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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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ABSTRACT

Introduction Portal vein obstruction (PVO) consists of anastomotic stenosis and thrombosis, 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 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 revascularisation 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.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This will be the first global collaboration between paediatric hepatologists, interventional radiologists and liver transplant surgeons to provide valuable information on portal vein obstruction (PVO) management and prevalence.
⇒ The strength of the Portal vein Obstruction Revascularisation Therapy After Liver transplantation (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.

Trial registration number Netherlands Trial Register (NL9261).

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 the 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 vein Obstruction Revascularisation Therapy After Liver transplantation (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. First, it will assess the overall prevalence of PVO after paediatric liver transplantation, including taking into account various risk groups. Second, 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. Third, it also intends to assess the efficacy of the individual portal vein revascularisation 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 intrahepatic or posthepatic origin (ie, 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 standardised paper case-report form (online supplemental 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 with or without stent placement, endovascular recanalisation, splenic artery or varices/cavernoma embolisation) 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 (online supplemental 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 patients with PVO (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 patients who underwent transplantation 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 restenosis or reocclusion. Primary patency ends when either restenosis or reocclusion occurs for the first time after intervention. Primary patency will be represented as percentages at 1 year, 3 years, 5 years, 10 years, 15 years 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 reocclusion 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 year, 3 years, 5 years, 10 years, 15 years and 20 years after treatment for PVO.

Secondary outcomes

Patient and graft survival

Patient survival is defined as the period from the date of first PVO intervention until the 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 retransplantation or death. Patients who are alive without a retransplantation at the end of the follow-up will be censored. The decision to retransplant is based on an assessment by the individual centre. Causes of retransplantation or death will be recorded. Patient and graft survival will be determined as percentages at 1 year, 3 years, 5 years, 10 years, 15 years 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 portosystemic 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, assessment criteria and postprocedural follow-up intended to optimise patient care.

Data management

Subject records will be pseudo-anonymised 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 V.26. Descriptive statistics will be applied using the mean and SD for variables with normal distribution, and median and IQRs for variables with skewed distribution. Dichotomous variables will be compared using the χ^2 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 World Medical Association 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 Center Groningen's Institutional review board 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 used 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 standardised 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 postprocedural 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 prioritised fundamental questions such as PVO prevalence and treatment effectiveness. Following the NAtural Course and Prognosis of PFIC and Effect of Biliary Diversion (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 patients with PVO 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 centralised review—and including laboratory analysis to harmonise findings and guide future analysis.

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