al. Patient Survival After Simultaneous ALPPS and Colorectal Resection. *World J Surg*2017;41(4):1119-25. doi: 10.1007/s00268-016-3818-1 [published Online First: 2016/11/12]

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(5):829-36; discussion 36-8. doi: 10.1097/sla.0000000000000947 [published Online First: 2014/11/08]
16. Kremer M, Manzini G, Hristov B, et al. Impact of Neoadjuvant Chemotherapy on Hypertrophy of the Future Liver Remnant after Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy. *J Am Coll Surg*2015;221(3):717-28.e1. doi: 10.1016/j.jamcollsurg.2015.05.017 [published Online First: 2015/08/02]
17. Asencio JM, Vaquero J, Olmedilla L, et al. "Small-for-flow" syndrome: shifting the "size" paradigm. *Med Hypotheses*2013;80(5):573-7. doi: 10.1016/j.mehy.2013.01.028
18. Vasavada BB, Chen CL, Zakaria M. Portal flow is the main predictor of early graft dysfunction regardless of the GRWR status in living donor liver transplantation - a retrospective analysis of 134 patients. *Int J Surg*2014;12(2):177-80. doi: 10.1016/j.ijsu.2013.12.006
19. Golriz M, Majlesara A, El Sakka S, et al. Small for Size and Flow (SFSF) syndrome: An alternative description for posthepatectomy liver failure. *Clin Res Hepatol Gastroenterol*2015 doi: 10.1016/j.clinre.2015.06.024
20. Guglielmi A, Ruzzenente A, Conci S, et al. How much remnant is enough in liver resection? *Dig Surg*2012;29(1):6-17. doi: 10.1159/000335713
21. Golriz M, Ashrafi M, Khajeh E, et al. Establishing a Porcine Model of Small for Size Syndrome following Liver Resection. *Can J Gastroenterol Hepatol*2017;2017:5127178. doi: 10.1155/2017/5127178 [published Online First: 2017/09/28]
22. Golriz M, El Sakka S, Majlesara A, et al. Hepatic Hemodynamic Changes Following Stepwise Liver Resection. *J Gastrointest Surg*2016;20(3):587-94. doi: 10.1007/s11605-015-3021-y [published Online First: 2015/11/18]
23. Kelly DM, Demetris AJ, Fung JJ, et al. Porcine partial liver transplantation: a novel model of the "small-for-size" liver graft. *Liver Transpl*2004;10(2):253-63. doi: 10.1002/lt.20073 [published Online First: 2004/02/06]
24. Man K, Fan ST, Lo CM, et al. Graft injury in relation to graft size in right lobe live donor liver transplantation: a study of hepatic sinusoidal injury in correlation with portal hemodynamics and intragraft gene expression. *Ann Surg*2003;237(2):256-64. doi: 10.1097/01.SLA.0000048976.11824.67 [published Online First: 2003/02/01]
25. Nagino M, Ando M, Kamiya J, et al. Liver regeneration after major hepatectomy for biliary cancer. *Br j Surg*2001;88(8):1084-91. doi: 10.1046/j.0007-1323.2001.01832.x [published Online First: 2001/08/08]
26. Troisi R, de Hemptinne B. Clinical relevance of adapting portal vein flow in living donor liver transplantation in adult patients. *Liver Transpl*2003;9(9):S36-41. doi: 10.1053/jlts.2003.50200
27. Troisi RI, Berardi G, Tomassini F, et al. Graft inflow modulation in adult-to-adult living donor liver transplantation: A systematic review. *Transplant Rev (Orlando)*2017;31(2):127-35. doi: 10.1016/j.trre.2016.11.002 [published Online First: 2016/12/19]
28. Pang YY. The Brisbane 2000 terminology of liver anatomy and resections. *HPB* 2002;4(2):99; author reply 99-100. doi: 10.1080/136518202760378489 [published Online First: 2008/03/12]

29. Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien-Dindo classification of surgical complications: five-year experience. *Ann Surg*2009;250(2):187-96. doi: 10.1097/SLA.0b013e3181b13ca2 [published Online First: 2009/07/30]
30. Rahbari NN, Garden OJ, Padbury R, et al. Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS). *Surgery*2011;149(5):713-24. doi: 10.1016/j.surg.2010.10.001 [published Online First: 2011/01/18]
31. Vivarelli M, Vincenzi P, Montalti R, et al. ALPPS Procedure for Extended Liver Resections: A Single Centre Experience and a Systematic Review. *PloS one*2015;10(12):e0144019. doi: 10.1371/journal.pone.0144019 [published Online First: 2015/12/25]
32. Schnitzbauer AA. A Comparison of Pitfalls after ALPPS Stage 1 or Portal Vein Embolization in Small-for-Size Setting Hepatectomies. *Visc Med*2017;33(6):435-41. doi: 10.1159/000480100 [published Online First: 2018/01/19]
33. Troisi R, Ricciardi S, Smeets P, et al. Effects of hemi-portocaval shunts for inflow modulation on the outcome of small-for-size grafts in living donor liver transplantation. *Am J Transplant*2005;5(6):1397-404. doi: 10.1111/j.1600-6143.2005.00850.x [published Online First: 2005/05/13]
34. Serenari M, Cescon M, Cucchetti A, et al. Liver function impairment in liver transplantation and after extended hepatectomy. *World J Gastroenterol*2013;19(44):7922-9. doi: 10.3748/wjg.v19.i44.7922 [published Online First: 2013/12/07]

Figure legends

Figure 1. Study design flow chart.

*Preoperative assessments: Baseline data (e.g., date of birth, gender, weight [kg], height [cm], diagnosis, prior treatment [chemotherapy], comorbidities, spleen size), total and future liver volume (measured by CT volumetry), and liver stiffness (measured by fibroscan). PVF, portal vein flow; PVP, portal vein pressure; HAF, hepatic artery flow; CVP, central vein pressure; MAP, mean arterial pressure; HR, heart rate; PEEP, positive end-expiratory pressure; PHLF, posthepatectomy liver failure.

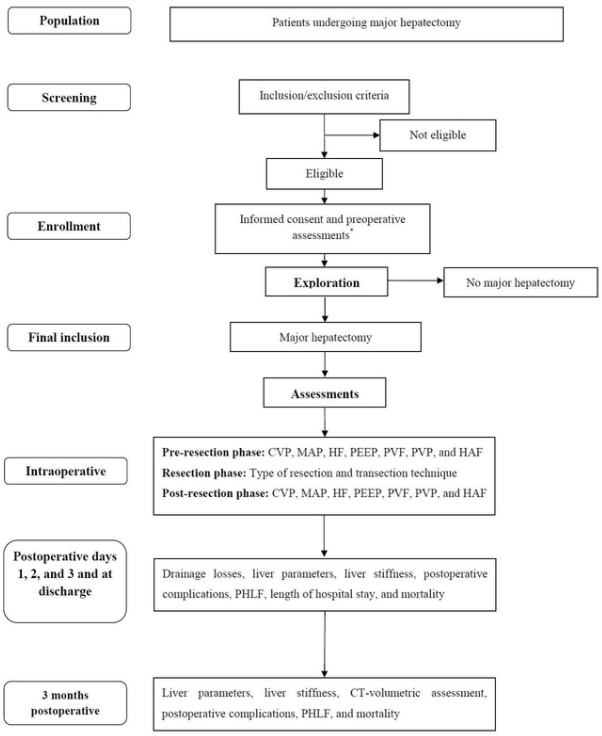

Fig. 1. Study design flow chart.
*Preoperative assessments: Baseline data (e.g., date of birth, gender, weight [kg], height [cm], diagnosis, prior treatment [chemotherapy], comorbidities, spleen size), total and future liver volume (measured by CT volumetry), and liver stiffness (measured by fibroscan). PVF, portal vein flow; PVP, portal vein pressure; HAF, hepatic artery flow; CVP, central vein pressure; MAP, mean arterial pressure; HR, heart rate; PEEP, positive end-expiratory pressure; PHLF, posthepatectomy liver failure.

90x90mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4, 7
	2b	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	3	Date and version identifier	7
Funding	4	Sources and types of financial, material, and other support	20
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 20
	5b	Name and contact information for the trial sponsor	NA
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	NA
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	9, 15

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5, 6
	6b	Explanation for choice of comparators	5, 6
Objectives	7	Specific objectives or hypotheses	6, 17
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6, 7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7, 8, Table 1
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	NA
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	NA
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	NA
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9, 15, 16, Table 2
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figures 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11, 12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	10, 11
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10, 11
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10, 11
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8, 10, 11
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	8

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12, 13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	NA
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	11
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	10
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	9, 10
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	7
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	NA

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7, 17, 18
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	18
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	11
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17, 18
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	11
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	9, 10
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	NA
	31b	Authorship eligibility guidelines and any intended use of professional writers	17, 18
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Additional file 3
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.