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Doppler ultrasound values after liver transplantation in children and their association with graft outcomes: a protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction Liver graft and patient survival in children have improved substantially over the years; nevertheless, graft-related complications persist as the most important risk factor for mortality and graft loss. Doppler ultrasound evaluation is routinely used after liver transplantation; however, there is no consensus defining normal values, timing or frequency of Doppler ultrasound postoperative evaluation. Identification of patients who require an intervention or change in postoperative management is therefore challenging.

Methods and analysis We will conduct a systematic review and meta-analysis to appraise and synthesise evidence describing Doppler ultrasound measurements and their association with graft complications in children who have received a liver transplant. We will search multiple databases: Ovid Medline, Embase, Wiley Cochrane Library, Web of Science—Science Citation Index Expanded, trial registry records and meeting abstracts using a combination of subject headings and keywords for liver transplantation, Doppler ultrasound and paediatric patients. All identified titles and abstracts of studies will be assessed for potential relevance. Selected studies will be retrieved and subjected to a second phase of screening, both selection phases will be done in duplicate by two independent reviewers, and discrepancies will be documented and resolved by a third reviewer. Data extraction will be done independently by two reviewers using a standardised data extraction form. Quality of evidence and risk of bias will be assessed, synthesised and pooled for meta-analysis if possible. We will perform a subgroup analysis if enough data are available.

Ethics and dissemination Strategies to disseminate our review include presenting in liver transplant review sessions, publishing in high-impact peer-reviewed medical journals, and presenting at national and international paediatric radiology and liver transplant meetings, conference presentations, events, courses and plain-language summaries. This knowledge will allow easier identification of patients with a higher risk of developing graft-related complications and could potentially improve patient and graft outcomes. We wish to disseminate our results to discover potential areas for future research and drive improved future practices and policies. Our target audience includes researchers, institutions, healthcare professionals, health system decision-makers, policy-makers and research funders community.

Trial registration number CRD42019119986.

Strengths and limitations of this study

- In this systematic review, following PRISMA-P 2015 guidelines, we will include studies that review paediatric liver transplant recipients, Doppler parameters and graft outcomes.
- We will perform a comprehensive search in databases and other sources of grey literature without restriction on study design, publication year or language.
- We will perform a two-phase screening by two independent reviewers, initially reviewing title and abstracts, followed by a full-text screening.
- From the selected studies, we will extract data including Doppler parameters, patients' and transplant characteristics.
- After quality assessment, we will obtain pooled estimates for dichotomous and continuous Doppler ultrasound parameters and perform a subgroup analysis when possible.

INTRODUCTION

Liver transplantation is the only curative treatment for selected patients with end-stage liver disease. Children account for only 7.8% of all liver transplants,[1] mainly due to specific challenges, such as more complex surgeries and particular paediatric pre-existing liver conditions including congenital, metabolic and oncological diseases.[2 3] Advances in surgical and interventional techniques and postoperative care have improved patient and graft survival over the years.[4 5] Nonetheless, postoperative graft-related complications, especially

hepatic artery thrombosis, stenosis and biliary strictures, persist as the most important risk factors for increased morbidity, mortality and liver graft loss.[3 4 6]

Early detection and intervention of postoperative graft complications are crucial for improving graft and patient survival.[6] Fortunately, Doppler ultrasound has proven to be effective in both children and adults to detect and predict multiple graft-related complications such as early vascular thrombosis and acute graft rejection, even before patients develop clinical signs.[7–10]

Diagnostic accuracy, availability and safety of Doppler ultrasound has positioned it as the standard follow-up imaging study after liver transplantation. However, despite its widespread application, there is no consensus defining normal values, timing or frequency of Doppler ultrasound after liver transplantation, particularly for children.[8 11] The most commonly accepted normal values and thresholds are extracted either from studies in the adult population or from studies with mixed populations that did not clearly describe the values obtained from children.[12–15] Although some authors have proposed normal ranges for Doppler values of graft vasculature in children,[16 17] these values vary depending on demographic or graft-related characteristics and their relationship with graft complications is unclear.

These limitations result in challenges in using Doppler measurements to determine which patients require an intervention or change in postoperative management. In view of these limitations, we aim to conduct a systematic review and meta-analysis to appraise and synthesise the evidence describing Doppler ultrasound measurements and evaluate their association with graft complications in children who have received a liver transplant.

OBJECTIVES

- To define normal Doppler ultrasound values of the hepatic artery, portal vein and hepatic veins after liver transplantation in children according to timing post-transplant, and patient's characteristics.
- To describe associations between Doppler ultrasound values after paediatric liver transplantation and graft-related outcomes.

METHODS AND ANALYSIS

Study design

We will perform a systematic review and meta-analysis targeting studies involving Doppler ultrasound in children after liver transplantation and its utility assessing graft-related outcomes. Our protocol follows the format recommended by the PRISMA-P guidelines.[18]

Eligibility criteria

The selection criteria will be stated a priori. Included studies must meet all of the following criteria:

- Population: We will include studies enrolling children from birth to less than 18 years old who received any kind of orthotopic liver transplantation and were assessed postoperatively with a Doppler ultrasound. Studies including both adult and children will be included if they provide a separate description for values in paediatric participants.
- Intervention: Studies that report Doppler ultrasound–specific measurements (flow velocity, resistive index, pulsatility index or acceleration time) or spectral Doppler characteristic (waveform analysis) from any of the vascular structures of the liver graft (hepatic artery, portal vein or hepatic veins).
- Timing: Studies that report Doppler ultrasound evaluation from skin closure up to 1 year after liver transplantation, since after 1 year, graft survival tends to plateau at around 80% to 85% up to 5 years after liver transplantation.[5]
- Outcome: Studies that report at least one of the following outcomes:
  The normal Doppler values of the hepatic artery, portal vein and hepatic vein in children after liver transplantation.
  Graft-related outcomes characterised by clinical or surgical scales, graft survival and/or graft-related complications including any of the following:

Vascular complications: Hepatic artery thrombosis (early/late, partial/complete (occlusion)), hepatic artery stenosis, hepatic artery dehiscence, portal vein thrombosis, portal vein stenosis, portal vein leak/dehiscence, hepatic veins thrombosis, monophasic flow, hepatic vein stenosis.

Non-vascular complications: Graft rejection (acute/chronic), biliary necrosis, biliary stenosis/strictures, hepatic abscess, post-transplant lymphoproliferative disease (PTLD).

- Study design: We will include original studies incorporating interventional (randomised controlled trials or quasi-randomised controlled trials) and observational studies (cohort studies, case–control studies, cross-sectional studies, case series or case reports).

Exclusion criteria

Studies will be excluded for any of the following criteria:

- Studies that exclusively evaluate adult patients even if participants underwent liver transplantation during childhood, studies that do not specify age population or restrictions, and studies that include both adult and children but do not provide separate analysis for children.
- Studies that evaluate Doppler ultrasound in pretransplant, intraoperative or in non-transplant settings.
- Doppler ultrasound devices or techniques used only to prove patency without any measurements of vascular structures.
- Doppler ultrasound performed more than 1 year after liver transplantation, or do not specify the timing of Doppler ultrasound.
- Studies without original data: letters to the editor, commentaries, editorials, discussion paper, review articles.

- Studies that do not specify graft outcome, type of complication or timing to develop complications or studies that report only systemic or non-graft–related complications (sepsis, cytomegalovirus infection, pneumonia).

Search strategy

A research librarian will design and execute a systematic and comprehensive search with input from the research team. We will search the following electronic databases: Ovid Medline, Ovid Embase, Wiley Cochrane Library and Web of Science—Science Citation Index Expanded. The search strategy will combine subject headings (eg, MeSH) and keywords for liver transplantation, Doppler ultrasound and paediatric patients. We will exclude animal studies, but will not apply any additional limits for language or date of publication, up to 30 November 2018. We will also search for trial registry records via ClinicalTrials.gov and meeting abstracts via Conference Proceedings Citation Index database. Finally, we will manually search for relevant studies using reference lists of retrieved citations and prior reviews on the topic. Search results will be managed in EndNote X7, and duplicate records will be removed prior to screening (online supplementary appendix 1).

Data extraction (selection and coding)

All identified titles and abstracts of studies reporting the normal Doppler ultrasound values or examining the association between Doppler ultrasound and graft-related complications in children after liver transplantation will be assessed for potential relevance. Selected studies will be retrieved and subjected to a second phase of screening for eligibility, as determined by the eligibility criteria listed above. We will perform a pilot screening exercise of 10% of the database to refine eligibility criteria. The primary screening of all studies will be done independently by two reviewers, by reviewing the titles and abstracts. Disagreement will be resolved through discussion or by a third reviewer if necessary. The selected studies will then be read by two reviewers to exclude any study that do not meet eligibility criteria as specified above. The justification for ineligibility will be documented for excluded studies in the second phase of screening. Researchers will not be blinded for author or journal details during the study selection and/or data extraction.

A standardised data extraction form (online supplementary appendix 2) will be piloted and then used to extract data from the reports of all included studies by two reviewers. Concerns will be identified and resolved through discussion with another author where necessary, discrepancies in extracted data will be resolved by consensus, and if consensus cannot be reached, decisions will be left to the senior author.

Extracted data will include the following details:

- Study methodology
  - Study design
  - Sources of funding
  - Publication details
- Study population
  - Number of participants
  - Participant's demographics
  - Indication for transplantation (cholestatic disease, metabolic disease, acute liver, failure, other)
  - Type of liver transplantation
    - Type of graft: Whole or split
    - Type of donor: Cadaveric or living donor
    - Primary or re-transplantation
- Doppler ultrasound details (exposure)
  - Ultrasound equipment features
  - Vascular structure analysed (hepatic artery, portal vein or hepatic veins)
  - Doppler ultrasound measurements/values: Spectral Doppler characteristic (waveform), specific measurements (flow velocity, resistive index, pulsatility index, acceleration time)
  - Timing of Doppler ultrasound in relation to transplantation and number of measurements
- Outcomes
  - Graft outcome and survival time
  - Graft-related complication: Vascular and/or non-vascular

The main outcome is graft status after liver transplantation. Patients could either have an uncomplicated graft or develop any graft-related vascular and/or non-vascular complications. Vascular complications include stenosis, thrombosis, leaks, dissections and aneurysms. Non-vascular complications include graft rejection (acute/chronic), biliary necrosis, biliary stenosis/strictures, hepatic abscess and PTLD.

Risk of bias (quality) assessment

Included studies will be assessed by two independent reviewers for methodological quality and risk of bias. Any disagreement will be resolved through discussion with the senior author. Since studies evaluating Doppler ultrasound after liver transplantation in children are expected to be mostly observational in design, the Newcastle-Ottawa scale for cohort and case–control studies will be used.[19 20]

Strategy for data synthesis

The results of our search and final selection will be reported in a PRISMA flowchart. We will present tables describing included study characteristics, their corresponding risk of bias and their findings with their effect measures. Where possible, quantitative findings will be pooled in a statistical meta-analysis. Since heterogeneity is expected, we will use a random-effects model to pool effect sizes for each outcome; study weights will be measured using the inverse variance method. Dichotomous outcomes will be reported, where possible, as pooled ORs and 95% CIs based on the random-effects model. Continuous outcomes will be reported using calculated weighted mean differences with their 95% CIs. Results will be presented in forest plot using Review Manager (RevMan V.5.3) software.

For pooling to be considered appropriate, (1) studies should have measured the same Doppler ultrasound parameter (eg, resistive index, peak systolic velocity, etc) at the same vascular site (eg, at the level of the anastomosis vs distal to it). (2) Studies should have similar populations (eg, all children at early postoperative stage after liver transplant). (3) Studies should have similar or related outcomes (eg, hepatic vein obstruction, hepatic vein stenosis and Budd-Chiari syndrome).

When data pooling is not possible, a narrative synthesis of findings will be performed. We will compare Doppler ultrasound values between patients who developed graft-related complications (both vascular and non-vascular) and those who did not. No comparison will be made with other diagnostic techniques. In case of essential missing data from eligible studies, we will try to retrieve it by contacting the study authors. When this is not possible, the potential impact of missing data on the results will be reported in the Discussion section.

We will describe statistical heterogeneity using I^2 index. Clinical heterogeneity will be assessed, when possible, by comparing the age and weight of populations, type of graft and vascular anastomosis, and indications for transplantation in all included studies. We will address clinical heterogeneity using subgroup and sensitivity analysis.

We will assess potential reporting bias using a funnel plot if a sufficient number of studies are identified (>10 studies). Visual assessment and variance-stabilising regression method will be used to test funnel plot asymmetry.

Analysis of subgroups or subsets

Depending on the number of studies included in the final analysis, intended subgroup analysis will evaluate findings in patients categorised by age (less than 1 year vs older than 1 year), weight (<10 kg or ≥10 kg), type of graft (whole or split, primary or re-transplant), type of vascular anastomosis (end-to-end or jump graft), and indications for transplant and specific graft outcomes.

If possible, we intend to explore graft outcomes by category (eg, graft survival, uncomplicated grafts, grafts with vascular complications and grafts with non-vascular complications) among all participants, and different vascular structures by Doppler measurements.

We will also test known associations between some ultrasound and Doppler measurements and specific graft-related complication, depending on the number of articles.

Patient and public involvement

The results of this systematic review will be shared with the public via presentations at scientific sessions as well as educational sessions that may include potential patients. Since this is a systematic review of previously published manuscripts, no direct patient interactions will occur.

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