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

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ABSTRACT

Introduction Liver resection is the only curative treatment for primary and secondary hepatic tumours. 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 TransHEpatic FLOW (THEFLOW) study is a single-centre, non-interventional cohort study, and aims to enrol 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, posthepatectomy liver failure and overall morbidity and mortality will be recorded. THEFLOW study was initiated on 25 March 2018 and is expected to progress for 2 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.

Strengths and limitations of this study

- The THEFLOW study is a single-centre, 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 haemodynamic 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 small for size and flow syndrome.

INTRODUCTION

Liver resection is the only curative treatment for many primary and secondary hepatic tumours.[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 needs novel predictive factors[9 10] and remains 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 (eg, two-staged hepatectomy, portal vein embolisation, 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

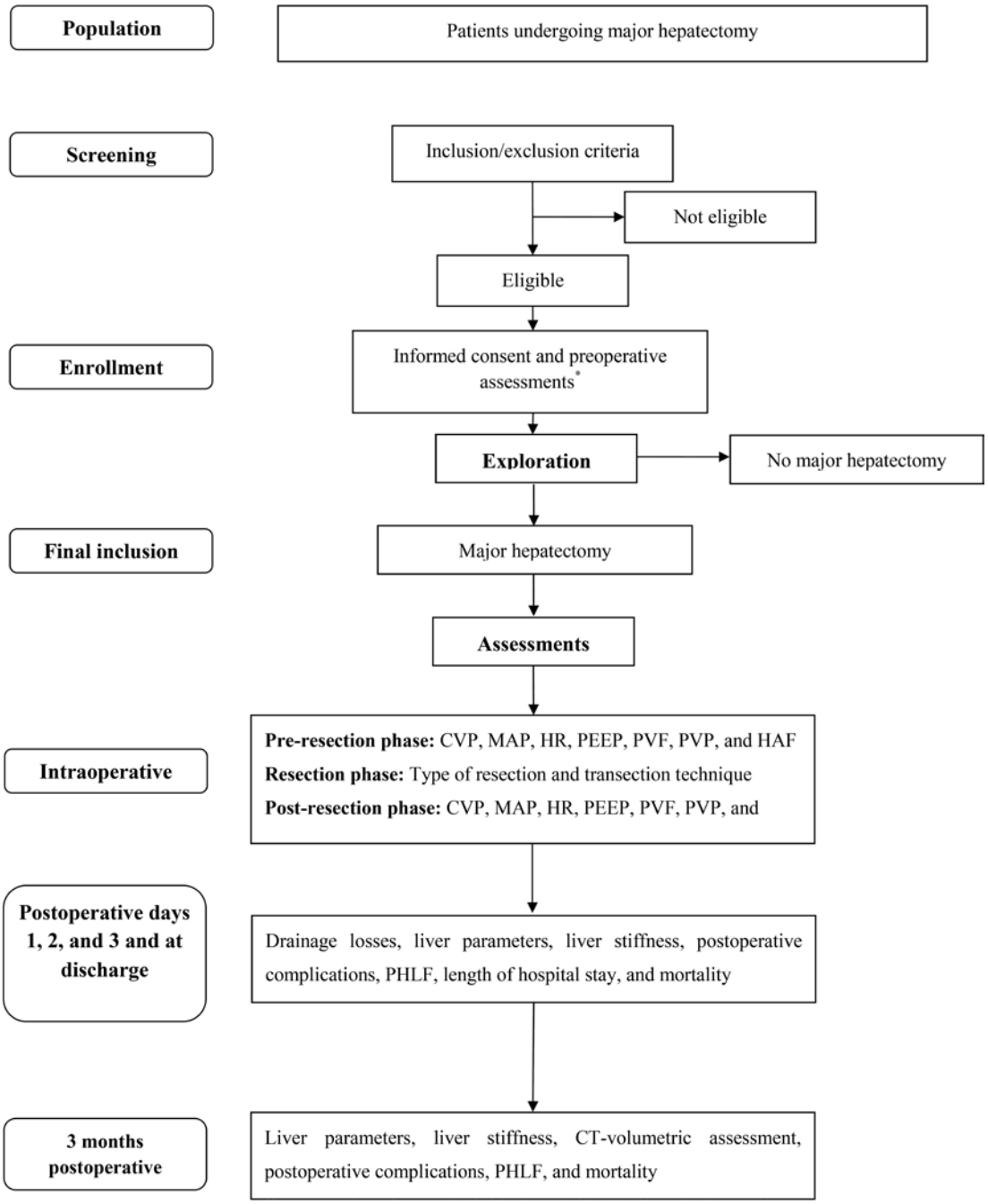

Figure 1 Study design flow chart. *Preoperative assessments: baseline data (eg, date of birth, gender, weight (kg), height (cm), diagnosis, prior treatment (chemotherapy), comorbidities, spleen size), total and future liver volume (measured by CT volumetry), and liver stiffness (measured by fibroscan).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

operated because of the high risk of PHLF or suffer from PHLF following major hepatectomy.

Findings from partial liver transplantation have revealed 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 pathophysiological consequences, causing cellular necrosis and SFSF.[8 23–25] Troisi *et al* suggested an upper limit of 250 mL/min/100 g 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

Box 1 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

of transhepatic flow with postoperative outcomes such as SFSF will be investigated.

METHODS AND ANALYSIS

Study settings

The THEFLOW study is a single-centre, non-interventional cohort study. The study aims to enrol 50 patients undergoing major liver resection (ie, 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 centre is a referral hepatopancreatobiliary centre that is highly specialised in the treatment of patients with advanced hepatobiliary cancer. It was initiated on 25 March 2018 and is expected to progress for 2 years.

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

Patient recruitment

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, that is, portal venous flow, hepatic artery flow (HAF) and 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 tumours may compress the vessels, precluding measurement of physiological flow or pressure. Patients with such tumours will be excluded from the study.

Outcome measures

After enrolment, demographic and baseline data (box 1) 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 2, 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.

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 3).

Secondary endpoint

Intraoperative outcomes, including vital signs, central vein pressure (CVP), mean arterial pressure (MAP), 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 4), length of hospital stay, postoperative

Table 2 THEFLOW study design according to the Standard Protocol Items: Recommendations for Interventional Trials 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

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

complications, PHLF and all-cause mortality will also be reported until POD 90 (tables 2 and 3).

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 minimising 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 analysed 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. In accordance with the European General Data Protection Regulations, all patient data will be collected anonymously. For statistical analysis, patient data will only be transferred in anonymised 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. On 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

Table 3 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 (mm Hg)
Hepatic artery flow (HAF)	HAF (mL/min)
Central vein pressure (CVP)	CVP (mm Hg)
Mean arterial pressure (MAP)	MAP (mm Hg)
Heart rate	Heart rate (beats/min)
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 hospitalisation
Laboratory findings	Presented in table 4
Postoperative complications	Each complication will be reported and graded according to the Clavien-Dindo classification[33]
Posthepatectomy liver failure (PHLF)	PHLF rate will be determined based on the ISGLS criteria[34]
Mortality	Death due to any cause at any time during the follow-up period

ISGLS, International Study Group of Liver Surgery.

Table 4 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 international normalized ratio (INR)
Tumour markers	Alpha fetoprotein (ng/mL), carcinoembryonic antigen (µg/L), and carbohydrate antigen 19–9 (U/mL)
Infection parameters	Leucocytes (/nL), C reactive protein (mg/L) and procalcitonin (ng/mL)
Cardiovascular parameters	Blood pressure, pulse, haemoglobin (g/dL) and haematocrit (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)

data management centre. 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 (ie, 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 p<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% CI.

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 embolisation and ALPPS.[29 30] However, despite promising primary results, complications remain high and dropouts due to inadequate liver regeneration are often, meaning many patients cannot be operated on further.[30] During the last years, findings from partial liver transplantation[31] 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 haemorrhage, cellular damage and production of reactive oxygen species,[32] 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 haemodynamic changes in normal and postchemotherapy 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 haemodynamic risk of SFSF may benefit from a different surgical strategy, for example, 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.

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Correction notice This article was previously published with an error. Author name Hackert Thilo should be Thilo Hackert.

Contributors AM, MG and AL developed the original concept of the trial. AM, MG, AL, MA-S 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, MA-S, CB, PT and PM contributed to drafting the protocol of the paper and the article. OS, TH, BM-S, MS, CB, PM, D-HC, KHW, KH and AM contributed to the revision of the final report. All authors read and approved the final manuscript.

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