BMJ Open

The prevalence, management, and efficacy of treatment in portal vein obstruction after paediatric liver transplantation: protocol of the retrospective international multicentre PORTAL registry

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-066343
Article Type:	Protocol
Date Submitted by the Author:	12-Jul-2022
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Keywords:	Paediatric hepatology < PAEDIATRICS, Paediatric transplant surgery < PAEDIATRIC SURGERY, Interventional radiology < RADIOLOGY & IMAGING

The prevalence, management, and efficacy of treatment in portal vein obstruction after paediatric liver transplantation: protocol of the retrospective international multicentre PORTAL registry

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LIST OF ABBREVIATIONS

PTA	Percutaneous Transluminal Angioplasty
PVAS	Portal Vein Anastomotic Stenosis
PVO	Portal Vein Obstruction
PVT	Portal Vein Thrombosis

ABSTRACT

Introduction: Portal vein obstruction (PVO) consists of anastomotic stenosis (PVAS) and thrombosis (PVT), which occurs due to a progression of the former. The aim of this large-scale international study is to assess the prevalence, current management practices, and efficacy of treatment in patients with PVO.

Methods and analysis: The Portal vein Obstruction Revascularisation Therapy After Liver transplantation (PORTAL) registry will facilitate an international, retrospective, multicentre, observational study, with 23 centres around the world already actively involved. Paediatric patients (aged <18 years) with a diagnosed PVO between 1 January 2001 and 1 January 2021 after liver transplantation will be eligible for inclusion. The primary endpoints are the prevalence of PVO, primary and secondary patency after PVO intervention, and current management practices. Secondary endpoints are patient and graft survival, severe complications of PVO, and technical success of revascularization techniques.

Ethics and dissemination: Ethical approval and informed consent will be obtained for each site in accordance with the national laws governing the conduct of clinical research. The results of this study will be disseminated via peer-reviewed publications and scientific presentations at national and international conferences.

Trial registration number: The PORTAL registry is registered in the Netherlands Trial Register at www.trialregister.nl (NL9261, 28-02-2021).

ARTICLE SUMMARY

Strengths and limitations of this study

- The PORTAL registry is the first global collaboration between paediatric hepatologists, interventional radiologists, and liver transplant surgeons.
- The registry will facilitate the large-scale aggregation of patient data at an international level, allowing the first comprehensive multicentre study investigating the prevalence of PVO in patients following paediatric liver transplantation.
- The study will gain an overview of current management strategies on a global level in terms of the definitions that are used to define a PVO, diagnostic methods, and treatment strategies.
- The study will also provide valuable information regarding the efficacy of conservative, endovascular, and surgical treatment strategies.
- Subjects in this study are limited to a retrospective cohort. Generalizability of the findings and conclusions will need to be interpreted with care given the heterogeneity and lack of a uniform definition of PVO.

INTRODUCTION

Liver transplantation is an established treatment for paediatric patients with end stage liver disease, metabolic liver diseases, hepatic malignancy, and acute liver failure.[1] Despite marked improvements in operating techniques, vascular complications, especially portal vein obstruction (PVO), remain common.[2] However, little is known regarding the prevalence, risk factors, and most optimal management strategies for this complication.

PVO consists of portal vein anastomotic stenosis (PVAS) or portal vein thrombosis (PVT). The rate of PVO after living donor liver transplantation has been reported to be 9-14%, in comparison with deceased donor liver transplantation, at <3%.[1] However, in specific risk groups, such as biliary atresia or young age transplantation, the prevalence of PVO is unknown, but thought to be higher.[1,3] The clinical course of PVO differs, from absence of symptoms to severe symptoms of portal hypertension (16% of patients have ascites and 26% have gastrointestinal bleeding from oesophageal varices).[4] There are a multitude of different treatment strategies, ranging from conservative management, endovascular therapy, or surgical options by means of mesorex bypass or other surgical shunts. A recent systematic review comparing the various treatments showed that there is no consensus on the most optimal strategy.[4] This is largely due to heterogeneity in the clinical characteristics of the patients who were treated, along with variation in the treatment protocol and postprocedural care across the single centre studies included.[4]

PORTAL is a multicentre, retrospective, observational registry of paediatric patients who have been diagnosed and treated for PVO after liver transplantation. The objective of the registry study is threefold. Firstly, it will assess the overall prevalence of PVO after paediatric liver transplantation, including taking into account various risk groups. Secondly, it will evaluate current management practices in terms of the experience of various centres, the composition of the team, the structure of care, screening, assessment criteria, postprocedural

care, and radiological follow-up after treatment. Thirdly, it also intends to assess the efficacy of the individual portal vein revascularization treatments.

METHODS AND ANALYSIS

Study design and participants

The study design takes the form of an international, retrospective, multicentre, observational registry of paediatric liver transplantation patients with PVO. Patients are eligible for inclusion if the following criteria are met: 1) the patient is diagnosed with PVO (PVAS or PVT) after liver transplantation (perioperative PVT will not be included in the analysis) and 2) the patient's age at the time of intervention (or time of diagnosis for patients who were treated conservatively) was <18 years, and 3) the date of intervention was between 1 January 2001 and 1 January 2021. Patients are excluded from the study if the following criteria are present: 1) patients suspected to have PVT of an either intra- or post-hepatic origin (i.e. severe fibrosis, cirrhosis, transplant failure, intrahepatic vascular changes, secondary PVT) and 2) patients with follow-up of less than 1 year.

Collection of data

Subjects will be identified through a retrospective review of the medical records of all patients who underwent liver transplantation at age <18. Data from subjects who are eligible for inclusion will be anonymously entered into either a REDCap database (https://redcap.umcg.nl) or a standardized paper case-report form (Supplementary file 1). Information regarding patient demographics, underlying disease, symptoms, treatment, and outcome will be gathered. The following types of interventions will be included: conservative treatment, endovascular treatments (percutaneous transluminal angioplasty [PTA] with or without stent placement,

endovascular recanalization, and splenic artery or varices/cavernoma embolization), and surgical treatments (all types of surgical shunts and splenectomy).

To determine the prevalence and current management practices, each centre will also complete a structured questionnaire that records the experience of the centre, the composition of the team, the structure of care, screening, assessment criteria, postprocedural care, and radiological follow-up after treatment (Supplementary file 2). In addition, the number of patients who underwent liver transplant between 1 January 2001 and 1 January 2020 within the total paediatric group and in subgroups will also be recorded, based on time of transplantation, age at transplantation, underlying disease (biliary atresia) and donor type (living or deceased liver donor).

Primary outcomes

Prevalence

The prevalence of PVO will be calculated as the total number of PVO patients (transplanted between 1 January 2001 and 1 January 2020 and diagnosed with PVO between 1 January 2001 and 1 January 2021) divided by the total number of transplanted patients at paediatric age between 1 January 2001 and 1 January 2020. As the majority of PVO cases are diagnosed within the first year after transplantation, we chose a minimum of 1 year follow-up time.

Primary and secondary patency

Primary patency is defined as the interval between index procedure to treat stenosis or occlusion and time to re-stenosis or re-occlusion. Primary patency ends when either re-stenosis or re-occlusion occur for the first time after intervention. Primary patency will be represented as percentages at 1, 3, 5, 10, 15 and 20 years after the diagnosis of PVO.

Secondary patency is defined as the interval between index procedure and time of failure to re-establish flow when re-occlusion cannot be achieved or is not successfully treated (including all the intervening manipulations designed to re-establish functionality in intercurrent PVO). Secondary patency will be represented as percentages at 1, 3, 5, 10, 15 and 20 years after treatment for PVO.

Secondary outcomes

Patient and graft survival

Patient survival is defined as the period from date of first PVO intervention until date of death. Patients who are alive at the end of the follow-up will be censored. Graft survival is defined as the period from the date of PVO intervention until the date of re-transplantation or death. Patients who are alive without a re-transplantation at the end of the follow-up will be censored. The decision to re-transplant is based on an assessment by the individual centre. Causes of re-transplantation or death will be recorded. Patient and graft survival will be determined as percentages at 1, 3, 5, 10, 15 and 20 years after treatment for PVO.

Freedom from severe PVO complications

Severe PVO complications are defined as severe signs of portal hypertension (ascites, variceal bleeding) or porto-systemic shunting (any grade of hepatic encephalopathy, hepatopulmonary syndrome, portopulmonary hypertension). Ascites will be diagnosed by physical examination or imaging. These complications will be determined following each intervention until the end of the follow-up.

Technical success

Technical success is defined as the success of the intervention during the procedure (re-establishment of portal flow, without residual stenosis) and will be based on an assessment by the individual centre.

Current management practice

Current management practice is defined as the workflow process that includes experience of centres/team, care structure, screening, and assessment criteria, and postprocedural follow-up intended to optimize patient care.

Data management

Subject records will be pseudo-anonymized by means of allocating each subject a unique study number. The local investigators will maintain a list with subject's name, date of birth, local ID, and unique study number. Data will be stored by the local investigators and coordinating centre for 15 years after termination of the study. All data and records generated during this study will be kept in accordance with institutional policies regarding subject privacy, and the data and records of all patients will not be used for any purpose other than conducting this study.

Statistical analysis

All data analyses will be performed with IBM SPSS Statistics version 26. Descriptive statistics will be applied using the mean and standard deviation for variables with normal distribution, and median and interquartile ranges (IQR) for variables with skewed distribution. Dichotomous variables will be compared using the Chi-square test or the Fisher exact test or both. Continuous variables will be compared using the Mann-Whitney U test. For the analysis of primary and secondary patency, freedom from severe PVO complications, and patient and graft survival, the Kaplan-Meier method will be used. P-values less than 0.05 will be considered statistically significant.

Follow-up

Follow-up data for this study will be collected up to and including 1 January 2021.

Patient and Public Involvement

Neither patients nor the public were involved in the design of this study.

ETHICS AND DISSEMINATION

This study will be conducted according to the principles of the declaration of Helsinki (adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013) and the local national laws governing the conduct of clinical research studies. For the Netherlands, the study protocol has been evaluated as one that does not fall under the Medical Research Involving Human Subjects Act (WMO) by the University Medical Centre Groningen's IRB on 3 February 2021 (METc 2021/072). To adhere to the General Data Protection Regulation (EU) 2016/679, a data transfer

agreement will be required to initiate the study. All active collaborating sites have obtained local IRB approval.

The results of this study will be disseminated by publication of peer-reviewed manuscripts, presentation in an abstract form at scientific meetings, and data sharing with other researchers through academically established means. The outcomes of this study will also be utilized to design an evidence-based, feasible diagnostic and therapeutic algorithm for paediatric patients with portal vein complications following liver transplantation, which will be implemented in the form of national/international guidelines.

DISCUSSION

Key findings

The PORTAL registry is the first global collaboration between paediatric hepatologists, interventional radiologists, and liver transplant surgeons and will lead to the creation of the largest possible cohort of patients who have experienced PVO after paediatric liver transplantation. Based on this large group of patients, we will gain the broadest insight into current management practices, prevalence numbers, and efficacy of the individual treatments.

Strengths and limitations

Current literature regarding patients with PVO after paediatric liver transplantation is based on single centre studies. It is therefore difficult to determine which patients with PVO should be treated, and also when and how. A recent systematic review of single centre studies showed that treatment protocols for PVO differed between centres and that findings on long-term results are scarce and difficult to compare between centres.[4] A major strength of this study is the large-scale aggregation of patient data that will occur in the PORTAL registry, which we consider is not only the best but the only feasible strategy to overcome the lack of standardized care. We

aim to include more than 15 paediatric liver transplantation centres across Europe, North America, South America, Asia, and Oceania. It is therefore expected that we will have a sufficient number of participants to provide substantive answers to the research questions, including prognostic information regarding long-term outcomes after treatment for patients, parents, and healthcare professionals.

In addition, there is currently no consensus on the optimal clinical pathway for patients who present with PVO, with individual centres managing patients through locally determined patient pathway protocols. This lack of consensus includes all aspects of the patient pathway: screening protocol, diagnostic criteria, decision to treat, choice of the treatment modality, and post-procedural care.[4,5] We therefore expect heterogeneous data on all these topics. In this regard, another strength of the registry is that it will allow the review of differing pathways and their associated outcomes within a large patient cohort undergoing various interventions, and thus provide data on the basis of which greater international consensus on the optimal management and treatment strategy in this patient population will be created.

Finally, while the retrospective design and risk of missing data is a limitation of the registry, we have attempted to reduce the amount of missing data by focusing on the most pressing questions, such as the prevalence and efficacy of treatment. This is supported by the recommendations of the NAPPED consortium, which stated that it was essential to keep it simple from the start.[6]

Implications for the future

This is the first such global registry in the field of paediatric liver transplant. The results of the PORTAL registry study will lead to more knowledge about current and past management practices, prevalence, and treatment of PVO patients after paediatric liver transplantation and will be the first step towards more consensus on patient management. It is expected that the

data from the PORTAL registry and the global collaboration will be used to accomplish the next step in improving the clinical care of PVO patients – a multidisciplinary guideline for screening, diagnosis, and treatment of PVO after paediatric liver transplantation. A prospective study is planned subsequent to this retrospective data analysis with this goal in mind. It will most likely rely on a slightly amended PORTAL registry, incorporating the knowledge gained from the retrospective analysis, integrating imaging studies – with a centralized review – and including laboratory analysis to harmonize findings and guide future analysis.

FUNDING AND DISCLOSURES

This research has not received a specific grant from any funding agency in the public, commercial or not-for-profit sectors. RPHB receives funding from the Netherlands Organization for Health Research and Development, and Siemens Healthineers.

AUTHORS' CONTRIBUTIONS

This study is conceptualized by BA, HVD and RB. All authors contributed to the study design and approved the final version of the manuscript.

DECLARATION OF COMPETING INTEREST

None

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PORTAL Registry

Portal vein Obstruction Revascularisation Therapy After Liver transplantation

Case Report Form (CRF) ON PAPER

Version 1.4, March 2022

Subject Number:_____

Please complete all forms as fully as possible.

Thank you for your cooperation.

Kind regards,

The PORTAL Registry team

Bader A. M. Alfares, coordinating researcher

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LIST OF AABREVIATIONS

CT	Computed Tomography
DSA	Subtraction Diagnostic Angiography
DUS	Doppler Ultrasound
IR	Interventional Radiology
MRB	Mesorex Bypass
MRI	Magnetic Resonance Imaging
PTA	Percutaneous Transluminal Angioplasty
PVAS	Portal Vein Anastomosis Stenosis
PVO	Portal Vein Obstruction
PVT	Portal Vein Thrombosis

Please calculate age into years with a decimal place, for example use 1.5 years instead of 1 years and 6 months. You can use the supplied calculator in an excel format.

PART I: BASELINE CRF

Gender:	○ Male ○ Female
Portal vein obstruction (PVO):	○ Yes ○ No
If applicable; Portal vein anastomosis stenosis (PVAS): Portal vein thrombosis (PVT):	 ○ Yes ○ No ○ Yes ○ No
Date/age first diagnosis PVAS and/or PVT:	__/__/_____, _____
Treatment performed:	○ Yes ○ No
If applicable; How many treatments?	 ○ 1 ○ 2 ○ 3 or more (please specify)
Date end of follow-up:	○ 01/01/2021 ○ Other (please specify): __/__/_____
Please specify reason if date end of follow-up is other than 01/01/2021:	○ Lost to follow-up ○ Death ○ Re-transplantation after PVO treatment ○ Other (please specify): _____
Age end of follow-up:	_____
Thrombosis portal vein or MRB/other surgical shunt without therapeutical options:	○ Yes ○ No
Date/age thrombosis portal vein or MRB/other surgical shunt without therapeutical options:	__/__/_____, _____
Re-transplantation after PVO treatment(s):	○ Yes ○ No
Date/ age diagnosis re-transplantation:	__/__/_____, _____
Cause of re-transplantation:	_____
Deceased after PVO treatment(s):	○ Yes ○ No
Date/age of death:	__/__/_____, _____
Please specify the cause of death:	_____
Medical history/comorbidities at baseline	
Primary disease:	○ Biliary atresia ○ Other (please specify): _____
Number of transplantations:	○ 1 ○ 2 ○ 3 or more (please specify) Date/age transplantation 1: __/__/_____, _____ Date/age transplantation 2: __/__/_____, _____

	Date/age transplantation 3: __/__/_____, _____ Date/age transplantation 4: __/__/_____, _____ Date/age transplantation 5: __/__/_____, _____ Date/age transplantation 6: __/__/_____, _____
Characteristics of last transplant before the first diagnosis PVO	
Date/age last transplantation:	__/__/_____, _____
Indication last transplantation:	○ Biliary atresia ○ Re-transplantation ○ Other (please specify): _____
Type last transplantation:	○ Living-donor ○ Deceased-donor
Size last transplantation:	○ Segment 2,3 ○ Segment 2,3,4 ○ Right segment ○ Full size
Size portal vein *(on pre-transplantation CT scan)*:	_____ mm ○ Unknown
Preventive portoplasty:	○ Yes ○ No
Venous jump/interposition graft portal vein:	○ Yes ○ No
Non-portal vascular complications within 30 days after last liver transplantation:	○ Yes ○ No
Number of non-portal vascular complications within 30 days after last liver transplantation:	○ 1 ○ 2 ○ 3 or more (please specify):
Characteristics of interventions of non-portal vascular complications within 30 days after last liver transplantation: **Intervention 1:** Date intervention Location intervention	 __/__/_____ ○ Hepatic artery ○ Hepatic vein

Type intervention	○ Surgical: thrombectomy ○ Surgical: new anastomosis ○ Surgical: reposition of vessel(s)○ IR PTA ○ IR PTA/stent ○ Other intervention(s) (text): _____
Intervention 2:	
Date intervention	__/__/_____
Location intervention	○ Hepatic artery ○ Hepatic vein
Type intervention	○ Surgical: thrombectomy ○ Surgical: new anastomosis ○ Surgical: reposition of vessel(s) ○ IR PTA ○ IR PTA/stent ○ Other intervention(s) (text): _____
Intervention 3:	
Date intervention	__/__/_____
Location intervention	○ Hepatic artery ○ Hepatic vein
Type intervention	○ Surgical: thrombectomy ○ Surgical: new anastomosis ○ Surgical: reposition of vessel(s)○ IR PTA ○ IR PTA/stent ○ Other intervention(s) (text): _____

PART II: INTERVENTION CRF (please fill in for each intervention in separate form)

CRF 2.1 GENERAL INFORMATION

Treatment characteristics	
Date/age intervention *(if conservative treatment, specify date/age of diagnosis)*:	__/__/_____, _____
Indication:	○ PVAS ○ PVT

CLINICAL CHARACTERISTICS AT DIAGNOSIS / TREATMENT

Clinical characteristics at intervention (6 months before intervention)	
Platelet count absolute number *(If known, please provide the unit of choice)*:	_____ ○ Unknown
Splenomegaly:	○ Yes ○ No ○ Unknown
Ascites:	○ Yes ○ No ○ Unknown
Recent gastrointestinal bleeding *(6 months before intervention)*:	○ Yes ○ No ○ Unknown
History of gastrointestinal bleeding *(during the whole period before intervention)*	○ Yes ○ No ○ Unknown
Imaging characteristics	
Modality of imaging:	○ DUS ○ CT ○ MRI ○ Transient elastography ○ Other (please specify): _____ ○ Unknown
If applicable; **DUS**	
PVAS (radiological interpretation):	○ Yes ○ No ○ Unknown
PVT (radiological interpretation):	○ Yes ○ No ○ Unknown
Anastomosis diameter:	_____ mm ○ Unknown
Anastomotic velocity:	_____ cm/s ○ Unknown
Pre-anastomotic velocity:	_____ cm/s ○ Unknown
Post-anastomotic velocity:	_____ cm/s ○ Unknown
Splenomegaly:	○ Yes ○ No ○ Unknown

Spleen size:	_____ cm ○ Unknown
If applicable;	
CT scan	
PVAS (radiological interpretation):	○ Yes ○ No ○ Unknown
PVT (radiological interpretation):	○ Yes ○ No ○ Unknown
Cavernous transformation portal vein:	○ Yes ○ No ○ Unknown
Anastomosis diameter:	_____ mm ○ Unknown
Splenomegaly:	○ Yes ○ No ○ Unknown
Spleen size:	_____ cm ○ Unknown
If applicable;	
MRI scan	
PVAS (radiological interpretation):	○ Yes ○ No ○ Unknown
PVT (radiological interpretation):	○ Yes ○ No ○ Unknown
Cavernous transformation portal vein:	○ Yes ○ No ○ Unknown
Anastomosis diameter:	_____ mm ○ Unknown
Splenomegaly:	○ Yes ○ No ○ Unknown
Spleen size:	_____ cm ○ Unknown
If applicable;	
Transient elastography (Fibroscan)	
Liver stiffness:	_____ kPa ○ Unknown
Spleen stiffness:	_____ kPa ○ Unknown

CRF 2.2 TREATMENT INFORMATION

Treatment type:	○ None, conservative with monitoring ○ PTA of portal vein anastomosis ○ PTA/stent of portal vein anastomosis ○ Mesorex bypass (MRB) ○ PTA of MRB anastomosis ○ PTA/stent of MRB anastomosis ○ Endovascular recanalization portal vein with PTA ○ Endovascular recanalization portal vein with PTA/stent ○ Splenic arterial embolism ○ Splenectomy ○ Other intervention(s) (text): _____
Endovascular specific treatment details	
Access endovascular intervention *(more than one answer is possible)*:	○ Trans-splenic ○ Trans-hepatic ○ Trans-mesenteric ○ Unknown
Pre-interventional pressure gradient stenosis:	_____ mmHg ○ Unknown
If applicable; Portal vein anastomosis stenosis:	PTA performed: ○ Yes ○ No Stent inserted: ○ Yes ○ No Post-interventional pressure gradient: _____ mmHg ○ Unknown
If applicable; PTA protocol How many dilatations in one treatment session?	○ 1 dilatation Balloon size used: _____ mm ○ Unknown Duration dilatation: _____ min ○ Unknown ○ 2 dilatations Balloon size used: _____ mm ○ Unknown Duration dilatation: _____ min ○ Unknown ○ 3 dilatations

	Balloon size used: _____ mm ○ Unknown Duration dilatation: _____ min ○ Unknown ○ More (please specify)
Embolization of collaterals	○ Yes ○ No
If applicable; Stent placement	Type stent: ○ Self-expandable ○ Balloon expandable ○ Unknown Stent manufacturer & type: _____ ○ Unknown Diameter: _____ mm ○ Unknown Length: _____ mm ○ Unknown
Embolization of collaterals	○ Yes ○ No
If applicable; Portal vein thrombosis:	Access endovascular intervention *(more than one answer is possible)*: ○ Trans-splenic ○ Trans-hepatic ○ Trans-mesenteric ○ Unknown Length recanalization: _____ cm ○ Unknown PTA performed: ○ Yes ○ No Stent inserted: ○ Yes ○ No Post-interventional pressure gradient: _____ mmHg ○ Unknown
If applicable; PTA protocol How many dilatations in one treatment session?	○ 1 dilatation Balloon size used: _____ mm ○ Unknown Duration dilatation: _____ min ○ Unknown ○ 2 dilatations Balloon size used: _____ mm ○ Unknown Duration dilatation: _____ min ○ Unknown ○ 3 dilatations Balloon size used: _____ mm ○ Unknown

	Duration dilatation: _____ min ○ Unknown ○ More (please specify)
Embolization of collaterals	○ Yes ○ No
If applicable; Stent placement	Type stent: ○ Self-expandable ○ Balloon expandable ○ Unknown Stent manufacturer & type: _____ ○ Unknown Diameter: _____ mm ○ Unknown Length: _____ mm ○ Unknown
Embolization of collaterals	○ Yes ○ No
Mesorex bypass preparation details	
Balloon occlusion portography performed:	○ Yes ○ No ○ Unknown
Liver biopsy performed:	○ Yes ○ No ○ Unknown
Are you willing to share the liver biopsy data?	○ Yes ○ No
Mesorex bypass specific treatment details	
Venous graft used:	○ Yes ○ No ○ Unknown
Prosthetic graft used:	○ Yes ○ No ○ Unknown
Location of venous graft:	○ Internal jugular vein ○ Iliac vein ○ Femoral vein ○ Saphenous vein ○ Other (please specify): _____ ○ Unknown
Type of venous graft:	○ Auto graft (patients' own venous graft) ○ Matched living donor (same as living liver donor) ○ Unmatched living donor (unmatched to living liver donor) ○ Matched deceased donor (same donor as deceased liver donor)

	○ Unmatched deceased donor (unmatched to deceased liver donor) ○ Unknown
Intraprocedural anticoagulation	
Intraprocedural anticoagulation:	○ Yes ○ No ○ Unknown
Unfractionated Heparin used:	○ Yes ○ No ○ Unknown
If yes; Dosage:	○ 50 IU/kg ○75IU/kg ○ 100 IU/kg ○ Other (please specify): _____ ○ Unknown
If no; please specify other intraprocedural anticoagulation	○ LMWH prophylactic dose ○ LMWH therapeutic dose ○ Other (please specify): _____ ○ Unknown
Postinterventional anticoagulation	
Postinterventional anticoagulation:	○ Yes ○ No ○ Unknown
How many types of anticoagulation?	○ 1 ○ 2 ○ 3 *Please specify in time sequence* ○ Unknown
If applicable; Anticoagulation 1: Sort:	○ Unfractionated Heparin ○ LMWH heparin prophylactic dose ○ LMWH therapeutic dose ○ Vitamin K antagonist ○ Acetylsalicylic acid ○ Other (please specify): _____ ○ Unknown
Duration:	○ Temporally ○ Lifelong ○ Unknown *If temporally;* please specify duration: _____ weeks/months/years ○ Unknown
Target level anticoagulation available?	○ Yes ○ No ○ Unknown *If applicable;* target INR: _____ ○ Unknown *If applicable;* anti-Xa: _____ U/ml ○ Unknown

If applicable; Anticoagulation 2:	
Sort:	○ Unfractionated Heparin ○ LMWH heparin prophylactic dose ○ LMWH therapeutic dose ○ Vitamin K antagonist ○ Acetylsalicylic acid ○ Other (please specify): _____ ○ Unknown
Duration:	○ Temporally ○ Lifelong ○ Unknown *If temporally;* please specify duration: _____ weeks/months/years ○ Unknown
Target level anticoagulation available?	○ Yes ○ No ○ Unknown *If applicable;* target INR: _____ ○ Unknown *If applicable;* anti-Xa: _____ U/ml ○ Unknown
If applicable; Anticoagulation 3:	
Sort:	○ Unfractionated Heparin ○ LMWH heparin prophylactic dose ○ LMWH therapeutic dose ○ Vitamin K antagonist ○ Acetylsalicylic acid ○ Other (please specify): _____ ○ Unknown
Duration:	○ Temporally ○ Lifelong ○ Unknown *If temporally;* please specify duration: _____ weeks/months/years ○ Unknown
Target level anticoagulation available?	○ Yes ○ No ○ Unknown *If applicable;* target INR: _____ ○ Unknown *If applicable;* anti-Xa: _____ U/ml ○ Unknown

FOLLOW-UP CRF

Direct post-procedural, up to two weeks (short term)	
Which modality do you use for radiological follow-up for this intervention *(more than one answer is possible)*?	○ DUS ○ CT ○ MRI ○ Transient elastography ○ Other (please specify): _____ ○ Unknown
If DUS; please specify last DUS within 2 weeks after intervention: Anastomotic velocity: Pre-anastomotic velocity: Post-anastomotic velocity:	 _____ cm/s ○ Unknown _____ cm/s ○ Unknown _____ cm/s ○ Unknown
If transient elastography; please specify last transient elastography within 2 weeks after intervention: Liver stiffness: Spleen stiffness:	 _____ kPa ○ Unknown _____ kPa ○ Unknown
Platelet count, last number within 2 weeks after intervention:	_____ ○ Unknown
Postinterventional complications	
Type:	○ Infection ○ Thrombosis ○ Bleeding
If thrombosis; Intervention performed ? *If yes;* Date/age intervention: Type intervention: Technical success:	 ○ Yes ○ No ○ Unknown __/__/_____, _____ ○ Interventional thrombolysis ○ Interventional thrombectomy ○ Surgical thrombectomy ○ Other (please specify): _____ ○ Unknown ○ Yes ○ No ○ Unknown

Postprocedural, after to two weeks of intervention (long term)	
Which modality do you use for follow-up for this intervention *(more than one answer is possible)*?	○ DUS ○ CT ○ MRI ○ Transient elastography ○ Other (please specify): _____ ○ Unknown
Severe PVO complications	
Severe complications of PVO after intervention:	○ Yes ○ No ○ Unknown
Which complications *(more than one answer is possible)*?	○ Ascites ○ Gastrointestinal bleeding ○ Hepatic encephalopathy (any grade) ○ Hepatopulmonary syndrome ○ Portopulmonary hypertension
Date/age first severe complication of PVO after intervention:	__/__/_____, _____

PORTAL Registry

Portal vein Obstruction Revascularisation Therapy After Liver transplantation

Site Specific Information Form

Part I: Current Management Practice

Version 1.4, March 2022

Investigator name:_____

Please complete all forms as fully as possible.

Thank you for your cooperation.

Kind regards,

The PORTAL Registry team

Bader A. M. Alfares, coordinating researcher

Hubert P. J. van der Doef & Reinoud P.H. Bokkers, principle investigators

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Experience of centers	
Since when does the liver transplantation program start?	__/__/_____
Since when does the living donor liver transplantation program start?	__/__/_____
Is a preventive portoplasty a standard procedure for a hypoplastic portal vein? *If yes;* when was the first performed?	○ Yes ○ No __/__/_____
Is a PTA a standard procedure? *If yes;* when was the first performed?	○ Yes ○ No __/__/_____
Is a stent placement a standard procedure? *If yes;* when was the first performed?	○ Yes ○ No __/__/_____
Is a MRB a standard procedure? *If yes;* when was the first performed?	○ Yes ○ No __/__/_____
Current composition of the team	
How many pediatric gastroenterologists-hepatologists who are responsible for the management of pediatric liver transplantation patients?	_____
How many pediatric radiologists who are responsible for the radiological management of pediatric liver transplantation patients?	_____
How many interventional radiologists who perform the procedures on children after liver transplantation (PTA/stent)?	_____
How many Hepato-Pancreato-Biliary surgeons who are responsible for the surgical management of pediatric liver transplantation patients?	_____
How many Hepato-Pancreato-Biliary surgeons who perform MRBs in children after liver transplantation?	_____
Current structure of the care	

Do you have a specialized team for PVO and other vascular problems after liver transplantation?	○ Yes ○ No
If yes; who is part of the team?	
Pediatric gastroenterologists-hepatologists:	○ Yes ○ No
Pediatric radiologists:	○ Yes ○ No
Interventional radiologists:	○ Yes ○ No
Hepato-Pancreato-Biliary surgeons:	○ Yes ○ No
Other (please specify):	_____
Do you have a specialized multi-disciplinary meeting for PVO and other vascular problems after liver transplantation?	○ Yes ○ No
If yes; who is part of the team?	
Pediatric gastroenterologists-hepatologists:	○ Yes ○ No
Pediatric radiologists:	○ Yes ○ No
Interventional radiologists:	○ Yes ○ No
Hepato-Pancreato-Biliary surgeons:	○ Yes ○ No
Other (please specify):	_____
Do you have a protocol for the care of patients with a PVO?	○ Yes ○ No
If yes; does it contain the following topics?	
Screening:	○ Yes ○ No
Diagnosis:	○ Yes ○ No
Indication for treatment:	○ Yes ○ No
Treatment:	○ Yes ○ No
Postprocedural care:	○ Yes ○ No
Is your center willing to share their protocol?	○ Yes ○ No
Screening	
What is/are the current radiological investigation(s) for screening for PVO in the outpatient department *(multiple answers are possible)*?	○ Doppler ultrasound (DUS) ○ CT scan ○ Transient Elastography (TE) ○ Other (please specify):_____

Is the PVO screening for patients with PVO risk factors similar to patients without PVO risk factors?	○ Yes ○ No
If yes; What is the current timing of the preferred radiological screening investigation in the outpatient department *(multiple answers are possible)*?	○ 3 months after transplantation ○ 6 months after transplantation ○ 9 months after transplantation ○ 1 year after transplantation ○ 2 years after transplantation ○ 3 years after transplantation ○ 4 years after transplantation ○ 5 years after transplantation ○ 6 years after transplantation ○ 7 years after transplantation ○ 8 years after transplantation ○ 9 years after transplantation ○ 10 years after transplantation ○ 11 years after transplantation ○ 12 years after transplantation ○ 13 years after transplantation ○ 14 years after transplantation ○ 15 years after transplantation ○ 16 years after transplantation ○ 17 years after transplantation ○ 18 years after transplantation ○ other
If no; what kind of risk factors do you use *(multiple answers are possible)*?	○ Biliary atresia ○ Living related liver transplantation ○ Venous jump/interposition graft portal vein ○ Age liver transplantation <1 year ○ Surgical intervention portal vein within 30 days after liver transplantation (thrombectomy, new anastomosis, reposition of vessel(s)) ○ other:
If no;	○ 3 months after transplantation

What is the current timing of the preferred radiological screening investigation in the outpatient department in patients with PVO risk factors *(multiple answers are possible)*?	○ 6 months after transplantation ○ 9 months after transplantation ○ 1 year after transplantation ○ 2 years after transplantation ○ 3 years after transplantation ○ 4 years after transplantation ○ 5 years after transplantation ○ 6 years after transplantation ○ 7 years after transplantation ○ 8 years after transplantation ○ 9 years after transplantation ○ 10 years after transplantation ○ 11 years after transplantation ○ 12 years after transplantation ○ 13 years after transplantation ○ 14 years after transplantation ○ 15 years after transplantation ○ 16 years after transplantation ○ 17 years after transplantation ○ 18 years after transplantation ○ other
If no; What is the current timing of the preferred radiological screening investigation in the outpatient department in patients without PVO risk factors *(multiple answers are possible)*?	○ 3 months after transplantation ○ 6 months after transplantation ○ 9 months after transplantation ○ 1 year after transplantation ○ 2 years after transplantation ○ 3 years after transplantation ○ 4 years after transplantation ○ 5 years after transplantation ○ 6 years after transplantation ○ 7 years after transplantation ○ 8 years after transplantation ○ 9 years after transplantation ○ 10 years after transplantation ○ 11 years after transplantation

	○ 12 years after transplantation ○ 13 years after transplantation ○ 14 years after transplantation ○ 15 years after transplantation ○ 16 years after transplantation ○ 17 years after transplantation ○ 18 years after transplantation ○ other
Assessment criteria	
What is your center's non-invasive radiological criteria to determine stenosis of the portal vein anastomosis? Please report the following: • Preferred radiological investigation(s) • Radiological criteria and radiological cut-off values *(with a reference if applicable)*	
Preferred radiological investigation(s):	○ Doppler ultrasound (DUS) ○ CT scan ○ Transient Elastography (TE) ○ Other (please specify):_____
Non-invasive radiological criteria and cut-off values *(with a reference if applicable)*:	*If applicable*; **DUS:** Pre-anastomotic velocity: ○ Yes ○ N/A *If yes;* cut-off value: _____ cm/s Post-anastomotic velocity: ○ Yes ○ N/A *If yes;* cut-off value: _____ cm/s Anastomotic velocity: ○ Yes ○ N/A *If yes;* cut-off value: _____ cm/s Anastomotic-to-pre-anastomotic velocity ratio: ○ Yes ○ N/A *If yes;* cut-off value: _____ Anastomotic diameter:

	○ Yes ○ N/A *If yes;* cut-off value: _____ mm Presence of turbulence: ○ Yes ○ N/A *If applicable*; **CT scan:** Anastomotic diameter: ○ Yes ○ N/A *If yes;* cut-off value: _____ mm Presence of collaterals: ○ Yes ○ N/A Presence of cavernoma: ○ Yes ○ N/A *If applicable*; **TE/SWE:** Liver stiffness: ○ Yes ○ N/A *If yes;* cut-off value: _____ kPa Spleen stiffness: ○ Yes ○ N/A *If yes;* cut-off value: _____ kPa
What is your center's interventional radiological criteria to determine stenosis of the portal vein anastomosis during an invasive portography? Please report the following: • Radiological criteria and radiological cut-off values *(with a reference if applicable)*:	
Interventional radiological criteria and cut-off values *(with a reference if applicable)*:	Pressure gradient anastomosis: ○ Yes ○ N/A *If yes;* cut-off value: <_____ mmHg Visual aspect anastomosis: ○ Yes ○ N/A *If yes;* cut-off value: _____ %

How does your center define technical success after interventional radiological treatment? Please report the following: • Radiological criteria and radiological cut-off values *(with a reference if applicable)*:	
Radiological criteria and radiological cut-off values *(with a reference if applicable)*:	Pressure gradient anastomosis: ○ Yes ○ N/A *If yes;* cut-off value: <_____ mmHg Drop in pressure gradient (%) from baseline: ○ Yes ○ N/A *If yes;* cut-off value: _____ % Residual venographic stenosis (%): ○ Yes ○ N/A *If yes;* cut-off value: _____ %
Postprocedural care	
PTA	
How many types of anticoagulation?	○ 1 ○ 2 ○ 3
Anticoagulation 1:	○ DOAC *If chosen;* please specify type:_____ ○ Unfractionated Heparin ○ LMWH prophylactic dose ○ LMWH therapeutic dose ○ Vitamin K antagonist ○ Acetylsalicylic acid ○ Other (please specify):_____
Duration anticoagulation 1:	○ Temporally ○ Lifelong ○ Unknown *If temporally;* please specify duration: ___ weeks/months/years
Therapeutic range anticoagulation 1:	INR: _____ anti-Xa: _____U/ml
Anticoagulation 2 *(if applicable)*:	○ DOAC *If chosen;* please specify type:_____ ○ Unfractionated Heparin

	○ LMWH prophylactic dose ○ LMWH therapeutic dose ○ Vitamin K antagonist ○ Acetylsalicylic acid ○ Other (please specify):_____
Duration anticoagulation 2:	○ Temporally ○ Lifelong ○ Unknown *If temporally;* please specify duration: ___ weeks/months/years
Therapeutic range anticoagulation 2:	INR: _____ anti-Xa: _____U/ml
Anticoagulation 3 *(if applicable)*:	○ DOAC *If chosen;* please specify type:_____ ○ Unfractionated Heparin ○ LMWH prophylactic dose ○ LMWH therapeutic dose ○ Vitamin K antagonist ○ Acetylsalicylic acid ○ Other (please specify):_____
Duration anticoagulation 3:	○ Temporally ○ Lifelong ○ Unknown *If temporally;* please specify duration: ___ weeks/months/years
Therapeutic range anticoagulation 3:	INR: _____ anti-Xa: _____U/ml
PTA/stent	
How many types of anticoagulation?	○ 1 ○ 2 ○ 3
Anticoagulation 1:	○ DOAC *If chosen;* please specify type:_____ ○ Unfractionated Heparin ○ LMWH prophylactic dose ○ LMWH therapeutic dose ○ Vitamin K antagonist ○ Acetylsalicylic acid

	○ Other (please specify):_________
Duration anticoagulation 1:	○ Temporally ○ Lifelong ○ Unknown *If temporally;* please specify duration: ___ weeks/months/years
Therapeutic range anticoagulation 1:	INR: _____ anti-Xa: _____U/ml
Anticoagulation 2 *(if applicable)*:	○ DOAC *If chosen;* please specify type:_____ ○ Unfractionated Heparin ○ LMWH prophylactic dose ○ LMWH therapeutic dose ○ Vitamin K antagonist ○ Acetylsalicylic acid ○ Other (please specify):_____
Duration anticoagulation 2:	○ Temporally ○ Lifelong ○ Unknown *If temporally;* please specify duration: ___ weeks/months/years
Therapeutic range anticoagulation 2:	INR: _____ anti-Xa: _____U/ml
Anticoagulation 3 *(if applicable)*:	○ DOAC *If chosen;* please specify type:_____ ○ Unfractionated Heparin ○ LMWH prophylactic dose ○ LMWH therapeutic dose ○ Vitamin K antagonist ○ Acetylsalicylic acid ○ Other (please specify):_____
Duration anticoagulation 3:	○ Temporally ○ Lifelong ○ Unknown *If temporally;* please specify duration: ___ weeks/months/years
Therapeutic range anticoagulation 3:	INR: _____

	anti-Xa: _____U/ml
MRB	
How many types of anticoagulation?	○ 1 ○ 2 ○ 3
Anticoagulation 1:	○ DOAC *If chosen;* please specify type:_____ ○ Unfractionated Heparin ○ LMWH prophylactic dose ○ LMWH therapeutic dose ○ Vitamin K antagonist ○ Acetylsalicylic acid ○ Other (please specify):_____
Duration anticoagulation 1:	○ Temporally ○ Lifelong ○ Unknown *If temporally;* please specify duration: ___ weeks/months/years
Therapeutic range anticoagulation 1:	INR: _____ anti-Xa: _____U/ml
Anticoagulation 2 *(if applicable)*:	○ DOAC *If chosen;* please specify type:_____ ○ Unfractionated Heparin ○ LMWH prophylactic dose ○ LMWH therapeutic dose ○ Vitamin K antagonist ○ Acetylsalicylic acid ○ Other (please specify):_____
Duration anticoagulation 2:	○ Temporally ○ Lifelong ○ Unknown *If temporally;* please specify duration: ___ weeks/months/years
Therapeutic range anticoagulation 2:	INR: _____ anti-Xa: _____U/ml
Anticoagulation 3 *(if applicable)*:	○ DOAC *If chosen;* please specify type:_____ ○ Unfractionated Heparin

	○ LMWH prophylactic dose ○ LMWH therapeutic dose ○ Vitamin K antagonist ○ Acetylsalicylic acid ○ Other (please specify):_____
Duration anticoagulation 3:	○ Temporally ○ Lifelong ○ Unknown *If temporally;* please specify duration: ___ weeks/months/years
Therapeutic range anticoagulation 3:	INR: _____ anti-Xa: _____U/ml
Radiological follow-up after treatment	
Is the radiological follow-up after all PVO interventions (PTA, PTA/stent, MRB) the same?	○ Yes (please fill in the radiological follow-up at all interventions) ○ No (please fill in the radiological follow-up for every intervention specific below)
All interventions	
Which modality do you use for follow-up *(more than one answer is possible)*?	○ DUS ○ CT ○ MRI ○ Transient elastography ○ Other (please specify): _____
How often is radiological follow-up carried out? *(more than one answer is possible)*?	○ 3 months after intervention ○ 6 months after intervention ○ 9 months after intervention ○ 1 year after intervention ○ 2 years after transplantation ○ 3 years after transplantation ○ 4 years after transplantation ○ 5 years after transplantation ○ 6 years after transplantation ○ 7 years after transplantation ○ 8 years after transplantation ○ 9 years after transplantation

	○ 10 years after transplantation ○ 11 years after transplantation ○ 12 years after transplantation ○ 13 years after transplantation ○ 14 years after transplantation ○ 15 years after transplantation ○ 16 years after transplantation ○ 17 years after transplantation ○ 18 years after transplantation ○ Other (please specify): _____
PTA	
Which modality do you use for follow-up *(more than one answer is possible)*?	○ DUS ○ CT ○ MRI ○ Transient elastography ○ Other (please specify): _____
How often is radiological follow-up carried out? *(more than one answer is possible)*?	○ 3 months after intervention ○ 6 months after intervention ○ 9 months after intervention ○ 1 year after intervention ○ 2 years after transplantation ○ 3 years after transplantation ○ 4 years after transplantation ○ 5 years after transplantation ○ 6 years after transplantation ○ 7 years after transplantation ○ 8 years after transplantation ○ 9 years after transplantation ○ 10 years after transplantation ○ 11 years after transplantation ○ 12 years after transplantation ○ 13 years after transplantation ○ 14 years after transplantation ○ 15 years after transplantation

	○ 16 years after transplantation ○ 17 years after transplantation ○ 18 years after transplantation ○ Other (please specify): _____
PTA/ stent	
Which modality do you use for follow-up *(more than one answer is possible)*?	○ DUS ○ CT ○ MRI ○ Transient elastography ○ Other (please specify): _____
How often is radiological follow-up carried out? *(more than one answer is possible)*?	○ 3 months after intervention ○ 6 months after intervention ○ 9 months after intervention ○ 1 year after intervention ○ 2 years after transplantation ○ 3 years after transplantation ○ 4 years after transplantation ○ 5 years after transplantation ○ 6 years after transplantation ○ 7 years after transplantation ○ 8 years after transplantation ○ 9 years after transplantation ○ 10 years after transplantation ○ 11 years after transplantation ○ 12 years after transplantation ○ 13 years after transplantation ○ 14 years after transplantation ○ 15 years after transplantation ○ 16 years after transplantation ○ 17 years after transplantation ○ 18 years after transplantation ○ Other (please specify): _____
MRB	

Which modality do you use for follow-up *(more than one answer is possible)*?	○ DUS ○ CT ○ MRI ○ Transient elastography ○ Other (please specify): _____
How often is radiological follow-up carried out? *(more than one answer is possible)*?	○ 3 months after intervention ○ 6 months after intervention ○ 9 months after intervention ○ 1 year after intervention ○ 2 years after transplantation ○ 3 years after transplantation ○ 4 years after transplantation ○ 5 years after transplantation ○ 6 years after transplantation ○ 7 years after transplantation ○ 8 years after transplantation ○ 9 years after transplantation ○ 10 years after transplantation ○ 11 years after transplantation ○ 12 years after transplantation ○ 13 years after transplantation ○ 14 years after transplantation ○ 15 years after transplantation ○ 16 years after transplantation ○ 17 years after transplantation ○ 18 years after transplantation ○ Other (please specify): _____

PORTAL Registry

Portal vein Obstruction Revascularisation Therapy After Liver transplantation

Site Specific Information Form

Part II: Prevalence Study

Version 1.4, March 2022

Investigator name:_____

Please complete all forms as fully as possible.

Thank you for your cooperation.

Kind regards,

The PORTAL Registry team

Bader A. M. Alfares, coordinating researcher

Hubert P. J. van der Doef & Reinoud P.H. Bokkers, principle investigators

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Prevalence				
From which period do you start inclusion for the prevalence study?	○ 01/01/2001 ○ Other (please specify): __/__/_____			
From which period do you start inclusion diagnosed PVO patients?	○ 01/01/2001 ○ Other (please specify): __/__/_____			
How many paediatric liver transplantations (LT) were performed since start inclusion? *Please include number of transplantations within different groups and time periods:*	Date of LT: 01/01/2001 - 01/01/2006	Date of LT: 01/01/2006 - 01/01/2011	Date of LT: 01/01/2011 - 01/01/2016	Date of LT: 01/01/2016 - 01/01/2020
All				
Biliary atresia				
Living donor liver transplantation				
Age at liver transplantation <2 years				
Age at liver transplantation <1 year				
Age at liver transplantation <1 year AND Living donor liver transplantation AND Biliary atresia				
Age at liver transplantation <1 year AND Deceased donor liver transplantation AND Biliary atresia				

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

Section/item	Item No	Description
Administrative information		
Title	1	PORTAL registry is a multicentre, retrospective, observational registry of patients who underwent liver transplantation and were diagnosed and treated for PVO at age <18 years
Trial registration	2a	The PORTAL registry is registered in the Netherlands Trial Register (NL9261). Registration date: 28-02-2021. Website: www.trialregister.nl
	2b	Appendix I
Protocol version	3	Issue date: 12 January 2021 Protocol amendment number: 4 Authors: BA, RB, HVD
Funding	4	N.A.
Roles and responsibilities	5a	All authors were actively involved in this study design and read and approved the final manuscript. BA, HVD and RB designed the original study protocol and initiated the study.
	5b	Trial Sponsor: University Medical Centre Groningen, Groningen, The Netherlands Reinoud P.H. Bokkers, MD PhD EBIR University Medical Centre Groningen (UMCG) Department of Radiology, Medical Imaging Centre Hanzeplein 1, 9721 GZ Groningen, the Netherlands Email: r.p.h.bokkers@umcg.nl Phone: +31-50-3616161

5c This sponsor source had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results

5d **Principal investigators and coordinating researcher**
Design and conduct of PORTAL registry
Preparation of protocol and revisions
Preparation of PORTAL registry-related items: site specific information form, case report form, and e-crf guidelines
Managing correspondence with collaborating centres
Publication of study reports

Lead investigators
In each participating centre, a lead investigator ((interventional) radiologist, paediatric hepatologist, and liver-transplant surgeon) will be identified, to be responsible for identification, recruitment, data collection and completion of (e)CRFs, along with follow up of study patients and adherence to study protocol and investigators brochure. One investigator per country will be chosen as a national coordinator

Project management office
Assistance with administrative issues
Data verification
Advice for Principal investigators and coordinating researcher

Medical Ethics Review Committee (METc in Dutch)
Agreement of final protocol and amendments (if applicable)

Contract Research Desk
Agreement of final clinical site agreement

Introduction

Background and rationale	6a	**Background:** Liver transplantation is the standard care for patients with end-stage liver disease, metabolic liver diseases, and acute liver failure. Despite marked improvements in operating techniques, vascular complications, and especially portal vein obstruction (PVO), occur frequently after paediatric liver transplantation. Prevalence numbers in the literature differ from 8-12%, which is probably related to the distribution of the risk factors (young age at liver transplantation, biliary atresia, living related liver transplantation) within the investigated population and small sample size (only single centre data is reported) **Rationale:** The PORTAL registry study will gather one of the largest international data sets on the characteristics of PVO in regard to current management practice, prevalence numbers, and efficacy of the individual treatments. Given the fact that the current data are only single-centre studies which do not have the adequate numbers to be able to give answers to such important questions on who, when and how to treat patients with PVO after liver transplantation. Therefore, PORTAL registry will be one of the first multicentre studies to analyze the diagnostic and therapeutic characteristics of PVO after paediatric liver transplantation to inform future quality of care initiatives for this group of patients which is regarded to be the only feasible strategy to obtain more insights on prevalence of PVO, and long-term efficacy of the individual PVO treatments in paediatric patients after liver transplantation
	6b	N.A.
Objectives	7	The objectives of this study are to assess the efficacy of the individual treatments for portal vein obstruction (PVO) after paediatric liver transplantation, the prevalence numbers of PVO, and the current management practice
Trial design	8	This is an international, multi-centre, retrospective, observational registry study

Methods: Participants, interventions, and outcomes

Study setting	9	PORTAL registry is a multicentre, retrospective, observational registry of patients who underwent liver transplantation and were diagnosed and treated for PVO. List of countries where data will be collected can be found in https://portalregistry.eu/
Eligibility criteria	10	The study aims to include approximately 400 paediatric patients. Patients will be included if the following inclusion criteria are present: 1. Treated for PVO (PVAS or PVT) after liver transplantation (all interventions are included and conservative treatment as well) 2. Age at intervention <18 years 3. Intervention in period 01-01-2001 and 01-01-2021 **Investigator requirements:** All Investigators must submit the following documentation to be considered approved investigators: 1. Signed and dated recent curriculum vitae 2. Signed Clinical Study Agreement (CSA) 3. Complete site qualification process and site initiation
Interventions	11a	N.A.
	11b	N.A.
	11c	N.A.
	11d	N.A.

Outcomes	12	**Primary outcome measures:** • Patency 1) Primary patency is defined from index procedure to treat stenosis or occlusion to time to re-stenosis or re-occlusion. Primary patency ends when either re-stenosis or re-occlusion occur for the first time post intervention 2) Secondary patency is from index procedure to time of failure to re-establish flow following re-occlusion. Secondary patency ends once re-occlusion cannot be or is not treated • Prevalence numbers The prevalence of PVO will be calculated as the total PVO patients divided by the total of transplanted patients at paediatric age. The total transplanted patients will be calculated from patients with one year follow-up and date of transplantation between 01-01-2000 and 01-01-2020, as a large proportion of the PVO occurs in the first year after liver transplantation **Secondary outcomes:** o Patient and graft survival Patient survival is defined from date of PVO intervention until date of death. Patients who are alive at the end of the follow-up will be censored. Graft survival is defined from date of PVO intervention until date of re-transplantation or death. Patients who are alive without a re-transplantation at the end of the follow-up will be censored. o Freedom of severe PVO complications Severe PVO complications are defined as severe signs of portal hypertension (ascites, gastrointestinal bleeding) or porto-systemic shunting (any grade of hepatic encephalopathy, hepatopulmonary syndrome, portopulmonary hypertension). This will be determined following each intervention until end of the follow-up o Technical success Technical success is defined as the success of the intervention during the procedure (re-establishment of portal flow, without residual stenosis) and is based on the assessment of the centre itself
Participant timeline	13	The data on prevalence numbers and efficacy of the treatments protocols are expected to be finalized in September 2022. Regarding data on current management practice, we aim to receive the paper-bases questionnaire in March 2022. Once the trial master file is completed by a participating centre, a virtual site initiation visit will be planned to discuss the study and to initiate the project officially
Sample size	14	We are expected that the study will consists of 400 paediatric patients

Recruitment	15	Clinical site personnel will collect the data and enter it in REDCap database as well as paper-based clinical site information form by local research personnel. Subject records will be pseudo-anonymized by means of allocating each subject with a unique study number

~~**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~~
~~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~~
~~Implementation~~	~~16c~~	~~Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions~~
~~Blinding (masking)~~	~~17a~~	~~Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how~~
	~~17b~~	~~If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial~~

Methods: Data collection, management, and analysis

Data collection methods	18a	A single questionnaire (Site Specific Information Form) is provided to acquire data on the prevalence and current management practice. Within this questionnaire, we will request the amount of transplanted patients within the total paediatric group and in subgroups based on time of transplantation, age at transplantation, underlying disease (biliary atresia) and donor type (living or deceased liver donor). Moreover, within this questionnaire, data on experience of the centres, multidisciplinary team, structure of care, screening protocol, and assessment criteria will be obtained. Data on efficacy of the individual portal vein revascularisation treatments will be registered in REDCap database (https://redcap.umcg.nl). Within the REDCap database, patients treated for PVO (PVAS or PVT) after liver transplantation are included with an age at intervention of <18 years). Inclusion period is within the last 20 years from 1-1-2001 until 1-1-2021
	18b	N.A.
Data management	19	Clinical site personnel will collect the data and enter it in REDCap database as well as paper-based clinical site information form by local research personnel. Subject records will be pseudo-anonymized by means of allocating each subject with a unique study number. The local investigators will keep a list with the subject names, date of birth, local ID, and unique study number. Data will be stored by the local investigators and coordinating centre for 15 years after termination of the study. All data and records generated during this study will be kept in accordance with institutional policies regarding subject privacy and the data and records of all patients will not be used for any purpose other than conducting this study
Statistical methods	20a	All data analyses will be performed by using IBM SPSS Statistics version 26. Descriptive statistics will be applied using the mean and standard deviation for variables with normal distribution, and median and interquartile ranges (IQR) for variables with skewed distribution. Dichotomous variables will be compared with the Chi-square test or the Fisher exact test or both. Continuous variables will be compared with the Mann-Whitney U test. For the analysis of the primary and secondary patency, freedom of severe PVO complications and patient and graft survival, the Kaplan-Meier test will used. P-values less than 0.05 will be considered statistically significant
	20b	N.A.
	20c	N.A.

Methods: Monitoring

Data monitoring	21a	To the extent applicable, the Site Parties shall permit the Study Monitor, Auditor, IRB and any official with a legal right to inspect and access all relevant documentation and Patient Data for monitoring of the progress of the Clinical Study, the proper collection and recording of Clinical Data, and altogether the good quality of the Clinical Study and compliance with applicable Law. Parties will make in good faith arrangements concerning the planning and follow-up of such audits or inspections. For the avoidance of doubt, no copying of the Patient Data is permissible and any access to the Patient Data shall be arranged for in the premises of the Study Site
	21b	N.A.
Harms	22	Due to the retrospective nature of the study, the risks of participation are minimal, and this study will not influence the on-going diagnostics and treatment of the included patients. Adverse events are not expected
Auditing	23	N.A.

Ethics and dissemination

Research ethics approval	24	Ethical approval has been obtained from the University Medical Centre Groningen's Institutional Review Board (METc 2021/072) prior to the start of the study
Protocol amendments	25	Any modifications to the protocol which may impact on the conduct of the study, potential benefit of the patient or may affect patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures, or significant administrative aspects will require a formal amendment to the protocol and therefore, IRB will be notified
Consent or assent	26a	If mandated by the local national laws, a waiver of informed consent will be requested governing the conduct of clinical research studies, and General Data Protection Regulation act. If a consent is claimed, the local investigator will assure that the consent forms are signed by study participants/their parents
	26b	N.A.

Confidentiality	27	All study-related information will be stored securely at the study site. All participant information will be stored in locked file in areas with limited access (only for authorized personnel). All reports, data collection, and administrative forms will be identified by a coded ID number only to maintain participant confidentiality. All records that contain names or other personal identifiers will be stored separately from study records identified by code number. All local databases will be secured with password-protected access systems. Forms, lists, logbooks, and any other listings that link participant ID numbers to other identifying information will be stored in a separate, locked file in an area with limited access
Declaration of interests	28	N.A.
Access to data	29	Only authorized personnel (project principal investigators and coordinating researcher) will have direct access to the data sets
Ancillary and post-trial care	30	N.A.
Dissemination policy	31a	The results of this study will be disseminated by publication of peer-reviewed manuscripts, presentation in an abstract form at scientific meetings, and data sharing with other researchers through academically-established means.
	31b	For each main paper, there are three co-author positions per centre available. Following the completion of the study, all collaborators can submit a proposal for a substudy
	31c	The outcome of this study will also be utilized to design an evidence-based, feasible therapeutic pathway for paediatric patients with portal vein complications following liver transplantation and implement this in an inter(national) guidelines

Appendices

Informed consent materials	32	N.A.
Biological specimens	33	N.A.

*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

The prevalence, management, and efficacy of treatment in portal vein obstruction after paediatric liver transplantation: protocol of the retrospective international multicentre PORTAL registry

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-066343.R1
Article Type:	Protocol
Date Submitted by the Author:	21-May-2023
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Primary Subject Heading:	Radiology and imaging
Secondary Subject Heading:	Paediatrics, Surgery
Keywords:	Paediatric hepatology < PAEDIATRICS, Paediatric transplant surgery < PAEDIATRIC SURGERY, Interventional radiology < RADIOLOGY & IMAGING

The prevalence, management, and efficacy of treatment in portal vein obstruction after paediatric liver transplantation: protocol of the retrospective international multicentre PORTAL registry

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LIST OF ABBREVIATIONS

PTA	Percutaneous Transluminal Angioplasty
PVAS	Portal Vein Anastomotic Stenosis
PVO	Portal Vein Obstruction
PVT	Portal Vein Thrombosis

ABSTRACT

Introduction: Portal vein obstruction (PVO) consists of anastomotic stenosis (PVAS) and thrombosis (PVT), which occurs due to a progression of the former. The aim of this large-scale international study is to assess the prevalence, current management practices, and efficacy of treatment in patients with PVO.

Methods and analysis: The Portal vein Obstruction Revascularisation Therapy After Liver transplantation (PORTAL) registry will facilitate an international, retrospective, multicentre, observational study, with 25 centres around the world already actively involved. Paediatric patients (aged <18 years) with a diagnosed PVO between 1 January 2001 and 1 January 2021 after liver transplantation will be eligible for inclusion. The primary endpoints are the prevalence of PVO, primary and secondary patency after PVO intervention, and current management practices. Secondary endpoints are patient and graft survival, severe complications of PVO, and technical success of revascularization techniques.

Ethics and dissemination: Medical Ethics Review Board of the University Medical Center Groningen has approved the study (METc 2021/072) . The results of this study will be disseminated via peer-reviewed publications and scientific presentations at national and international conferences.

Trial registration number: The PORTAL registry is registered in the Netherlands Trial Register at www.trialregister.nl (NL9261, 28-02-2021).

ARTICLE SUMMARY

Strengths and limitations of this study

- This will be the first global collaboration between paediatric hepatologists, interventional radiologists, and liver transplant surgeons to provide a valuable information on PVO management and prevalence.
- The strength of the PORTAL registry multicentre project is the combination of a survey to explore routine clinical practice and electronic database to investigate the prevalence and the efficacy of different therapeutic options.
- The PORTAL registry is not powered to evaluate the natural history of PVO following paediatric liver transplantation which therefore a definitive future study will be needed.

INTRODUCTION

Liver transplantation is an established treatment for paediatric patients with end stage liver disease, metabolic liver diseases, hepatic malignancy, and acute liver failure.[1] Despite marked improvements in operating techniques, vascular complications, especially portal vein obstruction (PVO), remain common.[2] However, little is known regarding the prevalence, risk factors, and most optimal management strategies for this complication.

PVO consists of portal vein anastomotic stenosis (PVAS) or portal vein thrombosis (PVT). The rate of PVO after living donor liver transplantation has been reported to be 9-14%, in comparison with deceased donor liver transplantation, at <3%.[1] However, in specific risk groups, such as biliary atresia or young age transplantation, the prevalence of PVO is unknown, but thought to be higher.[1,3] The clinical course of PVO differs, from absence of symptoms to severe symptoms of portal hypertension (16% of patients have ascites and 26% have gastrointestinal bleeding from oesophageal varices).[4] There are a multitude of different treatment strategies, ranging from conservative management, endovascular therapy, or surgical options by means of mesorex bypass or other surgical shunts. A recent systematic review comparing the various treatments showed that there is no consensus on the most optimal strategy.[4] This is largely due to heterogeneity in the clinical characteristics of the patients who were treated, along with variation in the treatment protocol and postprocedural care across the single centre studies included.[4]

PORTAL is a multicentre, retrospective, observational registry of paediatric patients who have been diagnosed and treated for PVO after liver transplantation. The objective of the registry study is threefold. Firstly, it will assess the overall prevalence of PVO after paediatric liver transplantation, including taking into account various risk groups. Secondly, it will evaluate current management practices in terms of the experience of various centres, the composition of the team, the structure of care, screening, assessment criteria, postprocedural

care, and radiological follow-up after treatment. Thirdly, it also intends to assess the efficacy of the individual portal vein revascularization treatments.

METHODS AND ANALYSIS

Study design and participants

The study design takes the form of an international, retrospective, multicentre, observational registry of paediatric liver transplantation patients with PVO. Patients are eligible for inclusion if the following criteria are met: 1) the patient is diagnosed with PVO (PVAS or PVT) after liver transplantation (perioperative PVT will not be included in the analysis) and 2) the patient's age at the time of intervention (or time of diagnosis for patients who were treated conservatively) was <18 years, and 3) the date of intervention was between 1 January 2001 and 1 January 2021. Patients are excluded from the study if the following criteria are present: 1) patients suspected to have PVT of an either intra- or post-hepatic origin (i.e. severe fibrosis, cirrhosis, transplant failure, intrahepatic vascular changes, secondary PVT) and 2) patients with follow-up of less than 1 year.

Collection of data

Subjects will be identified through a retrospective review of the medical records of all patients who underwent liver transplantation at age <18. Data from subjects who are eligible for inclusion will be anonymously entered into either a REDCap database (https://redcap.umcg.nl) or a standardized paper case-report form (Supplementary file 1). Information regarding patient demographics, underlying disease, symptoms, treatment, and outcome will be gathered. The following types of interventions will be included: conservative treatment, endovascular treatments (percutaneous transluminal angioplasty [PTA] with or without stent placement,

endovascular recanalization, splenic artery or varices/cavernoma embolization), and surgical treatments (all types of surgical shunts and splenectomy).

To determine the prevalence and current management practices, each centre will also complete a structured questionnaire that records the experience of the centre, the composition of the team, the structure of care, screening, assessment criteria, postprocedural care, and radiological follow-up after treatment (Supplementary file 2). In addition, the number of patients who underwent liver transplant between 1 January 2001 and 1 January 2020 within the total paediatric group and in subgroups will also be recorded, based on time of transplantation, age at transplantation, underlying disease (biliary atresia) and donor type (living or deceased liver donor).

Primary outcomes

Prevalence

The prevalence of PVO will be calculated as the total number of PVO patients (transplanted between 1 January 2001 and 1 January 2020 and diagnosed with PVO between 1 January 2001 and 1 January 2021) divided by the total number of transplanted patients at paediatric age between 1 January 2001 and 1 January 2020. As the majority of PVO cases are diagnosed within the first year after transplantation, we chose a minimum of 1 year follow-up time.

Primary and secondary patency

Primary patency is defined as the interval between index procedure to treat stenosis or occlusion and time to re-stenosis or re-occlusion. Primary patency ends when either re-stenosis or re-occlusion occur for the first time after intervention. Primary patency will be represented as percentages at 1, 3, 5, 10, 15 and 20 years after the diagnosis of PVO.

Secondary patency is defined as the interval between index procedure and time of failure to re-establish flow when re-occlusion cannot be achieved or is not successfully treated (including all the intervening manipulations designed to re-establish functionality in intercurrent PVO). Secondary patency will be represented as percentages at 1, 3, 5, 10, 15 and 20 years after treatment for PVO.

Secondary outcomes

Patient and graft survival

Patient survival is defined as the period from date of first PVO intervention until date of death. Patients who are alive at the end of the follow-up will be censored. Graft survival is defined as the period from the date of PVO intervention until the date of re-transplantation or death. Patients who are alive without a re-transplantation at the end of the follow-up will be censored. The decision to re-transplant is based on an assessment by the individual centre. Causes of re-transplantation or death will be recorded. Patient and graft survival will be determined as percentages at 1, 3, 5, 10, 15 and 20 years after treatment for PVO.

Freedom from severe PVO complications

Severe PVO complications are defined as severe signs of portal hypertension (ascites, variceal bleeding) or porto-systemic shunting (any grade of hepatic encephalopathy, hepatopulmonary syndrome, portopulmonary hypertension). Ascites will be diagnosed by physical examination or imaging. These complications will be determined following each intervention until the end of the follow-up.

Technical success

Technical success is defined as the success of the intervention during the procedure (re-establishment of portal flow, without residual stenosis) and will be based on an assessment by the individual centre.

Current management practice

Current management practice is defined as the workflow process that includes experience of centres/team, care structure, screening, and assessment criteria, and postprocedural follow-up intended to optimize patient care.

Data management

Subject records will be pseudo-anonymized by means of allocating each subject a unique study number. The local investigators will maintain a list with subject's name, date of birth, local ID, and unique study number. Data will be stored by the local investigators and coordinating centre for 15 years after termination of the study. All data and records generated during this study will be kept in accordance with institutional policies regarding subject privacy, and the data and records of all patients will not be used for any purpose other than conducting this study.

Statistical analysis

All data analyses will be performed with IBM SPSS Statistics version 26. Descriptive statistics will be applied using the mean and standard deviation for variables with normal distribution, and median and interquartile ranges (IQR) for variables with skewed distribution. Dichotomous variables will be compared using the Chi-square test or the Fisher exact test or both. Continuous variables will be compared using the Mann-Whitney U test. For the analysis of primary and secondary patency, freedom from severe PVO complications, and patient and graft survival, the Kaplan-Meier method will be used. P-values less than 0.05 will be considered statistically significant.

Follow-up

Follow-up data for this study will be collected up to and including 1 January 2021.

Patient and Public Involvement

Neither patients nor the public were involved in the design of this study.

ETHICS AND DISSEMINATION

This study will be conducted according to the principles of the declaration of Helsinki (adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013) and the local national laws governing the conduct of clinical research studies. For the Netherlands, the study protocol has been evaluated as one that does not fall under the Medical Research Involving Human Subjects Act (WMO) by the University Medical Centre Groningen's IRB on 3 February 2021 (METc 2021/072). To adhere to the General Data Protection Regulation (EU) 2016/679, a data transfer

agreement will be required to initiate the study. All active collaborating sites have obtained local IRB approval.

The results of this study will be disseminated by publication of peer-reviewed manuscripts, presentation in an abstract form at scientific meetings, and data sharing with other researchers through academically established means. The outcomes of this study will also be utilized to design an evidence-based, feasible diagnostic and therapeutic algorithm for paediatric patients with portal vein complications following liver transplantation, which will be implemented in the form of national/international guidelines.

DISCUSSION

Key findings

The PORTAL registry is the first global collaboration between paediatric hepatologists, interventional radiologists, and liver transplant surgeons and will lead to the creation of the largest possible cohort of patients who have experienced PVO after paediatric liver transplantation. Based on this large group of patients, we will gain the broadest insight into current management practices, prevalence numbers, and efficacy of the individual treatments.

Strengths and limitations

Current literature regarding patients with PVO after paediatric liver transplantation is based on single centre studies. It is therefore difficult to determine which patients with PVO should be treated, and also when and how. A recent systematic review of single centre studies showed that treatment protocols for PVO differed between centres and that findings on long-term results are scarce and difficult to compare between centres.[4] A major strength of this study is the large-scale aggregation of patient data that will occur in the PORTAL registry, which we consider is not only the best but the only feasible strategy to overcome the lack of standardized care. We

aim to include more than 15 paediatric liver transplantation centres across Europe, North America, South America, Asia, Africa, and Oceania. It is therefore expected that we will have a sufficient number of participants to provide substantive answers to the research questions, including prognostic information regarding long-term outcomes after treatment for patients, parents, and healthcare professionals.

In addition, there is currently no consensus on the optimal clinical pathway for patients who present with PVO, with individual centres managing patients through locally determined patient pathway protocols. This lack of consensus includes all aspects of the patient pathway: screening protocol, diagnostic criteria, decision to treat, choice of the treatment modality, and post-procedural care.[4,5] We therefore expect heterogeneous data on all these topics. In this regard, another strength of the registry is that it will allow the review of differing pathways and their associated outcomes within a large patient cohort undergoing various interventions, and thus provide data on the basis of which greater international consensus on the optimal management and treatment strategy in this patient population will be created.

Although the registry aimed to be as comprehensive as possible, its retrospective design and the risk of missing data posed limitations. To address this issue, we prioritized fundamental questions such as PVO prevalence and treatment effectiveness. Following the NAPPED consortium's advice for conducting a large-scale international registry, we kept the design straightforward.[6] However, this approach may have resulted in some outcomes being overlooked in this study, such as partial PVT following thrombectomy. Nevertheless, the data from this registry can provide a foundation for more detailed investigations and post-hoc analyses to further explore these outcomes

Implications for the future

This is the first such global registry in the field of paediatric liver transplant. The results of the PORTAL registry study will lead to more knowledge about current and past management practices, prevalence, and treatment of PVO patients after paediatric liver transplantation and will be the first step towards more consensus on patient management. It is expected that the data from the PORTAL registry and the global collaboration will be used to accomplish the next step in improving the clinical care of PVO patients – a multidisciplinary guideline for screening, diagnosis, and treatment of PVO after paediatric liver transplantation. A prospective study is planned subsequent to this retrospective data analysis with this goal in mind. It will most likely rely on a slightly amended PORTAL registry, incorporating the knowledge gained from the retrospective analysis, integrating imaging studies – with a centralized review – and including laboratory analysis to harmonize findings and guide future analysis.

FUNDING AND DISCLOSURES

This research has not received a specific grant from any funding agency in the public, commercial or not-for-profit sectors. RPHB receives funding from the Netherlands Organization for Health Research and Development, and Siemens Healthineers.

AUTHORS' CONTRIBUTIONS

This manuscript is designed, conceptualized, drafted by BA, HVD, and RB. BW, TC, GN, MD, DA, VB, GV, PK, MMK, AK, JQB, MMH, MLK, PM, MB, DP, MK, SS, HU, VM, MA, SFA, EG, FG, GC, JM, SS, MDS, VA, JWU, HE, DD, JM, SH, ES, JVP, MM, RP, CTF, LSN, MF, CJ, MIRD, PF, AAS, PMW, MRA, RTF, BM, RJH, RK, VP, AM, KS, GG, SM, GP, MS, TA, GM, WH, MB, RAJD, RHD contributed equally to the study design, methodology, and approved the final version of the manuscript.

DECLARATION OF COMPETING INTEREST

None

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PORTAL Registry

Portal vein Obstruction Revascularisation Therapy After Liver transplantation

Case Report Form (CRF) ON PAPER

Version 1.4, March 2022

Subject Number:_____

Please complete all forms as fully as possible.

Thank you for your cooperation.

Kind regards,

The PORTAL Registry team

Bader A. M. Alfares, coordinating researcher

Hubert P. J. van der Doef & Reinoud P.H. Bokkers, principle investigators

E: b.a.m.alfares@umcg.nl, h.p.j.van.der.doef@umcg.nl, r.p.h.bokkers@umcg.nl

LIST OF AABREVIATIONS

CT	Computed Tomography
DSA	Subtraction Diagnostic Angiography
DUS	Doppler Ultrasound
IR	Interventional Radiology
MRB	Mesorex Bypass
MRI	Magnetic Resonance Imaging
PTA	Percutaneous Transluminal Angioplasty
PVAS	Portal Vein Anastomosis Stenosis
PVO	Portal Vein Obstruction
PVT	Portal Vein Thrombosis

Please calculate age into years with a decimal place, for example use 1.5 years instead of 1 years and 6 months. You can use the supplied calculator in an excel format.

PART I: BASELINE CRF

Gender:	○ Male ○ Female
Portal vein obstruction (PVO):	○ Yes ○ No
If applicable; Portal vein anastomosis stenosis (PVAS): Portal vein thrombosis (PVT):	 ○ Yes ○ No ○ Yes ○ No
Date/age first diagnosis PVAS and/or PVT:	__/__/_____, _____
Treatment performed:	○ Yes ○ No
If applicable; How many treatments?	 ○ 1 ○ 2 ○ 3 or more (please specify)
Date end of follow-up:	○ 01/01/2021 ○ Other (please specify): __/__/_____
Please specify reason if date end of follow-up is other than 01/01/2021:	○ Lost to follow-up ○ Death ○ Re-transplantation after PVO treatment ○ Other (please specify): _____
Age end of follow-up:	_____
Thrombosis portal vein or MRB/other surgical shunt without therapeutical options:	○ Yes ○ No
Date/age thrombosis portal vein or MRB/other surgical shunt without therapeutical options:	__/__/_____, _____
Re-transplantation after PVO treatment(s):	○ Yes ○ No
Date/ age diagnosis re-transplantation:	__/__/_____, _____
Cause of re-transplantation:	_____
Deceased after PVO treatment(s):	○ Yes ○ No
Date/age of death:	__/__/_____, _____
Please specify the cause of death:	_____
Medical history/comorbidities at baseline	
Primary disease:	○ Biliary atresia ○ Other (please specify): _____
Number of transplantations:	○ 1 ○ 2 ○ 3 or more (please specify) Date/age transplantation 1: __/__/_____, _____ Date/age transplantation 2: __/__/_____, _____

	Date/age transplantation 3: __/__/_____, _____ Date/age transplantation 4: __/__/_____, _____ Date/age transplantation 5: __/__/_____, _____ Date/age transplantation 6: __/__/_____, _____
Characteristics of last transplant before the first diagnosis PVO	
Date/age last transplantation:	__/__/_____, _____
Indication last transplantation:	○ Biliary atresia ○ Re-transplantation ○ Other (please specify): _____
Type last transplantation:	○ Living-donor ○ Deceased-donor
Size last transplantation:	○ Segment 2,3 ○ Segment 2,3,4 ○ Right segment ○ Full size
Size portal vein *(on pre-transplantation CT scan)*:	_____ mm ○ Unknown
Preventive portoplasty:	○ Yes ○ No
Venous jump/interposition graft portal vein:	○ Yes ○ No
Non-portal vascular complications within 30 days after last liver transplantation:	○ Yes ○ No
Number of non-portal vascular complications within 30 days after last liver transplantation:	○ 1 ○ 2 ○ 3 or more (please specify):
Characteristics of interventions of non-portal vascular complications within 30 days after last liver transplantation: **Intervention 1:** Date intervention Location intervention	 __/__/_____ ○ Hepatic artery ○ Hepatic vein

Type intervention	○ Surgical: thrombectomy ○ Surgical: new anastomosis ○ Surgical: reposition of vessel(s)○ IR PTA ○ IR PTA/stent ○ Other intervention(s) (text): _____
Intervention 2:	
Date intervention	__/__/_____
Location intervention	○ Hepatic artery ○ Hepatic vein
Type intervention	○ Surgical: thrombectomy ○ Surgical: new anastomosis ○ Surgical: reposition of vessel(s) ○ IR PTA ○ IR PTA/stent ○ Other intervention(s) (text): _____
Intervention 3:	
Date intervention	__/__/_____
Location intervention	○ Hepatic artery ○ Hepatic vein
Type intervention	○ Surgical: thrombectomy ○ Surgical: new anastomosis ○ Surgical: reposition of vessel(s)○ IR PTA ○ IR PTA/stent ○ Other intervention(s) (text): _____

PART II: INTERVENTION CRF (please fill in for each intervention in separate form)

CRF 2.1 GENERAL INFORMATION

Treatment characteristics	
Date/age intervention *(if conservative treatment, specify date/age of diagnosis)*:	__/__/_____, _____
Indication:	○ PVAS ○ PVT

CLINICAL CHARACTERISTICS AT DIAGNOSIS / TREATMENT

Clinical characteristics at intervention (6 months before intervention)	
Platelet count absolute number *(If known, please provide the unit of choice)*:	_____ ○ Unknown
Splenomegaly:	○ Yes ○ No ○ Unknown
Ascites:	○ Yes ○ No ○ Unknown
Recent gastrointestinal bleeding *(6 months before intervention)*:	○ Yes ○ No ○ Unknown
History of gastrointestinal bleeding *(during the whole period before intervention)*	○ Yes ○ No ○ Unknown
Imaging characteristics	
Modality of imaging:	○ DUS ○ CT ○ MRI ○ Transient elastography ○ Other (please specify): _____ ○ Unknown
If applicable; **DUS**	
PVAS (radiological interpretation):	○ Yes ○ No ○ Unknown
PVT (radiological interpretation):	○ Yes ○ No ○ Unknown
Anastomosis diameter:	_____ mm ○ Unknown
Anastomotic velocity:	_____ cm/s ○ Unknown
Pre-anastomotic velocity:	_____ cm/s ○ Unknown
Post-anastomotic velocity:	_____ cm/s ○ Unknown
Splenomegaly:	○ Yes ○ No ○ Unknown

Spleen size:	_____ cm ○ Unknown
If applicable;	
CT scan	
PVAS (radiological interpretation):	○ Yes ○ No ○ Unknown
PVT (radiological interpretation):	○ Yes ○ No ○ Unknown
Cavernous transformation portal vein:	○ Yes ○ No ○ Unknown
Anastomosis diameter:	_____ mm ○ Unknown
Splenomegaly:	○ Yes ○ No ○ Unknown
Spleen size:	_____ cm ○ Unknown
If applicable;	
MRI scan	
PVAS (radiological interpretation):	○ Yes ○ No ○ Unknown
PVT (radiological interpretation):	○ Yes ○ No ○ Unknown
Cavernous transformation portal vein:	○ Yes ○ No ○ Unknown
Anastomosis diameter:	_____ mm ○ Unknown
Splenomegaly:	○ Yes ○ No ○ Unknown
Spleen size:	_____ cm ○ Unknown
If applicable;	
Transient elastography (Fibroscan)	
Liver stiffness:	_____ kPa ○ Unknown
Spleen stiffness:	_____ kPa ○ Unknown

CRF 2.2 TREATMENT INFORMATION

Treatment type:	○ None, conservative with monitoring ○ PTA of portal vein anastomosis ○ PTA/stent of portal vein anastomosis ○ Mesorex bypass (MRB) ○ PTA of MRB anastomosis ○ PTA/stent of MRB anastomosis ○ Endovascular recanalization portal vein with PTA ○ Endovascular recanalization portal vein with PTA/stent ○ Splenic arterial embolism ○ Splenectomy ○ Other intervention(s) (text): _____
Endovascular specific treatment details	
Access endovascular intervention *(more than one answer is possible)*:	○ Trans-splenic ○ Trans-hepatic ○ Trans-mesenteric ○ Unknown
Pre-interventional pressure gradient stenosis:	_____ mmHg ○ Unknown
If applicable; Portal vein anastomosis stenosis:	PTA performed: ○ Yes ○ No Stent inserted: ○ Yes ○ No Post-interventional pressure gradient: _____ mmHg ○ Unknown
If applicable; PTA protocol How many dilatations in one treatment session?	○ 1 dilatation Balloon size used: _____ mm ○ Unknown Duration dilatation: _____ min ○ Unknown ○ 2 dilatations Balloon size used: _____ mm ○ Unknown Duration dilatation: _____ min ○ Unknown ○ 3 dilatations

	Balloon size used: _____ mm ○ Unknown Duration dilatation: _____ min ○ Unknown ○ More (please specify)
Embolization of collaterals	○ Yes ○ No
If applicable; Stent placement	Type stent: ○ Self-expandable ○ Balloon expandable ○ Unknown Stent manufacturer & type: _____ ○ Unknown Diameter: _____ mm ○ Unknown Length: _____ mm ○ Unknown
Embolization of collaterals	○ Yes ○ No
If applicable; Portal vein thrombosis:	Access endovascular intervention *(more than one answer is possible)*: ○ Trans-splenic ○ Trans-hepatic ○ Trans-mesenteric ○ Unknown Length recanalization: _____ cm ○ Unknown PTA performed: ○ Yes ○ No Stent inserted: ○ Yes ○ No Post-interventional pressure gradient: _____ mmHg ○ Unknown
If applicable; PTA protocol How many dilatations in one treatment session?	○ 1 dilatation Balloon size used: _____ mm ○ Unknown Duration dilatation: _____ min ○ Unknown ○ 2 dilatations Balloon size used: _____ mm ○ Unknown Duration dilatation: _____ min ○ Unknown ○ 3 dilatations Balloon size used: _____ mm ○ Unknown

	Duration dilatation: _____ min ○ Unknown ○ More (please specify)
Embolization of collaterals	○ Yes ○ No
If applicable; Stent placement	Type stent: ○ Self-expandable ○ Balloon expandable ○ Unknown Stent manufacturer & type: _____ ○ Unknown Diameter: _____ mm ○ Unknown Length: _____ mm ○ Unknown
Embolization of collaterals	○ Yes ○ No
Mesorex bypass preparation details	
Balloon occlusion portography performed:	○ Yes ○ No ○ Unknown
Liver biopsy performed:	○ Yes ○ No ○ Unknown
Are you willing to share the liver biopsy data?	○ Yes ○ No
Mesorex bypass specific treatment details	
Venous graft used:	○ Yes ○ No ○ Unknown
Prosthetic graft used:	○ Yes ○ No ○ Unknown
Location of venous graft:	○ Internal jugular vein ○ Iliac vein ○ Femoral vein ○ Saphenous vein ○ Other (please specify): _____ ○ Unknown
Type of venous graft:	○ Auto graft (patients' own venous graft) ○ Matched living donor (same as living liver donor) ○ Unmatched living donor (unmatched to living liver donor) ○ Matched deceased donor (same donor as deceased liver donor)

	○ Unmatched deceased donor (unmatched to deceased liver donor) ○ Unknown
Intraprocedural anticoagulation	
Intraprocedural anticoagulation:	○ Yes ○ No ○ Unknown
Unfractionated Heparin used:	○ Yes ○ No ○ Unknown
If yes; Dosage:	○ 50 IU/kg ○75IU/kg ○ 100 IU/kg ○ Other (please specify): _____ ○ Unknown
If no; please specify other intraprocedural anticoagulation	○ LMWH prophylactic dose ○ LMWH therapeutic dose ○ Other (please specify): _____ ○ Unknown
Postinterventional anticoagulation	
Postinterventional anticoagulation:	○ Yes ○ No ○ Unknown
How many types of anticoagulation?	○ 1 ○ 2 ○ 3 *Please specify in time sequence* ○ Unknown
If applicable; Anticoagulation 1: Sort:	○ Unfractionated Heparin ○ LMWH heparin prophylactic dose ○ LMWH therapeutic dose ○ Vitamin K antagonist ○ Acetylsalicylic acid ○ Other (please specify): _____ ○ Unknown
Duration:	○ Temporally ○ Lifelong ○ Unknown *If temporally;* please specify duration: _____ weeks/months/years ○ Unknown
Target level anticoagulation available?	○ Yes ○ No ○ Unknown *If applicable;* target INR: _____ ○ Unknown *If applicable;* anti-Xa: _____ U/ml ○ Unknown

If applicable; Anticoagulation 2:	
Sort:	○ Unfractionated Heparin ○ LMWH heparin prophylactic dose ○ LMWH therapeutic dose ○ Vitamin K antagonist ○ Acetylsalicylic acid ○ Other (please specify): _____ ○ Unknown
Duration:	○ Temporally ○ Lifelong ○ Unknown *If temporally;* please specify duration: _____ weeks/months/years ○ Unknown
Target level anticoagulation available?	○ Yes ○ No ○ Unknown *If applicable;* target INR: _____ ○ Unknown *If applicable;* anti-Xa: _____ U/ml ○ Unknown
If applicable; Anticoagulation 3:	
Sort:	○ Unfractionated Heparin ○ LMWH heparin prophylactic dose ○ LMWH therapeutic dose ○ Vitamin K antagonist ○ Acetylsalicylic acid ○ Other (please specify): _____ ○ Unknown
Duration:	○ Temporally ○ Lifelong ○ Unknown *If temporally;* please specify duration: _____ weeks/months/years ○ Unknown
Target level anticoagulation available?	○ Yes ○ No ○ Unknown *If applicable;* target INR: _____ ○ Unknown *If applicable;* anti-Xa: _____ U/ml ○ Unknown

FOLLOW-UP CRF

Direct post-procedural, up to two weeks (short term)	
Which modality do you use for radiological follow-up for this intervention *(more than one answer is possible)*?	○ DUS ○ CT ○ MRI ○ Transient elastography ○ Other (please specify): _____ ○ Unknown
If DUS; please specify last DUS within 2 weeks after intervention: Anastomotic velocity: Pre-anastomotic velocity: Post-anastomotic velocity:	 _____ cm/s ○ Unknown _____ cm/s ○ Unknown _____ cm/s ○ Unknown
If transient elastography; please specify last transient elastography within 2 weeks after intervention: Liver stiffness: Spleen stiffness:	 _____ kPa ○ Unknown _____ kPa ○ Unknown
Platelet count, last number within 2 weeks after intervention:	_____ ○ Unknown
Postinterventional complications	
Type:	○ Infection ○ Thrombosis ○ Bleeding
If thrombosis; Intervention performed ? *If yes;* Date/age intervention: Type intervention: Technical success:	 ○ Yes ○ No ○ Unknown __/__/_____, _____ ○ Interventional thrombolysis ○ Interventional thrombectomy ○ Surgical thrombectomy ○ Other (please specify): _____ ○ Unknown ○ Yes ○ No ○ Unknown

Postprocedural, after to two weeks of intervention (long term)	
Which modality do you use for follow-up for this intervention *(more than one answer is possible)*?	○ DUS ○ CT ○ MRI ○ Transient elastography ○ Other (please specify): _____ ○ Unknown
Severe PVO complications	
Severe complications of PVO after intervention:	○ Yes ○ No ○ Unknown
Which complications *(more than one answer is possible)*?	○ Ascites ○ Gastrointestinal bleeding ○ Hepatic encephalopathy (any grade) ○ Hepatopulmonary syndrome ○ Portopulmonary hypertension
Date/age first severe complication of PVO after intervention:	__/__/_____, _____

PORTAL Registry

Portal vein Obstruction Revascularisation Therapy After Liver transplantation

Site Specific Information Form

Part I: Current Management Practice

Version 1.4, March 2022

Investigator name:_____

Please complete all forms as fully as possible.

Thank you for your cooperation.

Kind regards,

The PORTAL Registry team

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Experience of centers	
Since when does the liver transplantation program start?	__/__/_____
Since when does the living donor liver transplantation program start?	__/__/_____
Is a preventive portoplasty a standard procedure for a hypoplastic portal vein? *If yes;* when was the first performed?	○ Yes ○ No __/__/_____
Is a PTA a standard procedure? *If yes;* when was the first performed?	○ Yes ○ No __/__/_____
Is a stent placement a standard procedure? *If yes;* when was the first performed?	○ Yes ○ No __/__/_____
Is a MRB a standard procedure? *If yes;* when was the first performed?	○ Yes ○ No __/__/_____
Current composition of the team	
How many pediatric gastroenterologists-hepatologists who are responsible for the management of pediatric liver transplantation patients?	_____
How many pediatric radiologists who are responsible for the radiological management of pediatric liver transplantation patients?	_____
How many interventional radiologists who perform the procedures on children after liver transplantation (PTA/stent)?	_____
How many Hepato-Pancreato-Biliary surgeons who are responsible for the surgical management of pediatric liver transplantation patients?	_____
How many Hepato-Pancreato-Biliary surgeons who perform MRBs in children after liver transplantation?	_____
Current structure of the care	

Do you have a specialized team for PVO and other vascular problems after liver transplantation?	○ Yes ○ No
If yes; who is part of the team?	
Pediatric gastroenterologists-hepatologists:	○ Yes ○ No
Pediatric radiologists:	○ Yes ○ No
Interventional radiologists:	○ Yes ○ No
Hepato-Pancreato-Biliary surgeons:	○ Yes ○ No
Other (please specify):	_____
Do you have a specialized multi-disciplinary meeting for PVO and other vascular problems after liver transplantation?	○ Yes ○ No
If yes; who is part of the team?	
Pediatric gastroenterologists-hepatologists:	○ Yes ○ No
Pediatric radiologists:	○ Yes ○ No
Interventional radiologists:	○ Yes ○ No
Hepato-Pancreato-Biliary surgeons:	○ Yes ○ No
Other (please specify):	_____
Do you have a protocol for the care of patients with a PVO?	○ Yes ○ No
If yes; does it contain the following topics?	
Screening:	○ Yes ○ No
Diagnosis:	○ Yes ○ No
Indication for treatment:	○ Yes ○ No
Treatment:	○ Yes ○ No
Postprocedural care:	○ Yes ○ No
Is your center willing to share their protocol?	○ Yes ○ No
Screening	
What is/are the current radiological investigation(s) for screening for PVO in the outpatient department *(multiple answers are possible)*?	○ Doppler ultrasound (DUS) ○ CT scan ○ Transient Elastography (TE) ○ Other (please specify):_____

Is the PVO screening for patients with PVO risk factors similar to patients without PVO risk factors?	○ Yes ○ No
If yes; What is the current timing of the preferred radiological screening investigation in the outpatient department *(multiple answers are possible)*?	○ 3 months after transplantation ○ 6 months after transplantation ○ 9 months after transplantation ○ 1 year after transplantation ○ 2 years after transplantation ○ 3 years after transplantation ○ 4 years after transplantation ○ 5 years after transplantation ○ 6 years after transplantation ○ 7 years after transplantation ○ 8 years after transplantation ○ 9 years after transplantation ○ 10 years after transplantation ○ 11 years after transplantation ○ 12 years after transplantation ○ 13 years after transplantation ○ 14 years after transplantation ○ 15 years after transplantation ○ 16 years after transplantation ○ 17 years after transplantation ○ 18 years after transplantation ○ other
If no; what kind of risk factors do you use *(multiple answers are possible)*?	○ Biliary atresia ○ Living related liver transplantation ○ Venous jump/interposition graft portal vein ○ Age liver transplantation <1 year ○ Surgical intervention portal vein within 30 days after liver transplantation (thrombectomy, new anastomosis, reposition of vessel(s)) ○ other:
If no;	○ 3 months after transplantation

What is the current timing of the preferred radiological screening investigation in the outpatient department in patients with PVO risk factors *(multiple answers are possible)*?	○ 6 months after transplantation ○ 9 months after transplantation ○ 1 year after transplantation ○ 2 years after transplantation ○ 3 years after transplantation ○ 4 years after transplantation ○ 5 years after transplantation ○ 6 years after transplantation ○ 7 years after transplantation ○ 8 years after transplantation ○ 9 years after transplantation ○ 10 years after transplantation ○ 11 years after transplantation ○ 12 years after transplantation ○ 13 years after transplantation ○ 14 years after transplantation ○ 15 years after transplantation ○ 16 years after transplantation ○ 17 years after transplantation ○ 18 years after transplantation ○ other
If no; What is the current timing of the preferred radiological screening investigation in the outpatient department in patients without PVO risk factors *(multiple answers are possible)*?	○ 3 months after transplantation ○ 6 months after transplantation ○ 9 months after transplantation ○ 1 year after transplantation ○ 2 years after transplantation ○ 3 years after transplantation ○ 4 years after transplantation ○ 5 years after transplantation ○ 6 years after transplantation ○ 7 years after transplantation ○ 8 years after transplantation ○ 9 years after transplantation ○ 10 years after transplantation ○ 11 years after transplantation

	○ 12 years after transplantation ○ 13 years after transplantation ○ 14 years after transplantation ○ 15 years after transplantation ○ 16 years after transplantation ○ 17 years after transplantation ○ 18 years after transplantation ○ other
Assessment criteria	
What is your center's non-invasive radiological criteria to determine stenosis of the portal vein anastomosis? Please report the following: • Preferred radiological investigation(s) • Radiological criteria and radiological cut-off values *(with a reference if applicable)*	
Preferred radiological investigation(s):	○ Doppler ultrasound (DUS) ○ CT scan ○ Transient Elastography (TE) ○ Other (please specify):_____
Non-invasive radiological criteria and cut-off values *(with a reference if applicable)*:	*If applicable*; **DUS:** Pre-anastomotic velocity: ○ Yes ○ N/A *If yes;* cut-off value: _____ cm/s Post-anastomotic velocity: ○ Yes ○ N/A *If yes;* cut-off value: _____ cm/s Anastomotic velocity: ○ Yes ○ N/A *If yes;* cut-off value: _____ cm/s Anastomotic-to-pre-anastomotic velocity ratio: ○ Yes ○ N/A *If yes;* cut-off value: _____ Anastomotic diameter:

	○ Yes ○ N/A *If yes;* cut-off value: _____ mm Presence of turbulence: ○ Yes ○ N/A *If applicable*; **CT scan:** Anastomotic diameter: ○ Yes ○ N/A *If yes;* cut-off value: _____ mm Presence of collaterals: ○ Yes ○ N/A Presence of cavernoma: ○ Yes ○ N/A *If applicable*; **TE/SWE:** Liver stiffness: ○ Yes ○ N/A *If yes;* cut-off value: _____ kPa Spleen stiffness: ○ Yes ○ N/A *If yes;* cut-off value: _____ kPa
What is your center's interventional radiological criteria to determine stenosis of the portal vein anastomosis during an invasive portography? Please report the following: • Radiological criteria and radiological cut-off values *(with a reference if applicable)*:	
Interventional radiological criteria and cut-off values *(with a reference if applicable)*:	Pressure gradient anastomosis: ○ Yes ○ N/A *If yes;* cut-off value: <_____ mmHg Visual aspect anastomosis: ○ Yes ○ N/A *If yes;* cut-off value: _____ %

How does your center define technical success after interventional radiological treatment? Please report the following: • Radiological criteria and radiological cut-off values *(with a reference if applicable)*:	
Radiological criteria and radiological cut-off values *(with a reference if applicable)*:	Pressure gradient anastomosis: ○ Yes ○ N/A *If yes;* cut-off value: <_____ mmHg Drop in pressure gradient (%) from baseline: ○ Yes ○ N/A *If yes;* cut-off value: _____ % Residual venographic stenosis (%): ○ Yes ○ N/A *If yes;* cut-off value: _____ %
Postprocedural care	
PTA	
How many types of anticoagulation?	○ 1 ○ 2 ○ 3
Anticoagulation 1:	○ DOAC *If chosen;* please specify type:_____ ○ Unfractionated Heparin ○ LMWH prophylactic dose ○ LMWH therapeutic dose ○ Vitamin K antagonist ○ Acetylsalicylic acid ○ Other (please specify):_____
Duration anticoagulation 1:	○ Temporally ○ Lifelong ○ Unknown *If temporally;* please specify duration: ___ weeks/months/years
Therapeutic range anticoagulation 1:	INR: _____ anti-Xa: _____U/ml
Anticoagulation 2 *(if applicable)*:	○ DOAC *If chosen;* please specify type:_____ ○ Unfractionated Heparin

	○ LMWH prophylactic dose ○ LMWH therapeutic dose ○ Vitamin K antagonist ○ Acetylsalicylic acid ○ Other (please specify):_____
Duration anticoagulation 2:	○ Temporally ○ Lifelong ○ Unknown *If temporally;* please specify duration: ___ weeks/months/years
Therapeutic range anticoagulation 2:	INR: _____ anti-Xa: _____U/ml
Anticoagulation 3 *(if applicable)*:	○ DOAC *If chosen;* please specify type:_____ ○ Unfractionated Heparin ○ LMWH prophylactic dose ○ LMWH therapeutic dose ○ Vitamin K antagonist ○ Acetylsalicylic acid ○ Other (please specify):_____
Duration anticoagulation 3:	○ Temporally ○ Lifelong ○ Unknown *If temporally;* please specify duration: ___ weeks/months/years
Therapeutic range anticoagulation 3:	INR: _____ anti-Xa: _____U/ml
PTA/stent	
How many types of anticoagulation?	○ 1 ○ 2 ○ 3
Anticoagulation 1:	○ DOAC *If chosen;* please specify type:_____ ○ Unfractionated Heparin ○ LMWH prophylactic dose ○ LMWH therapeutic dose ○ Vitamin K antagonist ○ Acetylsalicylic acid

	○ Other (please specify):_________
Duration anticoagulation 1:	○ Temporally ○ Lifelong ○ Unknown *If temporally;* please specify duration: ___ weeks/months/years
Therapeutic range anticoagulation 1:	INR: _____ anti-Xa: _____U/ml
Anticoagulation 2 *(if applicable)*:	○ DOAC *If chosen;* please specify type:_____ ○ Unfractionated Heparin ○ LMWH prophylactic dose ○ LMWH therapeutic dose ○ Vitamin K antagonist ○ Acetylsalicylic acid ○ Other (please specify):_____
Duration anticoagulation 2:	○ Temporally ○ Lifelong ○ Unknown *If temporally;* please specify duration: ___ weeks/months/years
Therapeutic range anticoagulation 2:	INR: _____ anti-Xa: _____U/ml
Anticoagulation 3 *(if applicable)*:	○ DOAC *If chosen;* please specify type:_____ ○ Unfractionated Heparin ○ LMWH prophylactic dose ○ LMWH therapeutic dose ○ Vitamin K antagonist ○ Acetylsalicylic acid ○ Other (please specify):_____
Duration anticoagulation 3:	○ Temporally ○ Lifelong ○ Unknown *If temporally;* please specify duration: ___ weeks/months/years
Therapeutic range anticoagulation 3:	INR: _____

	anti-Xa: _____U/ml
MRB	
How many types of anticoagulation?	○ 1 ○ 2 ○ 3
Anticoagulation 1:	○ DOAC *If chosen;* please specify type:_____ ○ Unfractionated Heparin ○ LMWH prophylactic dose ○ LMWH therapeutic dose ○ Vitamin K antagonist ○ Acetylsalicylic acid ○ Other (please specify):_____
Duration anticoagulation 1:	○ Temporally ○ Lifelong ○ Unknown *If temporally;* please specify duration: ___ weeks/months/years
Therapeutic range anticoagulation 1:	INR: _____ anti-Xa: _____U/ml
Anticoagulation 2 *(if applicable)*:	○ DOAC *If chosen;* please specify type:_____ ○ Unfractionated Heparin ○ LMWH prophylactic dose ○ LMWH therapeutic dose ○ Vitamin K antagonist ○ Acetylsalicylic acid ○ Other (please specify):_____
Duration anticoagulation 2:	○ Temporally ○ Lifelong ○ Unknown *If temporally;* please specify duration: ___ weeks/months/years
Therapeutic range anticoagulation 2:	INR: _____ anti-Xa: _____U/ml
Anticoagulation 3 *(if applicable)*:	○ DOAC *If chosen;* please specify type:_____ ○ Unfractionated Heparin

Duration anticoagulation 3: Therapeutic range anticoagulation 3:	○ LMWH prophylactic dose ○ LMWH therapeutic dose ○ Vitamin K antagonist ○ Acetylsalicylic acid ○ Other (please specify):_____ ○ Temporally ○ Lifelong ○ Unknown *If temporally;* please specify duration: ___ weeks/months/years INR: _____ anti-Xa: _____U/ml
Radiological follow-up after treatment	
Is the radiological follow-up after all PVO interventions (PTA, PTA/stent, MRB) the same?	○ Yes (please fill in the radiological follow-up at all interventions) ○ No (please fill in the radiological follow-up for every intervention specific below)
All interventions	
Which modality do you use for follow-up *(more than one answer is possible)*?	○ DUS ○ CT ○ MRI ○ Transient elastography ○ Other (please specify): _____
How often is radiological follow-up carried out? *(more than one answer is possible)*?	○ 3 months after intervention ○ 6 months after intervention ○ 9 months after intervention ○ 1 year after intervention ○ 2 years after transplantation ○ 3 years after transplantation ○ 4 years after transplantation ○ 5 years after transplantation ○ 6 years after transplantation ○ 7 years after transplantation ○ 8 years after transplantation ○ 9 years after transplantation

	○ 10 years after transplantation ○ 11 years after transplantation ○ 12 years after transplantation ○ 13 years after transplantation ○ 14 years after transplantation ○ 15 years after transplantation ○ 16 years after transplantation ○ 17 years after transplantation ○ 18 years after transplantation ○ Other (please specify): _____
PTA	
Which modality do you use for follow-up *(more than one answer is possible)*?	○ DUS ○ CT ○ MRI ○ Transient elastography ○ Other (please specify): _____
How often is radiological follow-up carried out? *(more than one answer is possible)*?	○ 3 months after intervention ○ 6 months after intervention ○ 9 months after intervention ○ 1 year after intervention ○ 2 years after transplantation ○ 3 years after transplantation ○ 4 years after transplantation ○ 5 years after transplantation ○ 6 years after transplantation ○ 7 years after transplantation ○ 8 years after transplantation ○ 9 years after transplantation ○ 10 years after transplantation ○ 11 years after transplantation ○ 12 years after transplantation ○ 13 years after transplantation ○ 14 years after transplantation ○ 15 years after transplantation

	○ 16 years after transplantation ○ 17 years after transplantation ○ 18 years after transplantation ○ Other (please specify): _____
PTA/ stent	
Which modality do you use for follow-up *(more than one answer is possible)*?	○ DUS ○ CT ○ MRI ○ Transient elastography ○ Other (please specify): _____
How often is radiological follow-up carried out? *(more than one answer is possible)*?	○ 3 months after intervention ○ 6 months after intervention ○ 9 months after intervention ○ 1 year after intervention ○ 2 years after transplantation ○ 3 years after transplantation ○ 4 years after transplantation ○ 5 years after transplantation ○ 6 years after transplantation ○ 7 years after transplantation ○ 8 years after transplantation ○ 9 years after transplantation ○ 10 years after transplantation ○ 11 years after transplantation ○ 12 years after transplantation ○ 13 years after transplantation ○ 14 years after transplantation ○ 15 years after transplantation ○ 16 years after transplantation ○ 17 years after transplantation ○ 18 years after transplantation ○ Other (please specify): _____
MRB	

Which modality do you use for follow-up *(more than one answer is possible)*?	○ DUS ○ CT ○ MRI ○ Transient elastography ○ Other (please specify): _____
How often is radiological follow-up carried out? *(more than one answer is possible)*?	○ 3 months after intervention ○ 6 months after intervention ○ 9 months after intervention ○ 1 year after intervention ○ 2 years after transplantation ○ 3 years after transplantation ○ 4 years after transplantation ○ 5 years after transplantation ○ 6 years after transplantation ○ 7 years after transplantation ○ 8 years after transplantation ○ 9 years after transplantation ○ 10 years after transplantation ○ 11 years after transplantation ○ 12 years after transplantation ○ 13 years after transplantation ○ 14 years after transplantation ○ 15 years after transplantation ○ 16 years after transplantation ○ 17 years after transplantation ○ 18 years after transplantation ○ Other (please specify): _____

PORTAL Registry

Portal vein Obstruction Revascularisation Therapy After Liver transplantation

Site Specific Information Form

Part II: Prevalence Study

Version 1.4, March 2022

Investigator name:_____

Please complete all forms as fully as possible.

Thank you for your cooperation.

Kind regards,

The PORTAL Registry team

Bader A. M. Alfares, coordinating researcher

Hubert P. J. van der Doef & Reinoud P.H. Bokkers, principle investigators

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Prevalence				
From which period do you start inclusion for the prevalence study?	○ 01/01/2001 ○ Other (please specify): __/__/_____			
From which period do you start inclusion diagnosed PVO patients?	○ 01/01/2001 ○ Other (please specify): __/__/_____			
How many paediatric liver transplantations (LT) were performed since start inclusion? *Please include number of transplantations within different groups and time periods:*	Date of LT: 01/01/2001 - 01/01/2006	Date of LT: 01/01/2006 - 01/01/2011	Date of LT: 01/01/2011 - 01/01/2016	Date of LT: 01/01/2016 - 01/01/2020
All				
Biliary atresia				
Living donor liver transplantation				
Age at liver transplantation <2 years				
Age at liver transplantation <1 year				
Age at liver transplantation <1 year AND Living donor liver transplantation AND Biliary atresia				
Age at liver transplantation <1 year AND Deceased donor liver transplantation AND Biliary atresia				

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

Section/item	Item No	Description
Administrative information		
Title	1	PORTAL registry is a multicentre, retrospective, observational registry of patients who underwent liver transplantation and were diagnosed and treated for PVO at age <18 years
Trial registration	2a	The PORTAL registry is registered in the Netherlands Trial Register (NL9261). Registration date: 28-02-2021. Website: www.trialregister.nl
	2b	Appendix I
Protocol version	3	Issue date: 12 January 2021 Protocol amendment number: 4 Authors: BA, RB, HVD
Funding	4	N.A.
Roles and responsibilities	5a	All authors were actively involved in this study design and read and approved the final manuscript. BA, HVD and RB designed the original study protocol and initiated the study.
	5b	Trial Sponsor: University Medical Centre Groningen, Groningen, The Netherlands Reinoud P.H. Bokkers, MD PhD EBIR University Medical Centre Groningen (UMCG) Department of Radiology, Medical Imaging Centre Hanzeplein 1, 9721 GZ Groningen, the Netherlands Email: r.p.h.bokkers@umcg.nl Phone: +31-50-3616161

5c This sponsor source had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results

5d **Principal investigators and coordinating researcher**
Design and conduct of PORTAL registry
Preparation of protocol and revisions
Preparation of PORTAL registry-related items: site specific information form, case report form, and e-crf guidelines
Managing correspondence with collaborating centres
Publication of study reports

Lead investigators
In each participating centre, a lead investigator ((interventional) radiologist, paediatric hepatologist, and liver-transplant surgeon) will be identified, to be responsible for identification, recruitment, data collection and completion of (e)CRFs, along with follow up of study patients and adherence to study protocol and investigators brochure. One investigator per country will be chosen as a national coordinator

Project management office
Assistance with administrative issues
Data verification
Advice for Principal investigators and coordinating researcher

Medical Ethics Review Committee (METc in Dutch)
Agreement of final protocol and amendments (if applicable)

Contract Research Desk
Agreement of final clinical site agreement

Introduction

Background and rationale	6a	**Background:** Liver transplantation is the standard care for patients with end-stage liver disease, metabolic liver diseases, and acute liver failure. Despite marked improvements in operating techniques, vascular complications, and especially portal vein obstruction (PVO), occur frequently after paediatric liver transplantation. Prevalence numbers in the literature differ from 8-12%, which is probably related to the distribution of the risk factors (young age at liver transplantation, biliary atresia, living related liver transplantation) within the investigated population and small sample size (only single centre data is reported) **Rationale:** The PORTAL registry study will gather one of the largest international data sets on the characteristics of PVO in regard to current management practice, prevalence numbers, and efficacy of the individual treatments. Given the fact that the current data are only single-centre studies which do not have the adequate numbers to be able to give answers to such important questions on who, when and how to treat patients with PVO after liver transplantation. Therefore, PORTAL registry will be one of the first multicentre studies to analyze the diagnostic and therapeutic characteristics of PVO after paediatric liver transplantation to inform future quality of care initiatives for this group of patients which is regarded to be the only feasible strategy to obtain more insights on prevalence of PVO, and long-term efficacy of the individual PVO treatments in paediatric patients after liver transplantation
	6b	N.A.
Objectives	7	The objectives of this study are to assess the efficacy of the individual treatments for portal vein obstruction (PVO) after paediatric liver transplantation, the prevalence numbers of PVO, and the current management practice
Trial design	8	This is an international, multi-centre, retrospective, observational registry study

Methods: Participants, interventions, and outcomes

Study setting	9	PORTAL registry is a multicentre, retrospective, observational registry of patients who underwent liver transplantation and were diagnosed and treated for PVO. List of countries where data will be collected can be found in https://portalregistry.eu/
Eligibility criteria	10	The study aims to include approximately 400 paediatric patients. Patients will be included if the following inclusion criteria are present: 1. Treated for PVO (PVAS or PVT) after liver transplantation (all interventions are included and conservative treatment as well) 2. Age at intervention <18 years 3. Intervention in period 01-01-2001 and 01-01-2021 **Investigator requirements:** All Investigators must submit the following documentation to be considered approved investigators: 1. Signed and dated recent curriculum vitae 2. Signed Clinical Study Agreement (CSA) 3. Complete site qualification process and site initiation
Interventions	11a	N.A.
	11b	N.A.
	11c	N.A.
	11d	N.A.

Outcomes	12	**Primary outcome measures:** • Patency 1) Primary patency is defined from index procedure to treat stenosis or occlusion to time to re-stenosis or re-occlusion. Primary patency ends when either re-stenosis or re-occlusion occur for the first time post intervention 2) Secondary patency is from index procedure to time of failure to re-establish flow following re-occlusion. Secondary patency ends once re-occlusion cannot be or is not treated • Prevalence numbers The prevalence of PVO will be calculated as the total PVO patients divided by the total of transplanted patients at paediatric age. The total transplanted patients will be calculated from patients with one year follow-up and date of transplantation between 01-01-2000 and 01-01-2020, as a large proportion of the PVO occurs in the first year after liver transplantation **Secondary outcomes:** o Patient and graft survival Patient survival is defined from date of PVO intervention until date of death. Patients who are alive at the end of the follow-up will be censored. Graft survival is defined from date of PVO intervention until date of re-transplantation or death. Patients who are alive without a re-transplantation at the end of the follow-up will be censored. o Freedom of severe PVO complications Severe PVO complications are defined as severe signs of portal hypertension (ascites, gastrointestinal bleeding) or porto-systemic shunting (any grade of hepatic encephalopathy, hepatopulmonary syndrome, portopulmonary hypertension). This will be determined following each intervention until end of the follow-up o Technical success Technical success is defined as the success of the intervention during the procedure (re-establishment of portal flow, without residual stenosis) and is based on the assessment of the centre itself
Participant timeline	13	The data on prevalence numbers and efficacy of the treatments protocols are expected to be finalized in September 2022. Regarding data on current management practice, we aim to receive the paper-bases questionnaire in March 2022. Once the trial master file is completed by a participating centre, a virtual site initiation visit will be planned to discuss the study and to initiate the project officially
Sample size	14	We are expected that the study will consists of 400 paediatric patients

Recruitment	15	Clinical site personnel will collect the data and enter it in REDCap database as well as paper-based clinical site information form by local research personnel. Subject records will be pseudo-anonymized by means of allocating each subject with a unique study number

~~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~~
~~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~~
~~Implementation~~	~~16c~~	~~Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions~~
~~Blinding (masking)~~	~~17a~~	~~Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how~~
	~~17b~~	~~If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial~~

Methods: Data collection, management, and analysis

Data collection methods	18a	A single questionnaire (Site Specific Information Form) is provided to acquire data on the prevalence and current management practice. Within this questionnaire, we will request the amount of transplanted patients within the total paediatric group and in subgroups based on time of transplantation, age at transplantation, underlying disease (biliary atresia) and donor type (living or deceased liver donor). Moreover, within this questionnaire, data on experience of the centres, multidisciplinary team, structure of care, screening protocol, and assessment criteria will be obtained. Data on efficacy of the individual portal vein revascularisation treatments will be registered in REDCap database (https://redcap.umcg.nl). Within the REDCap database, patients treated for PVO (PVAS or PVT) after liver transplantation are included with an age at intervention of <18 years). Inclusion period is within the last 20 years from 1-1-2001 until 1-1-2021
	18b	N.A.
Data management	19	Clinical site personnel will collect the data and enter it in REDCap database as well as paper-based clinical site information form by local research personnel. Subject records will be pseudo-anonymized by means of allocating each subject with a unique study number. The local investigators will keep a list with the subject names, date of birth, local ID, and unique study number. Data will be stored by the local investigators and coordinating centre for 15 years after termination of the study. All data and records generated during this study will be kept in accordance with institutional policies regarding subject privacy and the data and records of all patients will not be used for any purpose other than conducting this study
Statistical methods	20a	All data analyses will be performed by using IBM SPSS Statistics version 26. Descriptive statistics will be applied using the mean and standard deviation for variables with normal distribution, and median and interquartile ranges (IQR) for variables with skewed distribution. Dichotomous variables will be compared with the Chi-square test or the Fisher exact test or both. Continuous variables will be compared with the Mann-Whitney U test. For the analysis of the primary and secondary patency, freedom of severe PVO complications and patient and graft survival, the Kaplan-Meier test will used. P-values less than 0.05 will be considered statistically significant
	20b	N.A.
	20c	N.A.

Methods: Monitoring

Data monitoring	21a	To the extent applicable, the Site Parties shall permit the Study Monitor, Auditor, IRB and any official with a legal right to inspect and access all relevant documentation and Patient Data for monitoring of the progress of the Clinical Study, the proper collection and recording of Clinical Data, and altogether the good quality of the Clinical Study and compliance with applicable Law. Parties will make in good faith arrangements concerning the planning and follow-up of such audits or inspections. For the avoidance of doubt, no copying of the Patient Data is permissible and any access to the Patient Data shall be arranged for in the premises of the Study Site
	21b	N.A.
Harms	22	Due to the retrospective nature of the study, the risks of participation are minimal, and this study will not influence the on-going diagnostics and treatment of the included patients. Adverse events are not expected
Auditing	23	N.A.

Ethics and dissemination

Research ethics approval	24	Ethical approval has been obtained from the University Medical Centre Groningen's Institutional Review Board (METc 2021/072) prior to the start of the study
Protocol amendments	25	Any modifications to the protocol which may impact on the conduct of the study, potential benefit of the patient or may affect patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures, or significant administrative aspects will require a formal amendment to the protocol and therefore, IRB will be notified
Consent or assent	26a	If mandated by the local national laws, a waiver of informed consent will be requested governing the conduct of clinical research studies, and General Data Protection Regulation act. If a consent is claimed, the local investigator will assure that the consent forms are signed by study participants/their parents
	26b	N.A.

Confidentiality	27	All study-related information will be stored securely at the study site. All participant information will be stored in locked file in areas with limited access (only for authorized personnel). All reports, data collection, and administrative forms will be identified by a coded ID number only to maintain participant confidentiality. All records that contain names or other personal identifiers will be stored separately from study records identified by code number. All local databases will be secured with password-protected access systems. Forms, lists, logbooks, and any other listings that link participant ID numbers to other identifying information will be stored in a separate, locked file in an area with limited access
Declaration of interests	28	N.A.
Access to data	29	Only authorized personnel (project principal investigators and coordinating researcher) will have direct access to the data sets
Ancillary and post-trial care	30	N.A.
Dissemination policy	31a	The results of this study will be disseminated by publication of peer-reviewed manuscripts, presentation in an abstract form at scientific meetings, and data sharing with other researchers through academically-established means.
	31b	For each main paper, there are three co-author positions per centre available. Following the completion of the study, all collaborators can submit a proposal for a substudy
	31c	The outcome of this study will also be utilized to design an evidence-based, feasible therapeutic pathway for paediatric patients with portal vein complications following liver transplantation and implement this in an inter(national) guidelines

Appendices

Informed consent materials	32	N.A.
Biological specimens	33	N.A.

*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.