Doppler Ultrasound Parameters in Children After Liver Transplantation

by

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ABSTRACT

Background: Liver transplantation is the only definite cure for patients with end-stage liver diseases. Patients that receive a liver transplant are routinely followed with periodic Doppler ultrasound because it is safe, widely available and effective to diagnose and predict some complications. While the meaning of certain Doppler ultrasound findings is clear, the diagnostic value of other routinely obtained parameters, such as the velocity of the flow, resistive index and spectrum pattern is less well understood, especially in children.

In our research project, we aim to investigate the accuracy of Doppler ultrasound parameters in pediatric liver recipients to diagnose and predict graft-related complications, in addition to determine the prognostic value of the Doppler ultrasound assessment performed immediately after liver transplantation.

Methods: We performed a systematic review to obtain potential normal values and thresholds of Doppler ultrasound parameters after pediatric liver transplantation. We searched for the published literature in multiple online databases and sources of gray literature. We determined the eligibility criteria *a priori* and performed a two-phase screening process independently by two reviewers. We extracted the data from the included studies, critically appraised their quality using the Newcastle Ottawa scale, and performed a meta-analysis of the available quantitative data.

After this, we carried out a retrospective cohort study to analyze the potential prognostic value of the immediate Doppler ultrasound assessment to predict development of complications that require invasive management. We included all pediatric patients at a single institution (Stollery Children's Hospital) that received a primary liver transplant between 2000 and 2019 and had a Doppler ultrasound assessment within 12 hours after the surgery. We extracted the clinical data from a local database and the Doppler ultrasound parameters from images from PACS. Descriptive statistics are presented in absolute values, percentages, median and interquartile range (IQR). Associations between predictors and outcomes were determined using univariate and multivariable logistic

regression and expressed as odds ratio (OR) or adjusted odds ratio (aOR) with 95% confidence intervals (95%CI). Receiver operator characteristic curve analysis was used to find optimal thresholds for predictors.

Results: Our final selection for our systematic review included 41 studies. All studies were observational, mainly with moderate quality, 12 of them had enough data to preformed a meta-analysis which showed the following findings: The hepatic artery resistive index (RI) was 0.15 lower in complicated grafts compared with uncomplicated (n=540, 95%CI: -0.19 to -0.11, p<.001). Findings associated with complications included a RI <0.6 (n=797, sensitivity=83%, specificity=87%, p<.001) for hepatic artery thrombosis, and a hepatic venous monophasic pattern (sensitivity=80%, specificity=78%, n=342, p<.001) for any graft complication.

In our cohort study, our sample included 79 liver recipients with a median age of 1.3 years (0.7 – 7.2), 25 (44%) were females and 45 (57%) had a living donor. The median time between LT and DUS was 1.8 hrs (1.1 – 3.9); 61 (77%) within 4 hrs.

Twenty-eight (35%) patients required invasive management, 51 (65%) had no or mild complications treated conservatively. The median time to detection was 11.5 days (IQR 4 - 49). The most common complications that required an intervention were hepatic artery stenosis (9, 17%), portal vein thrombosis (8, 15%), and biliary leak (8, 15%). The median follow-up was 3.16 years (IQR 1.5 – 7.0).

Univariate analysis showed that the portal vein velocity (PVV) measured distally to the anastomosis, was significantly lower in patients that required invasive management [43 cm/s (20 - 59 cm/s) vs 60 cm/s (40 – 94 cm/s), p=0.008]. The optimal cut-off value was <60 cm/s (sensitivity=81%, specificity=54%, AUC=0.69, 95%CI: 0.57 - 0.82). No other clinical or Doppler ultrasound parameter showed prognostic value.

Multivariate regression analysis showed a 6.4 times increase in the odds of requiring invasive management with a PVV<60 cm/s, compared with PVV≥60 cm/s, after adjusting for age, sex,

diagnosis, dialysis pre-transplant, operation time and hepatic artery peak systolic velocity (PSV) (aOR=6.38, 95%CI: 1.7 - 23.7, *p*=0.006).

Conclusion: A low hepatic artery RI, and a monophasic hepatic vein pattern showed statistically significant differences associated with graft complications.

Assessment of the PVV distal to the anastomosis within the first 12 hours after the surgery provides predictive value to identify patients at high-risk for developing graft-related complications that will require invasive management.

PREFACE

This thesis is an original work by Martha María Ruiz Ballesteros. One of the research projects included in this thesis received research ethics approval from the University of Alberta Research Ethics Board, Project Name: "Doppler Ultrasound Predictors of Graft-related Complications in the Immediate Post-Operative Period in Children after Liver transplantation", No. Pro00090622, Date of approval: Friday, May 8, 2018.

Chapter 1 consists of an introduction with the rationale for this research, a brief history of liver transplantation and postoperative Doppler ultrasound assessment in children, and an outline of this thesis.

Chapter 2 is a systematic review and meta-analysis of the published literature regarding Doppler ultrasound parameters in pediatric liver recipients. The protocol of this systematic review was registered on PROSPERO (ID: CRD42019119986), since December 18th, 2018, and published in the BMJ Open journal: "Ruiz MM, Alobaidi R, Noga ML, et al. Doppler ultrasound values after liver transplantation in children and their association with graft outcomes: a protocol for a systematic review and meta-analysis. BMJ Open 2019;9:e033887" doi: 10.1136/bmjopen-2019-033887.

Chapter 3 is a retrospective cohort study in which we analyzed the prognostic value of the Doppler ultrasound parameters in the immediate post-operative period in pediatric liver transplant recipients.

Finally, in **Chapter 4** I summarize the results of Chapters 2, and 3 and mention possible future directions.

Collaborations:

Lisa Bialy from the Alberta SPOR SUPPORT Knowledge Translation Unit provided expertise on managing the citation software EndNote X9, retrieved most of the articles for the secondary screening phase, and offered guidance during the analysis process for the systematic review (Chapter 2). The

search strategy for the systematic review was performed by Robin Featherstone from the Alberta SPOR SUPPORT Knowledge Translation Unit.

The design and statistical analysis for the systematic Review in Chapter 2, and for the retrospective cohort study in Chapter 3, were done in cooperation with Dr. Rashid Alobaidi. The statistical analysis of Chapter 3 was supervised and reviewed by Dr. Michael Hawkes and Dr. Braulio A. Marfil Garza.

Dr. James Shapiro provided clinical expertise and participated in the revision of the manuscripts. Dr. Michelle Noga assisted as a third reviewer for discrepancies in the first phase of screening in the systematic review, contributed to manuscript edits and provided clinical expertise, especially in radiology.

Dr. Roman Pabayo and Dr. Shelby Yamamoto provided expertise regarding the methodological design for potential future projects.

The data analysis in chapters 2, 3, and the conclusion in chapter 4 are my original work. I was responsible for the studies' design, data collection, analysis, as well as the manuscript composition.

The research for this thesis was led and supervised by Professor Ravi Bhargava at the University of Alberta. He was involved in the concept formation, manuscript composition and review process of all projects.

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I would also like to express my appreciation for Liza Bialy, Robin Featherstone and the University of Alberta Hospital's ultrasound technicians, for their contributions and beautiful images. Again, to my professors at the University of Alberta; Dr. Irina Dinu, Dr. Shelby Yamamoto, Dr. Dean Eurich, and Dr. Roman Pabayo, for their time, patience and teachings. Likewise, I want to thank the Mexican "Consejo Nacional de Ciencia y Tecnología" (*CONACyT*) for providing funding for my program.

Finally and most importantly, to my family: my brother, the most intelligent and kind human I know; my dad, who's unwavering willingness to learn has set an example to imitate all my life; my mom, the strongest and most genuine person I know, who's continuous support have helped me achieved all my goals, and to Dr. Braulio A. Marfil-Garza, "Boshi" for me, my best friend, number one fan, and the greatest husband I could have ever imagined.

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LIST OF COMMON ABBREVIATIONS

CEUS	Contrast Enhanced Ultrasound
CI	Confidence Interval
DUS	Doppler Ultrasound
EDV	End Diastolic Velocity
HA	Hepatic Artery
HAT	Hepatic Artery Thrombosis
HR	Hazard Ratio
HVO	Hepatic Vein Obstruction
HV	Hepatic Vein
HVV	Hepatic Vein Velocity
IVC	Inferior Vena Cava
LD	Living Donor
LT	Liver Transplant
NPV	Negative Predictive Value
NR	Not Reported
OR	Odds Ratio
PPV	Positive Predictive Value
PSV	Peak Systolic Velocity
PV	Portal Vein
PVS	Portal Vein Stenosis
PVV	Portal Vein Velocity
RCT	Randomized Controlled Trial
RI	Resistive Index
ROC	Receivers Operating Characteristic
SD	Standard Deviation
SE	Standard Error
SROC	Summary Receivers Operating Characteristic
VPI	Vein Pulsatility Index

CHAPTER 1

Introduction

Thesis Objective

We aim to appraise and synthesize the current literature regarding the Doppler ultrasound parameters and thresholds associated with graft outcomes in pediatric liver recipients, and to determine the prognostic value of Doppler parameters obtained immediately after liver transplant in children.

Background

Liver transplantation (LT) is performed to treat patients with end-stage liver disease. Doppler ultrasound (DUS) is routinely used post-operatively as part of the follow-up assessment in all patients because it is safe, widely available, and relatively inexpensive. However, despite being very effective in confirming the presence or absence of flow, many uncertainties remain regarding the diagnostic and prognostic value of some Doppler parameters, as well as their significance in the pediatric population.

The current proposed normal DUS values in children vary substantially, probably as a result of differences in the populations and design of each study. While some authors analyze combined populations including adults and children, others include only children. Also, some studies include all types of liver transplants, while others include just primary liver transplantation or living donor liver transplantation (LDLT). Furthermore, in some studies, authors do not adjust for confounding factors in their design, and when they do, those factors differ as well.

This lack of consensus hampers the decision-making process and could potentially misclassify high-risk into low-risk patients or vice versa. In the first case, we could delay proper treatment by

underestimating the real risk of complications, and in the second case, we could perform unnecessary invasive interventions in low-risk patients.

A representation of the causal pathway between liver transplant, Doppler ultrasound, graft complications and their relationship with other risk factors is shown in Figure 1.

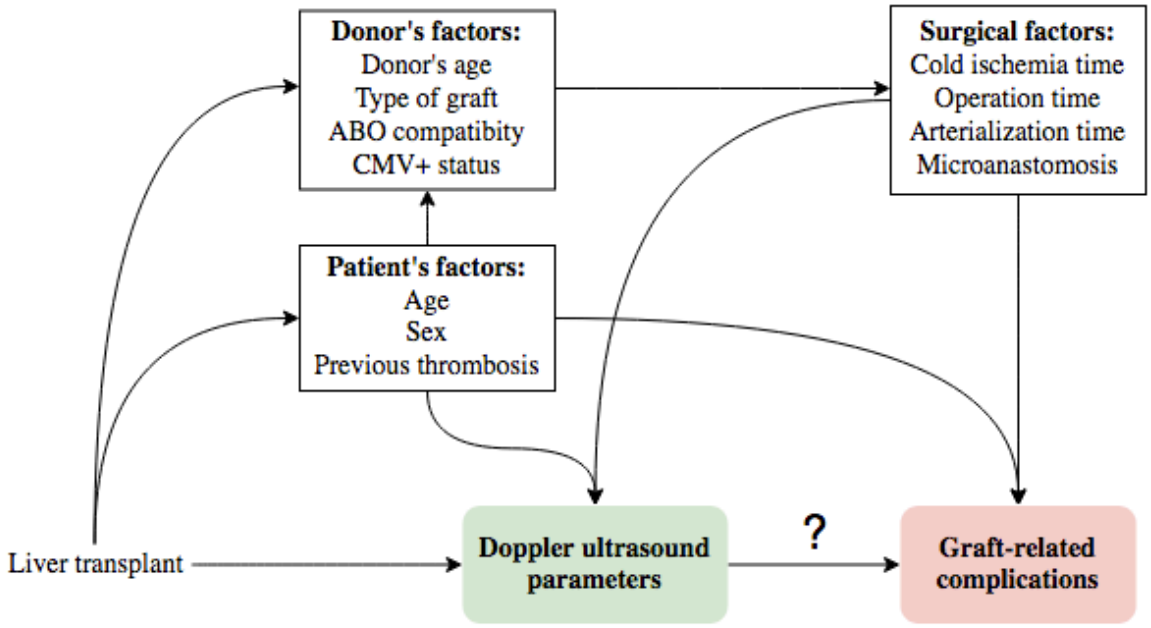

Figure 1. Direct acyclic graph of Doppler ultrasound parameters and graft complications.

In this thesis, I will address the associations of multiple Doppler ultrasound parameters with complications of the liver graft, in pediatric recipients.

History

History of Liver Transplantation

It is extraordinary how much liver transplantation has evolved in the last 5-6 decades. Before the 1950s, the world was completely unaware of the amazing potential possibilities and remarkable advances that were going to happen in the transplant field.

In the decade of the 1950s, pioneer scientists performed the first liver transplantations in dogs. Vittorio Staudacher in Milan in 1952 was just recently recognized as the first one to ever perform this procedure [1, 2]. After him, Stuart Welch in 1955 [1], Jack Cannon in 1956 [1], and Francis Moore in 1958 [3], also performed liver transplantations in big mammals, mostly dogs.

But it was Thomas Starzl, after experimenting and perfecting this technique also in dogs [4 5], who in 1963 performed the first human liver transplantation. The recipient was a pediatric patient with biliary atresia [6]. This was a ground-breaking moment in the history of liver transplantation. Although the initial patient did not survive [6], Starz's contributions set the ground rules for the current surgical procedure and post-operative care.

The following liver transplants were also pediatric patients of 19, 20 and 13 months of age performed for non-resectable hepatic cell-carcinoma, and extrahepatic biliary atresia. However, they had a high complication rate. Starzl reported a mortality of 8/20 recipients younger than 1-year-old, most of them due to hepatic artery thrombosis (HAT) [7], and liver necrosis and abscesses were also common [8].

Survival rates remained low during the following years, until in 1967 when the addition of monoclonal anti-thymocyte globulin, suggested by Professor Sir Roy Calne, increased survival rates significantly [9]. This development allowed the first case of a liver transplanted recipient who lived up to one year after transplantation. He also developed the "piggyback" technique that allowed cut-down liver transplants to be carried out safely in children [10].

Many more improvements came along subsequently. In 1970 advances in immunosuppression allowed increased survival to 15% in year 1. In 1979, after the discovery of cyclosporin, rejection rates dropped [11], allowing liver transplantation to be a more cost-effective practice, with survival rates of 73% at year 1 and 64% at year 5 [12]. After this, the number of liver transplantations increased exponentially [12]. Consequently, in 1983 the US National Institutes of Health considered liver transplantation as, not just an experimental but, definitive treatment for end-stage liver disease [3].

One particular challenge in pediatric recipients was determining the correct type of biliary reconstruction, especially in patients with biliary atresia. In these patients the main biliary duct might be absent or too small to permit an end-to-end duct anastomosis [7]. Biliary fistulas and obstruction were important causes of failure [13]. After a consensus, duct-to-jejunum anastomosis with a Roux limb technique was standardized and chosen as the best procedure and these cases [7].

In the following years, the number of all liver transplantation progressively increased. However, in contrast with adults, children had longer waiting times, presumably due to the lack of suitable donors. Surgical reduction of organs was proposed to address this problem. The first reduced-size LT was performed in 1984, followed by split-organ in 1988 by Pichlmayr [14]. The first successful living donor liver transplantation (LDLT) was done in 1989; a 27-year-old mother donated segments 2 and 3 to her 17 months-old child [15]. Shortly after this, the first adult-to-adult LDLT was performed in 1993 [16].

More surgical developments occurred later on. These include the first right lobe LT, duct-to-duct anastomosis, venoplasty techniques, microvascular surgery for hepatic artery and biliary reconstruction, and methods for portal inflow modulation, such as splenectomy, splenic artery ligation, and portocaval shunts [16].

History of Doppler Ultrasound

In 1961 the first DUS study to measure blood flow *ex vivo* was published [17]. In the 60s its applicability in humans was assessed, especially in cardiac and fetal imaging. After this, the advances for its use skyrocketed. In 1971 the first study of DUS assessment to evaluate the portal system was published [18]. In 1975 and 1976, its uses for liver transplant with grayscale modality [19, 20], and Doppler in the portal system were assessed in multiple studies [21, 22]. The benefits of evaluating these patients with DUS became evident and in 1986, DUS was proposed as a screening test after LT for hepatic artery thrombosis [23], and in the same year, another study demonstrated the high correlation between DUS and angiographic findings [24].

More studies depicted the importance of a pre-surgical anatomical evaluation to detect potential surgical challenges, such as portal vein thrombosis, cavernous malformation, anatomical variants, or tumors in the native liver. In 1986 Taylor et al. published a study using a portable DUS assessing 20 patients including children and adults, 15 of them receiving liver transplantation. The preoperative assessment detected multiple pre-existing complications and vascular variants, while the post-operative assessment correlated with angiographic finding, proving the tremendous value of DUS in this setting [24]. A summary of the historical events of LT and DUS is shown in Figure 2.

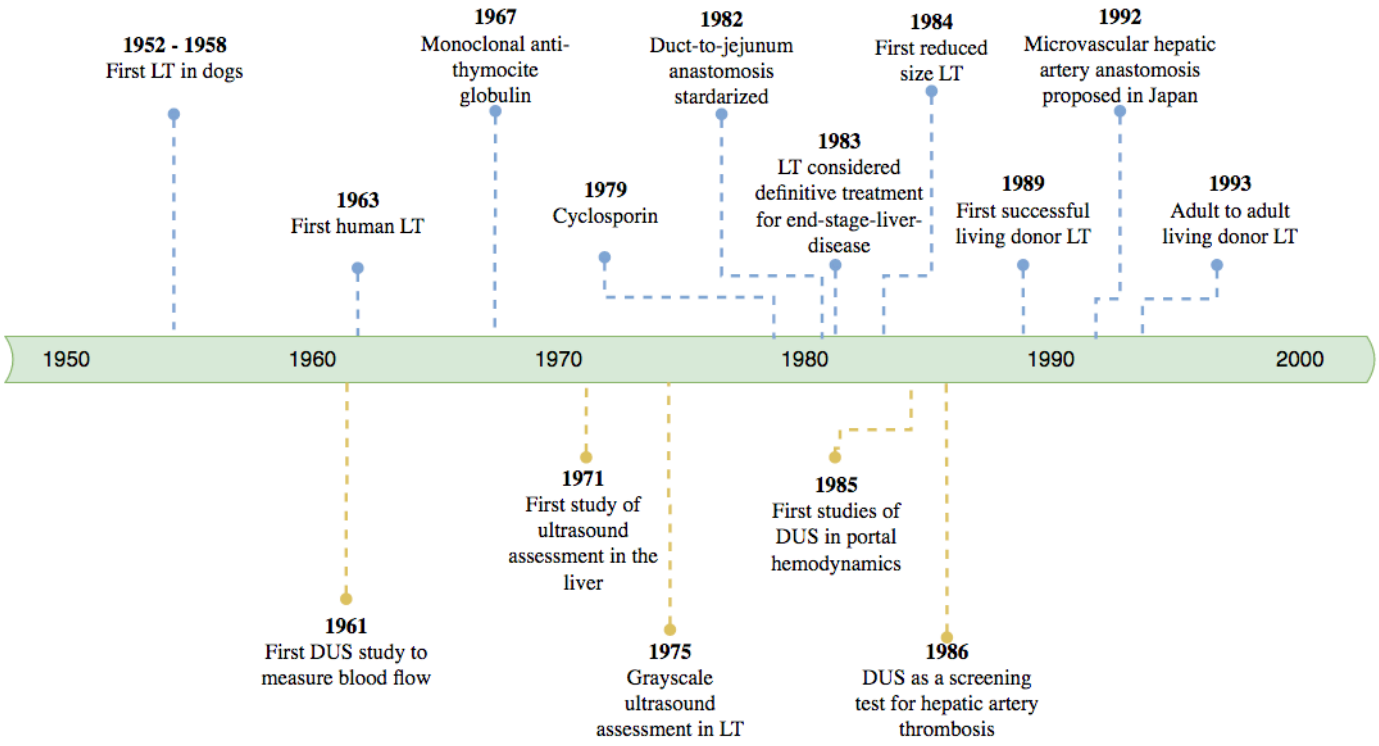

Figure 2. Timeline of pediatric liver transplantation (LT) and Doppler ultrasound (DUS) historical events.

Epidemiology

Until 1977, only approximately 200 liver transplantations including adult and children had been performed [3]. The number of transplants has increased progressively over the last years, reaching up to 8250 in the US just in 2018, the highest annual number ever; 563 of these were performed in

children [25]. In the United States, around 700 new pediatric patients entered the waiting list in 2018, by the end of 2018, 527 potential candidates remained [25].

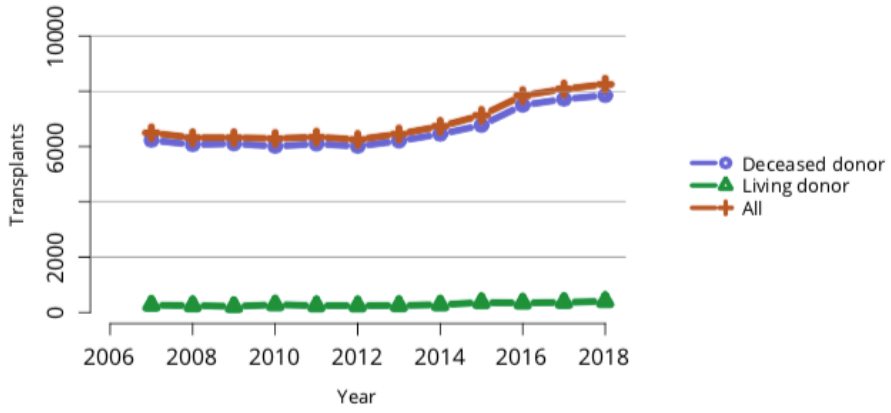

Figure 3. All liver transplant recipient including adult and pediatric, retransplant, and multi-organ recipients. (Extracted from OPTN 2019 report).

Liver transplantation is a complex procedure that requires a highly specialized multidisciplinary team and a properly equipped infrastructure; thus, it is only performed in a few centres. Furthermore, pediatric liver transplantation represents only 7.8% of all liver transplantations [26]. In the United States in 2018, only 21 programs were exclusively performing pediatric liver transplants, compared to 88 performing adult only LT and 28 both adult and pediatric [25].

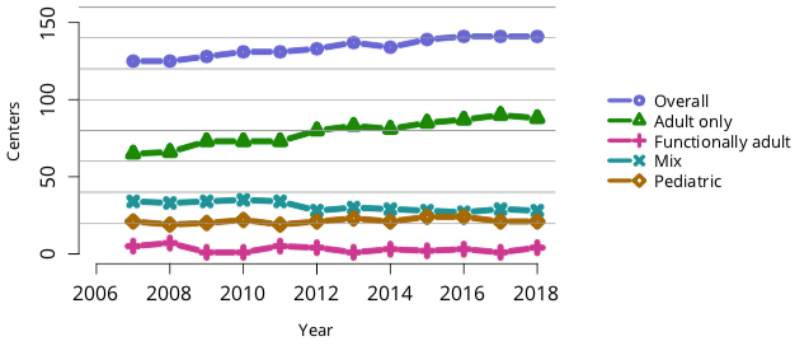

Figure 4. Number of centers performing pediatric and adult liver transplants by center's age mix (Extracted from OPTN 2019 report).

In North America, most pediatric liver transplants are from deceased donors (88%) compared to living donors (11.5%), but the proportion of living donor LT in children has been increasing in the last few decades [27]. The number of pediatric split liver transplants have also increased. For example, in the US they were 14.4% pediatric split liver transplants in 2008, and 19.2% in 2018 [25].

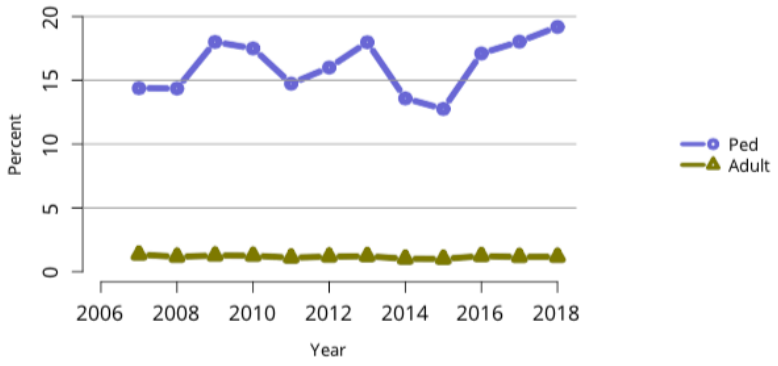

Figure 5. Split liver transplants in children and adults (Extracted from OPTN 2019 report).

In Canada from 2009 to 2018 there were 388 pediatric liver transplants, compared to 3701 adults [28]. In 2018 there were 37 whole liver transplants and 4 split liver transplants [28].

The indications for pediatric LT in Canada are similar to the rest of the world. From 2009 to 2018 (excluding Quebec) biliary atresia and metabolic diseases were the most common indications for liver transplantation in patients younger than 18 years old [28].

At the University of Alberta, the first adult liver transplantation was carried out by Dr. Norman Kneteman in 1989, and the first pediatric liver transplant in June 1990. Since then and up to 2018, 235 primary pediatric liver transplants and 40 re-transplants have been performed at the Stollery Children's Hospital. In 1998 Dr. James Shapiro and Dr. Kneteman performed the first emergency living-related donor liver transplant in Canada on a two-year-old recipient [29].

The Stollery Children's Hospital remains as Alberta's only pediatric liver transplant site, as serves all of Western Canada for this transplant resource.

Differences in adults and children

Age is the main but not the only difference between adult and children recipients. The proportion of LT recipients is greater in the 50-64 years age group, with most pediatric recipients being younger than 5 years-old [25]. In contrast with adults, children receive more grafts from living donors, tend to have more complex surgeries, have had more previous surgeries, and have different pre-existing liver conditions including congenital, metabolic, and oncological diseases [30, 31].

Transplants can be obtained from living or cadaveric donors, and the graft used can be whole, partial or split. In the US in 2018, of the 563 pediatric LT, 62 were living donor transplantations. Whole organ transplant was the most common (62.4%) followed by partial (19.5%) and split livers (19.2%) [25], while in adults 94.5% received a whole organ and 1% a split organ [25].

Children undergo surgery with more acuity than adults, with higher Model of End-stage Liver Disease MELD/PELD scores (25.8% with listing status as 1A or 1B) [25]. This has presumably been attributed to the lack of available organs. In response, policies allow the use of split grafts and ABO

incompatibility donors [25]. Children also have more transplants by exception than adults 74.2% vs 34.3% [25].

Another important difference is the cause of transplantation. The most common indication of liver transplantation in children in 2018 were cholestatic biliary diseases, including biliary atresia (33.1 %), followed by metabolic diseases (16.3%) [25 27], whereas in adults, chronic hepatic liver disease and hepatocarcinoma were the most common [27].

Most pediatric patients have a history of previous abdominal surgery, such as porto-enteroanastomosis due to biliary atresia [7]. A cohort of pediatric patients with biliary atresia showed that 537/695 (77.2%) had previous abdominal surgery [31]. Biliary atresia is associated with other congenital abnormalities such as bowel malrotation, polysplenia, and vascular abnormalities in up to 25% of the cases including anteduodenal portal vein [24, 32-34]. Surgeons consider these pre-existing conditions when guiding the decision to choose certain techniques since these entities can difficult or complicate the transplantation.

Moreover, some complications present more frequently in children that in adults. For example, early hepatic artery thrombosis (defined as less than 7 to 14 day for listing criteria [35] or as presented within 1 [36, 37, 35] or 2 months after LT [38]) is more frequent in children compared to adults (8.3% vs 2.9%. $p < 0.001$, OR = 3.2, 95% CI 2.8–3.8) [39]. The reason for this is unknown, but the smaller caliber of the vessels may be one important risk factor. On the other hand, children with HAT have a lower mortality rate as compared to adults (25% vs 34.3%)[39].

A summary of the main differences between adult and children transplantation is presented in Table 1.

Table 1. Differences between pediatric and adult liver transplantation.

Differences	Children	Adults
Most common age group LT	< 5 years old (64.8%)	50-64 years (52.2%)
LT centres	21	88
LT total	3,530*	13,393**
LT in Canada (2009 - 2018) [28]	388	3701
Indication for LT	Biliary atresia Metabolic diseases	Chronic liver diseases Hepatocellular carcinoma
Technical aspects [31]	Smaller vessels More previous surgeries	Less anatomical variants
Urgency	1A status: 14.2%	1A status: 2.6%
Incompatible ABO	5.2%	-
Living donor	11%	4.4%
Whole liver	62.4%	94.5%
Split livers	19.2%	1%
Liver plus other organ transplants	8.8%	9.7%

Data from the OPTN 2019 report, in US 2018 [25,] unless specified otherwise.
*From 2006 to 2018.
**From 2008 to 2018.

Survival

Outcomes are excellent after primary pediatric liver transplant, with patient survival ranging from 81 to 94% at the first year, 81 to 91% at 5 years, and 78 to 88% at 10 years [25, 40]. These are lower in cases of re-transplantation. For example, in the US, the 5-year graft survival was 83.2% for primary pediatric liver transplant, and 69.6% for retransplantation [25]. In the first year after liver transplant, leading causes of death include sepsis, graft failure and cardio/cerebrovascular complications [25, 40 41].

Graft survival in children is also great, it ranges from 73%, to 94% at 1 year, 67% to 91% at 5 years, and 63% to 88% at 10 years [40 42]. Around 12% of all pediatric recipients will require retransplantation, with the main indications being hepatic artery thrombosis, chronic rejection, and primary graft dysfunction [42, 43]. However, graft survival rates are worst in retransplantations, compared with primary transplants (68% vs 82.6%, in the first year [41], decreasing to 49% vs 73.9% at year 4 [43]). Another factor that affect graft survival is the type of donor. In US in 2017, graft failure was as high as 7% at 1 year among deceased donors [43].

Graft-Related Complications

We refer to "graft-related complications" as a set of undesirable conditions in the liver graft or vasculature developed after transplantation, that can manifest changes in the Doppler ultrasound parameters obtained from the hepatic vascular structures. This term excludes systemic or extrahepatic complications (E.g. CMV infection, pneumonia, and sepsis).

They can be classified as vascular and non-vascular. Vascular complications include; hepatic artery thrombosis (HAT), hepatic artery stenosis (HAS), portal vein thrombosis (PVT), portal vein stenosis (PVS) and hepatic vein stenosis (HVS). Of these, the most common are HAT, which represents 7.5%, and portal vein thrombosis 3.2% [40]. Non-vascular complications include primary allograft non-function, rejection, biliary strictures, or biliary leaks. Of these, the most common are biliary complications with an incidence between 5 and 20% [44], and primary allograft non-function with an incidence of 5.4% [40].

Sometimes classification of patients according to their type of complication can difficult because some non-vascular complications may be a consequence of a vascular impairment. For example, due to the biliary system vascular supply, patients may develop biliary strictures or parenchymal abscesses after hepatic artery abnormalities. One case series showed that 100% of patients requiring revascularization developed biliary strictures [45].

After liver transplantation, as a standard practice, all patients receive frequent DUS assessment to monitor the status of the graft. When an abnormality is detected or suspected, management usually change. This could allow a prompt detection and treatment of complications or even potentially prevent one. This is why DUS evaluation is crucial in the post-operative care of all liver graft recipients.

Doppler Ultrasound Physics

The Doppler effect, described by Christian Doppler in 1842, refers to the change in the frequency of a wave in relation to an observer [46]. The pitch increases as the object that produces the sound (emitter) gets closer to the listener and decreases as it moves away. For example, the change in the pitch of a moving ambulance perceived by a person; when the ambulance is far away, it is perceived with a lower pitch, but then it gets closer, the pitch increases, conversely when it drives away. This principle is identical to the physics behind Doppler ultrasound.

Doppler ultrasound is a method that allows a measurement of the speed of intravascular blood flow, where the probe sends an ultrasonic wave (sound) which is reflected by the red blood cells and "listened" by the same probe, acting as the observer. The Doppler shift frequency is the variation between the transmitted and received ultrasound waves.

The Doppler signal depends on three factors:

1. The velocity of the blood flow.
2. The ultrasound frequency.

3. The angle of insonation. When the beam of ultrasound is aligned toward the direction of the flow, the Doppler signal will rise.

Two imaging methods use the Doppler shift frequencies to analyze flow: the color-flow mode and the pulse wave or spectral Doppler. Color Doppler mode displays a map of colors on a region of interest (ROI), usually a vessel, codified by colors according to the velocity and direction of the flow. On the other hand, in the pulse-wave or spectral mode, the velocity of the flow is analyzed from a small sample area, usually in the center of the vessels, and shown in a graph that displays a signal wave or shape called "spectrum", normally reported in cm/s [47] Figure 6.

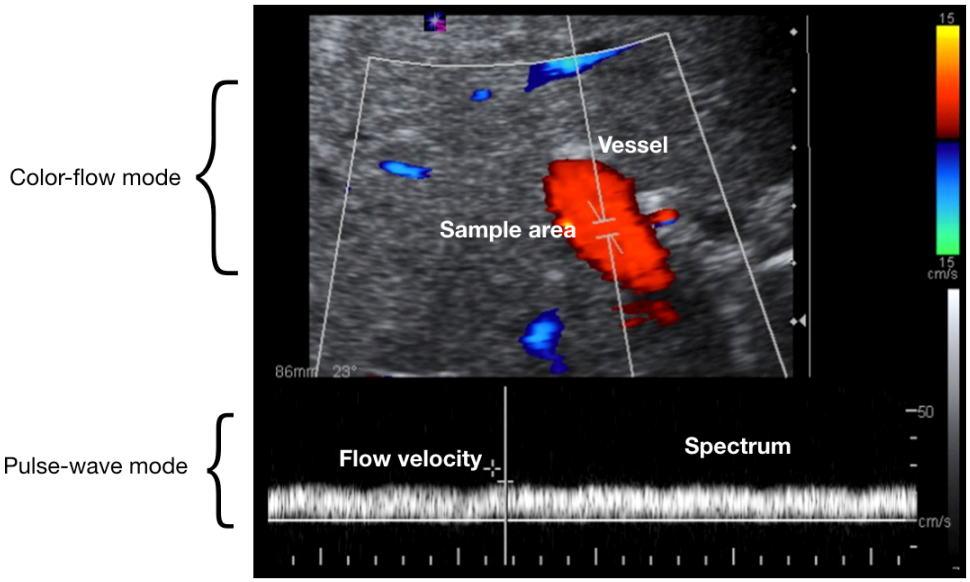

Figure 6. Doppler imaging in color-flow and pulse-wave modes.

Doppler ultrasound is used extensively to assess almost every vascular structure in the body. In the post-transplant liver, it is considered a surrogate of angiography because it is relatively inexpensive, widely available, can be done at the bedside, and less invasive and risky. Therefore, it is the standard follow-up study used after liver transplantation.

Justification

Despite DUS widespread application, there is no consensus defining normal values, timing, or frequency of Doppler ultrasound after liver transplantation, particularly for children [48, 49]. There is variability in recommendations regarding the frequency in asymptomatic patients: In asymptomatic children, some authors have proposed DUS on day 1, and every 3 days [49], while others recommend DUS on day 1, 3 and 5. [50]

The most commonly accepted normal values and thresholds are extracted either from studies in the adult population or from studies with mixed populations with unclear differentiation of the values obtained from children [51, 52]. Although some authors have proposed normal ranges for Doppler values of graft vasculature in children [53, 54], 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.

Systematic reviews provide a comprehensive summary of the current literature, useful information for clinical practice and guidance for future research [55]. They are considered high evidence with limited bias by the GRADE system [56]. Given the lack of consensus in the DUS parameters in pediatric liver recipients, we aim to conduct a systematic review and meta-analysis to appraise and synthesize the literature describing Doppler ultrasound measurements and evaluate their association with graft complications in children who have received a liver transplant.

CHAPTER 2

Doppler Ultrasound Parameters in Pediatric Liver Transplant Recipients. A Systematic Review and Meta-analysis

Hypothesis and objectives

We hypothesize that the Doppler Ultrasound values differ in uncomplicated and complicated patients. Our objectives were to define potential normal Doppler ultrasound values of the hepatic artery, portal vein, and hepatic veins after liver transplantation in children, and to describe associations between Doppler ultrasound values after pediatric liver transplantation and graft-outcomes.

Abstract

Background: Vascular compromise is the leading cause of mortality after liver transplantation. Although Doppler ultrasound (DUS) assessment is routinely performed, there is no consensus defining normal values in children. This hampers identification of patients that might benefit from a change in management, or more invasive assessment leading to a change in management.

Objective**:** To evaluate the association of DUS parameters with graft status, and to possibly identify normal and abnormal parameters for DUS in children.

Materials and methods: Our protocol is registered on the International Prospective Register of Systematic Reviews PROSPERO (ID: CRD42019119986), since December 18th, 2018. We searched multiple databases using a combination of subject headings for liver transplantation, Doppler ultrasound, and children, without restriction on publication date or language. Studies of all designs were eligible if DUS parameters were obtained within one year after liver transplantation, and the outcome of the graft was specified. We used a random effects model to calculate pool estimates for

continuous and dichotomous variables of each DUS parameter comparing complicated versus uncomplicated grafts.

Results: Forty-one non-randomized studies were included (n=2194). We were able to pool twelve studies for quantitative analysis to obtain the following estimates:

The hepatic artery resistive index (RI) was 0.15 lower in complicated grafts compared with uncomplicated (n=540, 95%CI: -0.19 to -0.11, p<.001). The RI was <0.6 in hepatic artery thrombosis (n=797, sensitivity=83%, specificity=87%, p<.001). The hepatic venous flow showed a monophasic pattern in complicated grafts (sensitivity=80%, specificity=78%, n=342, p<.001).

Conclusion*:* A low hepatic artery RI, and a monophasic hepatic vein pattern showed statistically significant differences associated with graft complications. The scare number of studies where the exact DUS values were provided, and the high clinical heterogeneity hampered calculation for pooled estimates for every parameter.

Introduction

Liver transplantation is the definitive curative treatment for end stage-liver disease. Although this procedure is done more frequently in adults than children [26], pediatric liver transplantation is considered more technically challenging [30, 57].

Advances in surgical techniques, interventional procedures, and postoperative care have improved patient and graft survival [27, 40, 42, 58]. Nonetheless, postoperative graft-related complications, persist as the most important risk factors for liver graft loss, the leading cause of mortality (1.6%) [39-41, 58]. Around 12% of children that receive a primary liver transplant will require re-transplantation, with hepatic artery thrombosis (HAT), chronic rejection, and primary graft dysfunction being the main indications [40, 42, 43]. Hence, early detection of complications is crucial.

Doppler ultrasound (DUS) is routinely performed post-operatively because of its efficacy, availability, and safety [50, 59]. It can detect and predict multiple graft-related complications [60] even before patients exhibit clinical signs or elevated liver enzymes [49, 59, 61-65]. However, the suggested normal values of DUS after liver transplantation differ, particularly for children [48, 49].

The most commonly accepted parameters are extracted from adult studies or from studies with combined populations of adults and children [51, 52, 66, 67]. However, using them for children may be inappropriate due to the differences between pediatric and adult transplant, including different indications for transplantation [25, 41], preexisting abdominal surgeries and types of donors and grafts [27, 41].

Although some authors have proposed normal DUS values for children [53, 54], there is no consensus for these or their relationship to specific graft complications. These limitations challenge the interpretation of DUS measurements in determining which patients might benefit from an intervention or change in postoperative management.

There are no systematic reviews analyzing the relationship between Doppler ultrasound parameters and graft outcome, in children or adults nor providing a summary of the proposed normal thresholds to diagnose or predict complications.

The purpose of this systematic review is to define normal Doppler ultrasound values of the hepatic artery, portal vein, and hepatic veins after liver transplantation in children. Secondarily, to describe associations between Doppler ultrasound values after pediatric liver transplantation and graft-outcomes.

Methods

We performed 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 [68], and is registered on the International Prospective Register of Systematic Reviews (PROSPERO) with the following ID: CRD42019119986. We followed the Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies PRISMA-DTA statement [69]. No ethics approval was necessary as this is a protocol for a systematic review and no consent to participate is required.

Protocols for systematic reviews provide a clear statement with the objectives, and definition of the methods, including characteristics of the comparator and outcomes that will be analyzed. These are important to pre-specify to protect the data against potential biases driven by the results of an ongoing research. Additionally, publishing protocols reduces the risk of duplication and promote potential collaboration [70].

The PRISMA guidelines were developed by the Enhancing the Quality and Transparency Of health Research (EQUATOR) group to appropriately report a systematic review. Later on, an extension of the PRSMA guidelines was developed for systematic reviews of diagnostic test accuracy PRISMA-DTA [69, 71]. The use of a reporting guideline improves the quality of a systematic review, promotes adherence, standardization of reporting and better communication for the reader [72]. Some high-impact journals also require a PRISMA checklist for publishing systematic reviews and meta-analysis [71].

Eligibility Criteria

The selection criteria were stated *a priori*. Included studies met all of the following criteria:

Inclusion Criteria:

- Population: Studies enrolling children from birth to less than 18 years old who received any type of orthotopic liver transplantation and were assessed postoperatively with a Doppler

ultrasound. We also included studies that assessed both adult and children if they provided a separate description for pediatric 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 one year after liver transplantation.
- 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 characterized 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 (Randomized control trials or quasirandomized control trials) and observational studies (cohort studies, case-control studies, cross-sectional studies, case series or case-reports).

Exclusion 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 pre-transplant, intraoperative or in non-transplant settings.
- Studies that evaluate Doppler ultrasound devices or techniques used only to prove patency without any measurements of vascular structures.

- Studies that analyze Doppler Ultrasound performed more than 1 year after liver transplantation, or do not specify the timing of Doppler ultrasound in their methods.
- 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, CMV infection, pneumonia). We included case reports and case series for three main reasons; 1) we sought for a highly specific population, 2) DUS assessment has minimal variations since it is part of the routine follow-up worldwide, and 3) complications are uncommon since pediatric liver transplantation is not a frequent procedure, graft complications are also infrequent and have been decreasing over time [41].

Since our selection criteria described a very specific type of population, and the intervention is routinely used in clinical practice, we decided to include case reports and case series if they met the selection criteria.

Search Strategy

A research librarian designed and executed a systematic and comprehensive search with input from the research team, from the following electronic databases: Ovid Medline, Ovid Embase, Wiley Cochrane Library, and Web of Science - Science Citation Index Expanded. The search strategy combined subject headings (e.g., MeSH) and keywords for liver transplantation, Doppler ultrasound, and pediatric patients. We excluded animal studies but did not apply any additional limits for language or date of publication. We s earched for trial registry records via ClinicalTrials.gov and meeting abstracts via Conference Proceedings Citation Index database. Finally, we manually searched for relevant studies using reference lists of retrieved citations and prior reviews on the topic. Search results were managed in EndNote X7, removing duplicates prior to screening. Search strategy (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 were assessed for potential relevance independently by two reviewers. A standardized data extraction form (Appendix 2) was piloted and then used to extract data from the reports of all included studies by one reviewer. Concerns were identified and resolved through discussion with another author where necessary, discrepancies in extracted data were resolved by consensus.

A standardized data extraction form was piloted and then used to extract data from the reports of all included studies by one reviewer. Concerns were identified and resolved through discussion with another author where necessary, discrepancies in extracted data were resolved by consensus. Researchers were not blinded for author or journal details during the study selection and/or data extraction.

Risk of Bias (Quality) Assessment.

Included studies were assessed for methodological quality and risk of bias. Since all studies evaluating Doppler ultrasound after liver transplantation in children are observational in design, we used the Newcastle-Ottawa scale [73] to assess cohort and case-control studies. Case series and case reports were assessed using the tool recommended by Murad et at. [74].

Data Synthesis and Analysis

We retrieved data for demographic, clinical and DUS parameters, and outcomes. Flow velocities tended to be higher at the anastomosis and decrease distally [75], thus, we analyzed the hepatic artery and portal vein velocities at multiple locations according to their measurement site, relative to the anastomosis. We combined studies of Budd Chiari syndrome and hepatic vein obstruction (HVO) to be able to pool similar outcomes.

If multiple measurements were assessed in a study, we analyzed the one closest to day 1, since graft related complications that appear in the immediate postoperative period have disastrous consequences that can lead to graft-failure and even the need of a re-transplantation [43], furthermore, some complications that appear in the early postoperative period, might not manifest clinical or laboratory abnormalities [38, 76].

We retrieved data for the following Doppler parameters:

- Hepatic artery: Resistive index (RI), Peak systolic velocity (PSV) at the level of the anastomosis, PSV distal to the anastomosis, End diastolic velocity (EDV), Acceleration time (AT), Pulsatility index (PI).
- Portal vein; Portal vein mean velocity (PVV) at the level of the anastomosis, PVV distal to the anastomosis.
- Hepatic veins; Hepatic vein velocity (HVV) and hepatic vein pattern.
- Other measurements reported: RI of transcapsular vessels, portal vein flow volume (ml/min), inferior vena cava (IVC) velocity, spleen vein velocity, and intrahepatic artery PSV.

A meta-analysis is a method used to obtain a weighted average from data of individual studies. Not all systematic reviews include a meta-analysis, sometimes due to the scarce data available, but most importantly, because a meta-analysis might not be appropriate when high data heterogeneity is present. Furthermore, in the particular case of systematic reviews of diagnostic test accuracy, besides considering variations from population or co-morbidities, we also have to consider the thresholds used in each study [55, 77].

A common problem in performing a meta-analysis with medical imaging is the rapid changeover of equipment. Ultrasound technology, for example, can result in new hardware releases by various manufacturers every few years, making it difficult to accumulate enough studies to perform a traditional meta-analysis [55]. Nevertheless, studies of meta-analyses of diagnostic test accuracy have shown that even with a small number of individual studies, using the appropriate model could reduce bias, even when heterogeneity is present [55 77]. For this reason, we decided to perform a meta-analysis despite the small number of articles retrieved for each parameter. However, there is still a risk of

selection bias in scenarios with lower prevalence outcomes [78], and risk of undetected heterogeneity especially when including a small number of studies [78].

We determined the following conditions to pooled data: Studies should have similar population, measure the same parameter in the same place relative to the anastomosis, and have enough data to compare DUS values of patients who developed graft-related complications (both vascular and non-vascular) and those who did not.

We used a random effects model to pool effect sizes for each outcome; study weights were measured using the inverse variance method. Authors reported DUS parameter as dichotomous and/or continuous variables

Dichotomous variables were pooled from individual participant data from each study, estimates are reported as pooled sensitivities, specificities, and odds ratios with 95% confidence intervals based on the random-effects model. We used the summary receiver operating characteristic (SROC) curve to graph the combined estimates of studies that used dichotomous variables. Continuous outcomes are reported using calculated weighted mean differences with their 95% confidence intervals. We used the Review Manager (RevMan 5.3) software for these comparisons and to develop the forest plots [79].

We described statistical heterogeneity using I^2 index. Clinical heterogeneity was assessed by comparing the outcome of populations, type of graft and parameter evaluated. We addressed outcome heterogeneity using subgroup and sensitivity analysis. In variables were data pooling was not possible, a narrative synthesis of findings is provided.

Analysis of Subgroups

For the comparison of the RI and the HVV, we divided the outcome into subgroups depending on their outcomes. We did not have enough studies to do a subgroup analysis for the rest of the DUS parameters.

Results

A total of 2390 studies were identified from Databases, 84 more were identified from other sources, including gray literature. After removing duplicates, the remaining 1533 studies were assessed reviewing the title and abstracts by two investigators independently. Total agreement was 85%, with a Kappa statistic of 0.602. First 92 Discrepancies were solved after discussion, the remaining 139 were solved by a third reviewer, representing 11% of the total.

For the second phase of screening, 374 full text of selected studies were scan for eligibility, as determined by the eligibility criteria listed above. We performed a pilot screening exercise of 10% of the database to refine eligibility criteria. This screening phase was also done independently by two reviewers. 66 studies were selected. Disagreements were resolved through discussion; no third reviewer was necessary in this phase. The justification for ineligibility was documented for excluded studies in the second phase of screening. The selection process if exemplify in Figure 7. PRISMA flowchart.

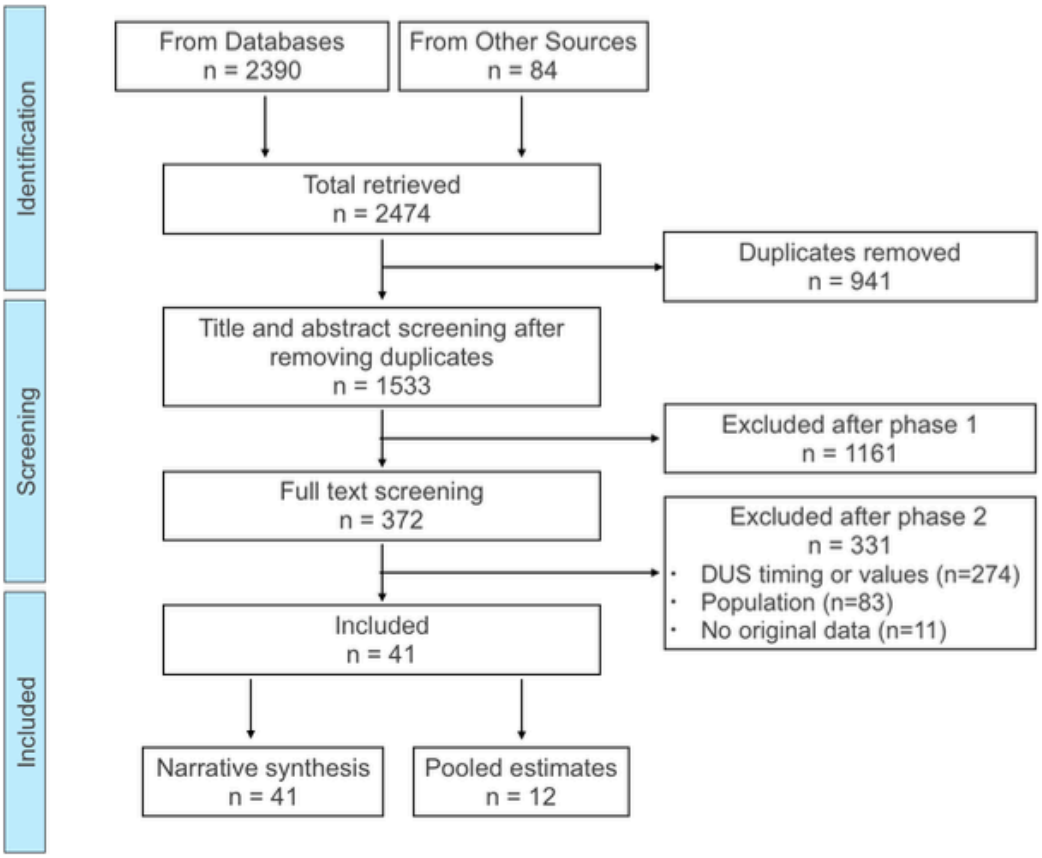

Figure 7. PRISMA flowchart.

Main reason for exclusion was: Inadequate intervention; Doppler ultrasound did not specify values. 274 studies (73.2%). There were 5 studies not included in the final analysis because they did not specify values or timing of the DUS. One study was excluded because it was an abstract with the same information as other full text study [80].

The final selection was 41 studies. The included articles were published between 1990 and 2019; 37 full text, 2 abstracts and 2 poster presentations Table 2.

Table 2. Summary of included articles.

Author(s)	Year	Country	Study design	Participants (n)	Age (years)*	Follow-up**	DUS parameter	Outcome
Ahmad et al.	2017	Canada	RC	120	3.17	12	HA RI, HA PVS	Any graft complication
Akamatsu et al.	2004	Japan	RC	70	14	9	HVV	Hepatic vein obstruction
Britton et al.	1992	England	PC	41	5.58	1.2 to 4	VPI	Acute rejection
Cheng et al.	2004	Taiwan	RC	112	2.08	44 (3.67 yrs, range 0.75-9.5)	HVV	Hepatic vein stenosis
Cobo et al.	2018	Spain	RC (abstract)	28	NR	1-2 days	HA RI	Hepatic artery thrombosis
Fujimoto et al.	1997	Japan	PC	120	4.2	32 (range 13-64)	HA PSV, HA PI	Hepatic artery thrombosis
Fujimoto et al.	1995	Japan	CS	3	NR	31, 28, 14	HVV PVV	Hepatic vein stenosis
Gu et al.	2015	China	RC	144	0.67	7 days	HA RI, HA PVS	Hepatic artery thrombosis
Hak et al.	2018	France	RC	28	0.32	NR	HVV	Hepatic vein obstruction
Hall et al.	1990	USA	RC	4	NR	NR	HA RI	Hepatic artery thrombosis
Hasegawa et al.	2002	Japan	CR	1	1	5	HA PSV, HA RI, HA EDV	Acute rejection
Hawkins et al.	2015	USA	CC	21	2.8	47 (range: 0.4-78)	PVV	Portal vein stenosis
Herden et al.	2013	Germany	RC (Abstract)	37	NR	NR	HA PSV, HA RI, PVV	Acute graft failure
Hermann et al.	2011	Germany	RC	137	4.1	53	HA RI HA PSV	Not specified
Herrmann et al.	2011	Germany	PC and RC (Poster)	99	NR	NR	HA PSV, HA RI, PVV	Any graft complication
Hsu et al.	2016	Taiwan	RC	70	2.3	6	PVV	Portal vein stenosis
Huang et al.	2012	Taiwan	RC	11	NR	2	PVV	Portal vein stenosis
Huang et al.	1998	Taiwan	CS	12	3.4	1	PVV	Any vascular complication
Jamieson et al.	2014	Canada	RC	110	NR	42	HA RI, HA PVS, PVV, HV pattern	Any graft complication
Jéquier et al.	2003	Swizerland	PC and RC	39	NR	NR	HVV pattern	Acute rejection
Jones et al.	2010	New Zeland	CR	1	8	7	HA RI, PVV	Acute graft rejection
Kaneko et al.	2004	Japan	RC	70	4.6	NR	RI	Hepatic artery thrombosis
Kawano et al.	2009	Japan	RC	133	NR	55 (range 3–174)	PVV	Portal vein stenosis
Lee et al.	1996	USA	RC	167	2.4	2.1 yrs for LD, 1.7 for RCD	PVV	Portal vein stenosis
Lee et al.	2018	Australia	RC (Poster)	21	NR	NR	HA PSV, HA RI, PVV, HVV, HV pattern	No complications
Liao et al.	2019	Taiwan	CC	37	NR	3.3 yrs, median	HA RI, AT	Biliary complication
Lu et al.	2018	Taiwan	RC	262	2.94	7.4 yrs (range, 0.04-17) yrs	HVV	Hepatic vein obstruction
Miraglia et al.	2016	Italy	CR	1	2	21 days	HVV	Hepatic artery stenosis
Nakajima et al.	1994	Japan	CR	1	2.5	48 days	Intrahepatic HA PSV and PVV	Any graft complication
Nakanishi et al..	2004	Japan	RC	4	NR	7 days	HA PSV, PI, PVV, HVV and pattern	Any graft complication
Ou et al.	2011	Taiwan	PC	105	2.75	95	PVV	Portal vein thrombosis
Saad et al.	1998	Japan	PC	110	4.2	NR	PVV	Portal vein complications

Saad et al.	2007	USA	CS	2	1.6	37 - 67	HA RI	Arterioportal fistulae
Someda et al.	1995	Japan	PC	46	4.3	16 days - 22 months	HA PSV, PI, PVV, HVV and pattern	Any vascular complication
Sugimoto et al.	2000	Japan	CR	1	8	4	HA PSV. HA RI, HA RI, PVV	Any graft complication
Suzuki et al.	2008	Brazil	RC	79	6.4	42	HVV	Hepatic vein stenosis
Suzuki et al.	2008	Brazil	RC	61	5.8	15	PVV	Portal vein stenosis
Tang et al.	2000	Japan	CS	1	1	NR	HA RI	Hepatic artery stenosis
Vannevel et al.	2010	Belgium	CR	1	6	NR	Intrahepatic PV	Portal cavernoma
Wakiya et al.	2012	Japan	CR	1	0.5	NR	HA PSV, HA RI, PVV	Hepatic artery stenosis
Zhang et al.	2009	China	CS	3	8.6	NR	PVV	Not specified

Abbreviations: CC; Case control, CR; Case report, CS; Case series, DUS; Doppler ultrasound, EDV; end diastolic velocity, HA; hepatic artery, HV; hepatic vein, HVV; hepatic vein velocity, LD; living donor, NR; not reported, PC; Prospective cohort, PSV; peak systolic velocity, PV; portal vein, PVV; portal vein velocity, RC; Retrospective cohort, RCD; Reduced cadaveric donor, RI; resistive index, USA; United States of America, VPI; vein pulsatility index.

* mean

** mean months unless specify otherwise.

Twelve studies had enough data to be included in the final meta-analysis. Case-reports and case-series were not included in the meta-analysis since they lacked a comparison group (n=12) but were describe in the narrative synthesis.

Quality Assessment

As we expected because of the nature of the exposure, we did not find any randomized trials. The most common type of study design was retrospective cohort (20 articles) 47.6%. Two studies had a mixed prospective and retrospective design, 5 studies were prospective, 2 case-control studies, 5 case series, and 7 case reports.

Only 16 articles (38%) clearly stated their selection criteria. Seven cohort studies did not specify their recruitment method, 2 studies recruited their patients according to their outcome (known portal vein thrombosis[81], or uncomplicated patients,[82] 2 studies from consecutive angiographies or venographies performed for suspected complications [83, 84] the rest of the cohort studies recruited their patients from consecutive LT or from databases.

One study had significant missing information due to non-visualized anastomosis. Three of the 8 patients with portal vein stenosis did not have DUS measurements due to anastomosis not visualized. [85]

One study selected patients that received Percutaneous Transhepatic Portal Venography (PTPV) for suspicion of portal hypertension.[84]

One study analyzed the use of DUS intraoperatively as well as follow-up, however, this intervention changed the management in some patients, we decided not to include it in the final analysis. [86]

From case controls, one study selected cases of complicated patients with 26 match controls[87]. The other case-control study selected all percutaneous transhepatic portal venography for suspected portal vein stenosis [84], this is concerning for selection bias.

To assess risk of bias we used the modified Newcastle Ottawa tool with Selection of participants (4 possible stars), Comparability (2 stars), and Outcome (3 stars) with a maximum of 9.

Twelve studies had studies had good quality (41.4%) [53, 54, 57, 61, 81, 85, 86, 88-92], 5 studies had moderate quality (17.2%) [83, 84, 93-95], 12 studies had poor risk of bias (41.4%) [63, 82, 87, 96-103] Table 3.

We were unable to assess for publication bias using a funnel plot as this requires a minimum of 10 studies, something which was not present for any DUS value [104-107].

Table 3. Quality assessment of cohort and case-control studies.

Study Details	Selection			Comparability			Outcome			
Author(s)	**Representativeness of exposed**	**Selection of non-exposed**	**Ascertainment of exposure**	**Outcome not present at start of study**	**Controls for baseline features**	**Controls for other factors**	**Assessment of outcome**	**Follow-up long enough**	**Adequacy of follow-up**	**Overall Quality**
Ahmad et al.	1	1	1	1	1	0	1	1	1	Good
Akamatsu et al.	0	0	0	1	1	0	1	1	0	Poor
Britton et al.	1	1	1	1	0	0	0	1	0	Poor
Cheng et al.	1	1	1	1	0	0	0	0	0	Poor
Cobo et al.	1	1	1	1	1	0	0	0	0	Poor
Fujimoto et al.	1	1	1	1	0	0	0	1	1	Poor
Gu et al.	1	0	1	1	1	0	1	0	0	Fair
Hak et al.	0	0	1	1	1	0	1	0	1	Fair
Hall et al.	0	0	1	1	1	0	1	0	0	Fair
Hawkins et al.	0	1	1	1	0	0	1	0	0	Fair
Liao et al.	1	0	1	1	0	0	1	1	0	Poor
Lu et al.	0	1	1	1	0	0	1	1	0	Poor
Nakanishi et al..	0	1	0	1	1	0	1	0	0	Fair
Ou et al.	1	1	1	1	1	1	0	1	1	Good
Saad et al.	1	1	1	1	0	0	0	0	0	Poor
Someda et al.	1	1	1	1	1	0	1	1	1	Good
Suzuki et al.	1	1	0	1	1	0	1	1	0	Good
Suzuki et al.	1	1	0	1	1	0	1	1	1	Good

Doppler Ultrasound Parameters

Twenty-six studies specified the characteristics of DUS assessment, including equipment, model, probe and scanning personnel [53, 54, 57, 61, 63, 81, 83-95, 98, 108-113]. Most studies did not specify the frequency of DUS assessment (26/41, 63.4%). Sixteen studies reported frequency assessment [53, 57, 61, 63, 84, 86, 88-90, 93, 95, 98, 108, 110, 113, 114], with almost all performing daily assessment during the first 3 days, with follow-up scanning ranging between daily to twice a week for the first two weeks. All centres would do additional scanning based on clinical concern.

Doppler measurements were reported as bivariate variables (with cut-off values) and/or continuous variables (with means and SD) from the following parameters:

- Hepatic Artery Resistive Index (HA RI).
- Hepatic Artery Peak Systolic Velocity (HA PSV).
- Portal vein velocity (PVV).
- Hepatic vein velocity (HVV).
- Hepatic vein waveform pattern.

We decided to separate the HA and PV velocities further into variables according to their site of assessment, either at the site of the anastomosis, or distally. Since velocities tend to be higher in the level of the anastomosis, and decrease progressively distally, we believe that it would be incorrect to analyze them together.

Most included studies reported multiple DUS parameters the most common being portal vein velocity (PVV) (46.3%), followed by RI (41.5%) and peak systolic velocity (PSV) (29.3%). A summary of the individual studies with comparative groups for a quantitative analysis are shown as continuous and in Table 4, and as dichotomous variables in Table 5. Quantitative analysis of pooled estimates is shown summarized in Table 6.

Table 4. Doppler parameters as continuous variables from individual studies.

DUS parameter	Author	Complicated (n)	Complicated Mean ± SD	Uncomplicated (n)	Uncomplicated Mean ± SD	*p*	Outcome
RI	Gu	11	0.62 ± 0.1	133	0.75 ± 0.09	<0.05	Hepatic artery thombosis
	Hall	4	0.52 ± 0.05	70	0.67 ± 0.1	NR	Hepatic artery thombosis
	Jamieson	37	0.5 ± 0.35	73	0.75 ± 0.15	0.001	Any graft complication
	Kaneko	7	0.52 ± 0.08	63	0.71 ± 0.1	NR	Hepatic artery thombosis
	Liao	11	0.58 ± 0.13	26	0.72 ± 0.21	0.027	Biliary complication
	Ou	8	0.65 ± 0.09	97	0.74 ± 0.07	0.013	Portal vein thrombosis
PSV distal	Jamieson	37	50 ± 42	73	107 ± 44	0.03	Any graft complication
	Ou	8	61.5 ± 19.18	97	47.6 ± 14.07	0.013	Portal vein thrombosis
PSV anast	Ahmad	50	132 ± 85.5	70	134 ± 88.2	0.87	Any graft complication
PVV distal	Jamieson	24	30 ± 44	81	72 ± 46	<0.05	Vascular complication
	Ou	8	8.25 ± 1.98	97	18.36 ± 4.43	0.003	Portal vein thombosis
	Suzuki	12	49.6 ± 3.8	49	47.5 ± 15.5	0.779	Portal vein stenosis
PVV anast	Hawkins	12	211.35 ± 72	10	52.3 ± 20	0.002	Portal vein stenosis
	Suzuki 1	12	165.1 ± 38.7	49	76 ± 41.8	<0.001	Portal vein stenosis
HVV	Hak	8	162 ± 37.5	20	58.6 ± 37.5	NR	Budd chiari syndrome
	Jamieson	37	25 ± 14	73	40 ± 32	0.04	Any graft complication
	Suzuki (2)	12	202.3 ± 81.1	67	130.7 ± 67.2	0.01	Hepatic vein obstruction

Abbreviations: DUS; Doppler ultrasound, HV; hepatic vein, HVV; hepatic vein velocity, NR; not reported, PSV; peak systolic velocity,
PVV; portal vein velocity, RI; resistive index. SD; standard deviation.

Table 5. Doppler parameters as dichotomous variables from individual studies.

DUS parameter	Author	Total n	Cut-off	Sensitivity	Specificity	AUC	*p-value*	Outcome
RI	Gu	144	<0.6	81.8%	95.2%	0.93	<0.05	Hepatic artery thombosis
	Kaneko	70	<0.6	83.0%	85.0%	NR	NR	Hepatic artery thombosis
	Liao	37	≤0.57	63.6%	92.3%	0.736	0.027	Biliary complication
	Ou	105	<0.65	67.5%	87.6%	NR	0.013	Portal vein thrombosis
	Herden	377	<0.55 or >0.8	51.0%	NR	NR	NR	Graft failure
PSV distal	Gu	144	≤37	63.6%*	76.5%	0.75	NR	Hepatic artery thombosis
	Ou	105	>70	37.5%	90.7%	NR	0.027	Portal vein thrombosis
PSV	Ahmad	120	< 50 and > 200	NR	NR	0.508	0.87	Any graft complication
PVV distal	Ou	105	<10	87.5%	99.0%	NR	0.003	Portal vein thrombosis
PVV	Hawkins	21	>180	83.0%	71.0%	0.672	0.002	Portal vein stenosis
	Hsu	70	>49.6	83.3%	81.2%	0.938	0.007	Portal vein stenosis
	Suzuki	61	>106	100.0%	79.6%	NR	<0.001	Portal vein stenosis
HVV	Hak	28	>126	50.0%	80.0%	NR	NR	Hepatic vein obstruction
	Suzuki (2)	79	>126	92.0%	57.0%	NR	0.01	Hepatic vein obstruction
HV pattern	Jamieson	96	Monophasic	66.7%	88.9%	NR	0.04	Any graft complication
	Jequier	30	Monophasic	92.1%	48.0%	NR	0.001	Acute rejection
	Someda	46	Monophasic	100.0%	78.3%	NR	NR	Any vacular complication
	Suzuki (2)	79	Monophasic	42.0%	86.0%	NR	NR	Hepatic vein obstruction

Abbreviations: AUC; area under the curve, DUS; Doppler ultrasound, HV; hepatic vein, HVV; hepatic vein velocity, NR; not reported, PSV; peak systolic velocity, PVV; portal vein velocity, RI; resistive index.

Parameters at the anastomosis unless specified otherwise.

*when combined with RI<0.6.

Table 6. Pooled analysis of Doppler parameters.

Parameter	Cut-off	Sensitivity (95%CI)	Specificity (95%CI)	OR (95%CI)	*p*	I^2	Outcome	Mean difference (95%CI) *	*p*	I^2	Outcome
RI	<0.6	83% (72% - 96%)	87% (78% - 84%)	675 (201.7 - 2258.7	<0.001	0	HAT	-0.15 (-0.19 - -0.11)	<0.001	38%.	Any graft complication
PVV (cm/s)											
Distal	-	-	-	-	-	-	-	11.6 (-24.1 - 0.8)	0.07	94%	Vascular complications
At the anastomosis	-	-	-	-	-	-	-	127.8 (48.3 - 207.4)	0.002	97%	PVS
HVV (cm/s)	> 126	75% (51% - 91%)	62% (52% - 72%)	47.6 (0.29 - 7816.9	0.14	89 %	HVO	52 (-35.9 – 140.0)	0.25	97%	Vascular complications
HV pattern	Monophasic	80% (68% - 90%)	78% (78% - 87%)	10.1 (4.4 - 23.2)	<0.001	0%	HVO	-	-	-	-

Abbreviations: CI; Confidence interval, DUS; Doppler ultrasound, HA; Hepatic artery, HAT; hepatic artery thrombosis, HVO; hepatic vein obstruction, HV; hepatic vein, HVV; hepatic vein velocity, OR; odds ratio, PSV; peak systolic velocity, PVS; portal vein stenosis. PVV; portal vein velocity, RI; resistive index. SD; standard deviation.

* Mean difference between complicated vs uncomplicated patients

- Pooling not appropriate or possible

The hepatic artery RI thresholds ranged from 0.57 to 0.65. A RI of < 0.6 had a pooled sensitivity of 83% (95%CI of 0.72 - 0.96) and specificity of 87% (95%CI of 0.78 - 0.84) for the diagnosis of HAT (n=797, OR=675.00, 95% CI 201.72 to 2258.73, p<.001, I^2=0%) Figure 14. The RI was lower in complicated grafts (0.52 to 0.65) vs uncomplicated grafts (0.67 to 0.75) [54, 57, 83, 87, 93, 110], with a pooled mean difference of 0.15 lower in complicated grafts compared with uncomplicated grafts (n=540, 95%CI: -0.19 to -0.11, p<.001, I^2 of 38%). In the subgroup analysis, the RI remained significantly lower in complicated patients, regardless of the outcome Figure 8.

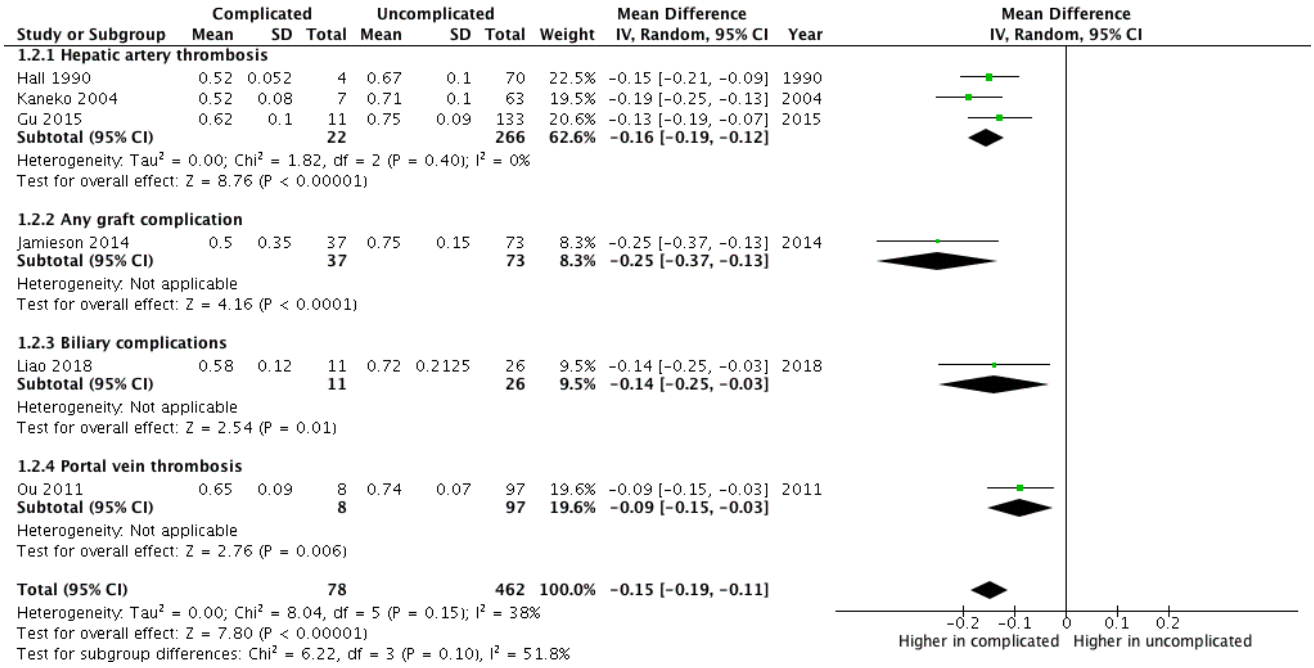

Figure 8. Forest plot of the RI as continuous variable.

One study analyzed the hepatic artery PSV distal to the anastomosis using a cut-off value of ≤ 37 cm/s (sensitivity of 63.6% and a specificity of 76.5%) for HAT [93], while another analyzed a different cut-off of > 70 cm/s (sensitivity of 37.5% and specificity of 90.7%, p=.027) for portal vein thrombosis [57]. Three studies analyzed the hepatic artery PSV at the anastomosis [53, 54, 95]; two of them did not provide data for group comparison [54, 95], while the other reported an Area Under the Curve (AUC) of

0.5085 of the hepatic artery PSV, indicating that no cut-off value could predict graft complications, with similar means between complicated and uncomplicated grafts (132 vs 134 cm/s) [53].

Three studies assessed the portal vein velocity (PVV) distal to the anastomosis [54, 57, 92], with a pooled mean difference of 11.6 cm/s lower in complicated patients (n=227, 95%CI: -24.07 to 0.79 cm/s, p=.07, I^2 of 94%) Figure 9.

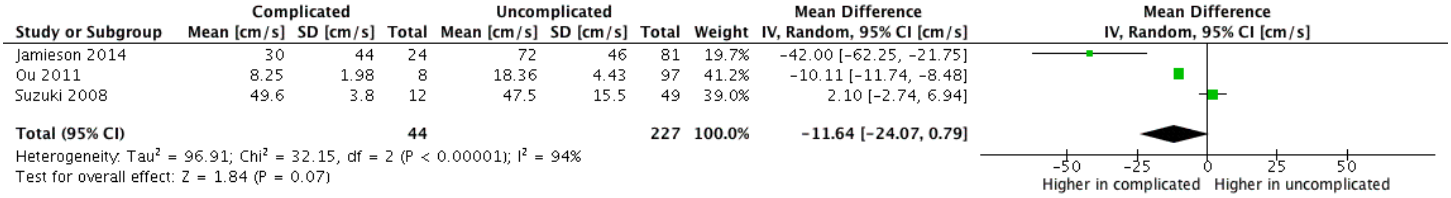

Figure 9. Forest plot of the PVV distal to the anastomosis as continuous variables.

In contrast, the studies reporting the PVV measured at the anastomosis [84, 92] showed a mean difference of 127.82 cm/s higher in grafts with portal vein stenosis, compared to uncomplicated grafts (n=82, 95%CI: 48.26 to 207.39, p=.002, I^2 of 90%) Figure 10.

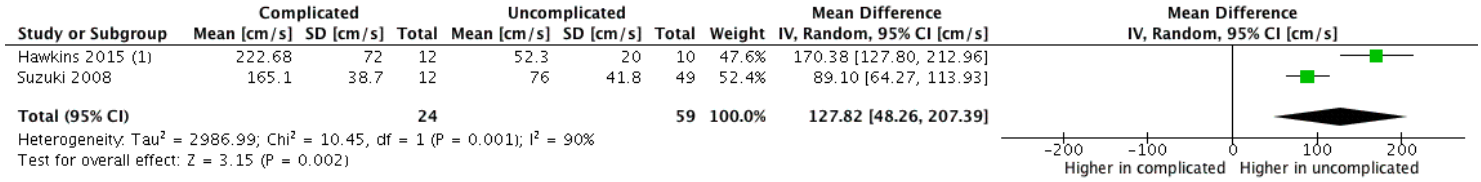

Figure 10. Forest plot of the PVV at the anastomosis as continuous variables.

All the authors used different cut-offs (>180 cm/s[84], >49.6[85], and >106 cm/s[92]), thus pooling was not considered appropriate for this DUS parameter as a dichotomous variable Figure 14.

Pooled analysis for the hepatic vein velocity (HVV) showed that a cut-off of >126 cm/s had a sensitivity of 75% and specificity of 62% for hepatic vein obstruction [91, 94] (n=107, OR 47.61, 95% CI: 0.29 to 7816.9, p=.14, I^2 of 89%) Figure 12.

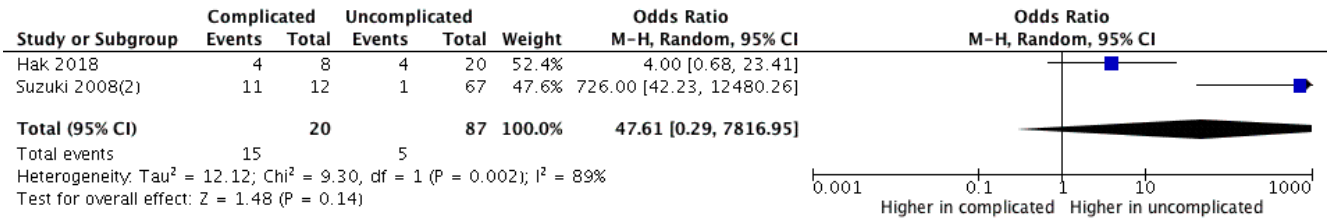

Figure 11. Forest plot of the HVV as dichotomous variable.

The mean difference was 52 cm/s higher in the complicated grafts (n=217, 95%CI: -35.9 to 140.1 cm/s, p=.25, I^2 of 97%) [54, 91, 94], this difference was not statistically significant, however, in the subgroup analysis, including just hepatic vein obstruction as the complication, the HVV was significantly higher in the complicated group with a mean difference of 93.29 cm/s (n=107, 95%CI: 64.3 to 122.3, p<.001, I^2 of 15%) Figure 12.

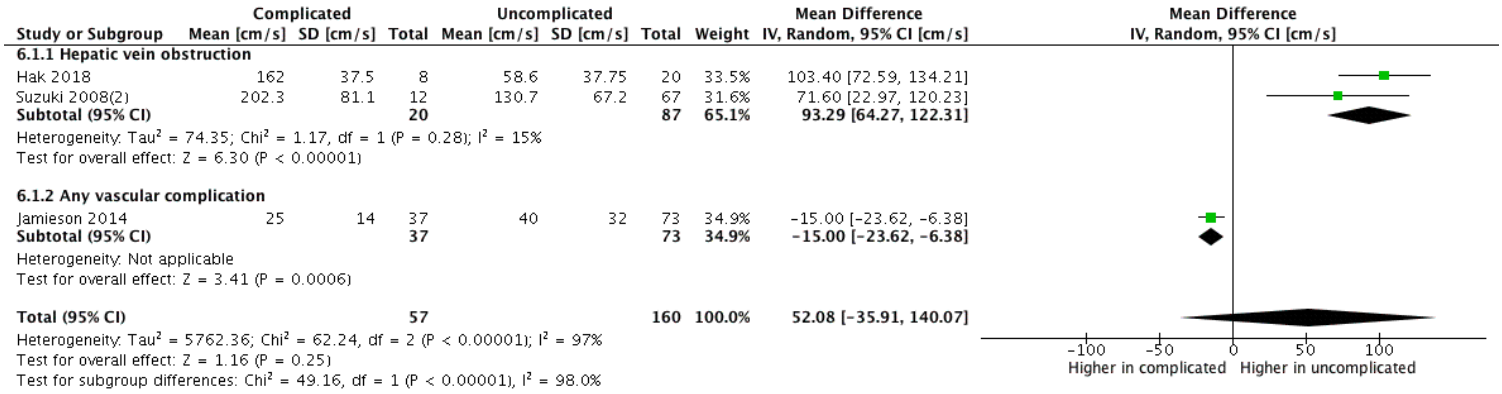

Figure 12. Forest plot of the HVV as continuous variables.

The presence of monophasic hepatic venous flow compared to any other type of waveform showed a pooled sensitivity of 80% (95%CI: 0.68 to 0.90), and specificity of 78% (95%CI from 0.78 to 0.87), for any graft related complication (n=251, OR 10.06, 95%CI: 4.37 to 23.16, p <.001, I^2 = 0%) Figure 13.

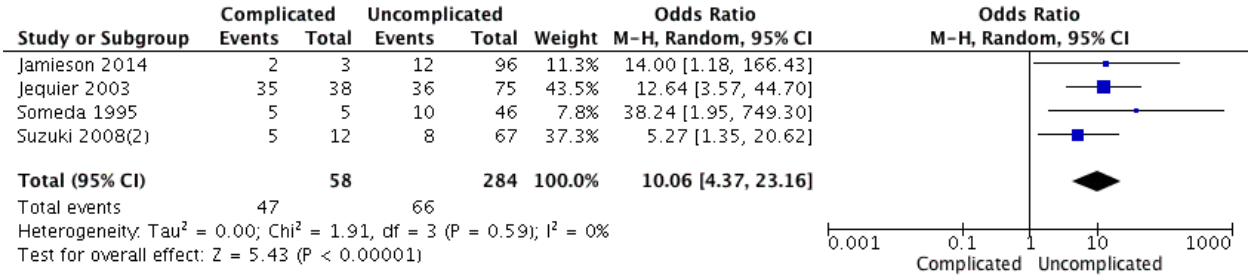

Figure 13. Forest plot of the monophasic hepatic vein flow pattern.

A summary of all the DUS parameters reported as dichotomous variables with the proposed cutoffs and sites of measurement relative to the anastomosis is shown in Figure 14, and also presented graphically as a Summary Receiver Operating Characteristic Curve in Figure 15.

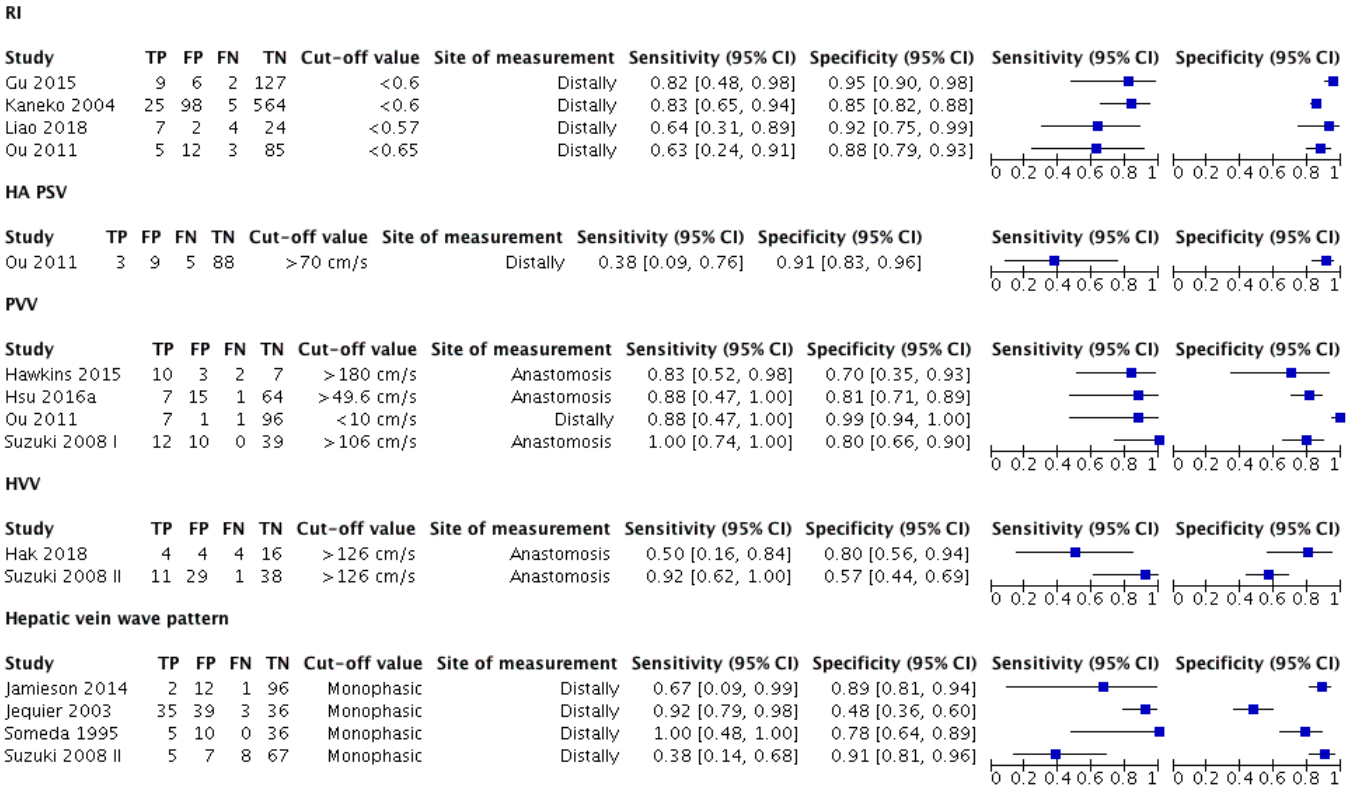

Figure 14. Forest plot of DUS parameters as dichotomous variables with cut-off values and site of measurements.

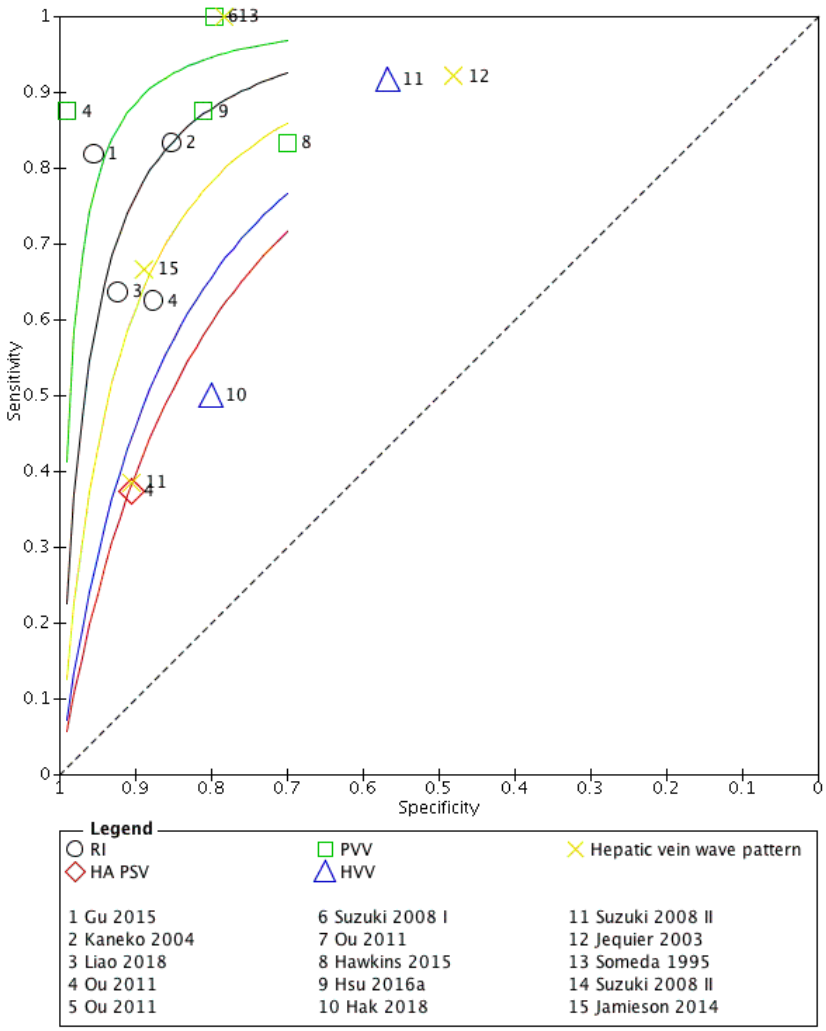

Figure 15. SROC curve of studies with dichotomous variables. The curves represent the summary of each DUS parameter, and the numbers each individual study.

Analysis of acceleration time was reported in only one study with a value of 0.13 s for complicated grafts and 0.11 s for uncomplicated grafts (p=0.17), for biliary complications [87]. Other parameters associated with complications include higher intrahepatic arterial and portal vein velocities in graft rejection ($p<0.05$)[54], hepatic vein velocity ratio > 4.1 in Budd Chiari syndrome [94], hepatic veins venous pulsatility index (>0% considered damped) in graft rejection [63], and average spleen size of 17 cm with thrombocytopenia in portal vein stenosis [81].

Discussion

Absent intravascular flow is almost always considered abnormal, with these patients requiring intraoperative evaluation or more invasive imaging for confirmation and treatment. However, absent flow on DUS is seen in only 12% to 40% of arterial complications [51, 67, 115]. A recurring diagnostic dilemma arises when flow is present, but the DUS parameter have changed or seem abnormal. Defining normal and abnormal DUS values could help guide appropriate changes in patient management and surveillance.

The most important biases we detected from these studies involved the selection of participants, where the eligibility criteria were not specified and/or the recruitment method was either unclear, based on the patient's outcome or based on the patient's underlying risk. One study had significant missing information (3/8 patients) due to non-visualized anastomosis [85]. For studies where important information was missing for quantitative analysis, our attempts to contact the authors were unsuccessful [93, 94]. Furthermore, there are known clinical predictors of early hepatic artery thrombosis [116], portal vein stenosis [92], and graft failure [27, 41]. However, these confounders were not usually considered, and a multivariate adjustment was rarely performed.

We found that the DUS parameters associated with complications include a RI <0.6, and a monophasic hepatic veins flow pattern [117]. Included studies showed variability in the suggested RI cut-offs (RI <0.57, <0.57, <0.6 and <0.65). Moreover, these differ from the normal values proposed currently (RI = 0.5 – 0.8 [51, 52, 117, 118], with a RI cut-off <0.4 [75]) extracted from studies that included adults and children [67].

Few studies analyzed the PSV, furthermore, they used different cut-offs and sites of measurements, restricting the possibility for quantitative analysis.

The main PVV at the anastomosis was 127.8 cm/s higher in complicated grafts (95%CI: 48.3 - 207.4 cm/s, p=0.002) but this estimate had high data heterogeneity (I^2=95%).

The PVV distally to the anastomosis did not show statistically significant differences between complicated and uncomplicated grafts (11.6 cm/s, 95% CI: -24.1 - 0.8, p=0.07). Nonetheless, one study reported high accuracy of PVV distal to the anastomosis using a cut-off of <10 cm/s (sensitivity of 88% and specificity of 99% p=.003) for portal vein thrombosis [57].

The HVV did not show statistically significant differences between complicated and uncomplicated grafts. In contrast, the subgroup analysis considering just HVO as the outcome was statistically significant and had low heterogeneity (I^2 of 15% for HVO, vs I^2 of 94%.for any graft complication).

Pooled analysis was not possible for several parameters, however, suggested cut-offs from individual studies are provided in Table 4. The published cut-offs with the highest accuracy include the combination of RI <0.6 with PSV distal to the anastomosis ≤37 cm/s with a sensitivity of 63.6% and specificity of 99.5%. to predict HAT [93], and a PVV at the anastomosis >106 cm/s with a sensitivity of 100% and specificity of 79.6% to predict vein stenosis [92].

A *tardus parvus* pattern has been widely described in vascular stenosis [119-122]. Acceleration times have been reported in only two pediatric studies, showing longer acceleration times in complicated grafts, however, this difference was not statistically significant [54, 87].

Multiple complications can alter the hepatic artery PSV in different ways. While an increase in PSV is seen in arterial stenosis [123], hepatic vein obstruction [124] , portal thrombosis [57] and portal hypertension, a low PSV is associated with hepatic artery thrombosis [54]. This is an example of the interdependence of arterial, portal venous, and systemic venous flow of the liver and a more robust analysis requires the assessment of all vessels [57, 125-129].

Limitations

The main limitation of this systematic review is related to the factors that compromised our ability to calculate pooled estimates for every parameter. This was due to a lack of studies where the exact DUS values were provided, lack of clarity on where the values were measured in the vessel relative to the anastomosis, and high clinical heterogeneity. Measurement at the anastomotic site is difficult [51, 85, 123],

or not routinely performed [115], and high inter- and intraobserver variation have been reported [130]. The clinical heterogeneity was due to high variability in the age groups, the DUS parameters measured, and differences in the outcomes.

Many meta-analyses commonly include a small number of studies. A study of the Cochrane Library database meta-analyses showed that more than half included less than 3 studies [131]. The main disadvantage is that the analysis of data heterogeneity it difficult in meta-analysis with a low number of studies. This is especially concerning when authors use a fixed-model approach, which assumes no between-study variability [78, 131].

We acknowledge that in our study, despite using a random-effect model and assessing data heterogeneity using the I^2 index, undetected heterogeneity could still be possible due to the low number of included studies [131]. However, there is evidence that the meta-analysis size has a small effect on heterogeneity [131, 132], and other methods for meta-analysis for diagnostic accuracy exist, such as the summary receiver operating characteristic (SROC) curve approach, and hierarchical models (also known as multilevel models)[78].

We were unable to assess for publication bias due to the small number of papers found for any particular DUS value [104, 107]. However, the PRISMA-DTA statement, does not include publication bias in their guidelines arguing that there is limited evidence that this is an issue for systematic reviews of diagnostic studies, and there is not a statistically powerful test to reliably assess for publication bias in the contest of diagnostic test accuracy systematic reviews **[69].**

Defining multiple DUS abnormalities for specific outcomes is difficult, as many complications are interrelated. For example, stenoses can lead to partial thromboses. While the flow velocity could be high at first, eventually it could be extremely slow before a complete thrombosis occurs. Furthermore, patients that have hepatic artery abnormalities might impair the perfusion to the graft leading to biliary strictures, likely related to concurrent ischemia to the biliary system[45].

Some articles have proposed that in systematic reviews of diagnostic studies the data extraction phase should be done by more than one person to reduce errors and risk of bias [55]. In our study, the data extraction phase was done by one reviewer, this might have potentially introduced bias.

Potential areas of research include the evaluation of combined DUS parameters (from arterial, venous and portal system simultaneously), differences in parameters over time, and intrahepatic parameters. Further studies should report the timing of DUS assessment related to the liver transplant date, specify the exact site of measurement in regard of the anastomosis, and provide means and standard deviations of continuous in addition to dichotomous variables with proposed optimal cut-offs, and previously published suggested cut-offs.

Conclusion

This systematic review will provide comprehensive and objective analysis of the relationship between Doppler ultrasound measurements and graft-outcomes, filling the gap between known radiological evidence and clinical practice.

In conclusion, a low hepatic artery RI, and a monophasic hepatic vein pattern showed statistically significant differences associated with graft complications. No statistically significant differences were seen in the portal vein velocity distal to the anastomosis or the hepatic vein velocity between complicated and uncomplicated patients.

CHAPTER 3

Predictive Value of the Immediate Postoperative Doppler Ultrasound Evaluation in Pediatric Liver Recipients

Hypothesis and objective

Our hypothesis was that Doppler Ultrasound values obtained in the immediate post-operative period differ in patients that will develop a severe complication, compared with patients managed conservatively. The objective of this study was **t**o analyze the prognostic value of multiple parameters of DUS in the immediate postoperative period following liver transplantation in children.

Abstract

Background: Doppler ultrasound (DUS) is routinely used to assess graft status after liver transplantation (LT). Although early post-surgical assessment is encouraged, the exact prognostic value of DUS parameters is unknown.

Objective To determine the prognostic value of DUS parameters obtained in the immediate postoperative period.

Methods We included all children (<18 years) receiving a primary LT at our center from 2000 to 2019 who were assessed with DUS within 12 hours after LT. Our primary outcome was development of any graft-related complication requiring invasive management compared to patients with no, or mild complications, managed conservatively.

Descriptive statistics are presented in absolute values, percentages, median and interquartile range (IQR). Associations between predictors and outcomes were determined using univariate analysis and multivariable logistic regression are expressed as odds ratio (OR) or adjusted odds ratio (aOR) with

95% confidence intervals (95%CI). Receiver operator characteristic curve (ROC) analysis was used to find optimal thresholds for predictors.

Results: Our sample included 79 liver recipients with a median age of 1.3 years (0.7 – 7.2), 25 (44%) were females and 45 (57%) had a living donor. The median time between LT and DUS was 1.8 hrs (1.1 – 3.9); 61 (77%) within 4 hrs.

Twenty-eight (35%) patients had a complication that required invasive management vs 51 (65%) patients that had no, or mild complications treated conservatively. The median time to detection was 11 days (IQR 4 - 46). Regardless their type of management, the most common complications were portal vein thrombosis (10, 21%), biliary leak (9, 19%), and biliary stricture (7, 15%). The median follow-up was 3.2 years (IQR 1.5 – 7); two of these 28 patients had vascular complications detected on the immediate post-op DUS.

Univariate analysis showed that the median portal vein velocity (PVV) distal to the anastomosis was lower in the invasive management group [43 (20 - 59) vs 60 (40 – 94), p=0.008]. The optimal cut-off value to predict invasive management was <60 cm/s (sensitivity=81%, specificity=54%, AUC=0.69 [95%CI: 0.57 - 0.82]). No other clinical or DUS parameter showed statistically significant differences between patients with invasive management vs conservative management.

A multivariate logistic regression analysis showed a 6.4 times increase in the odds of having a complication requiring invasive management with a PVV<60 cm/s compared with PVV≥60 cm/s, after adjusting for age, sex, diagnosis, dialysis pre-transplant, operation time and hepatic artery peak systolic velocity (aOR 6.37; 95%IC 1.71-23.72, *p*=0.006).

Conclusion Immediate DUS assessment provides valuable information to identify high-risk patients through the PVV distal to the anastomosis. No other DUS parameter showed statistically significant differences in the invasive management vs the conservative management groups.

Introduction

Immediate post-operative Doppler ultrasound (DUS) assessment is routinely performed from the first day after liver transplantation (LT) to predict graft status and detect any complication [50, 53, 93, 133, 134]. This assessment is crucial, since graft failure is the leading cause of death [25], and most complications present in the early post-operative period. DUS abnormalities predominantly present in the first two weeks, with the highest incidence for vascular complications on the first day after LT [76]. Thus, immediate post-operative DUS assessment acts as a baseline study for further comparison, facilitating interpretation of future imaging studies and patient management.

When DUS abnormalities are present, prompt surgical intervention can improve graft and patient survival [134]. Multiple studies have shown that DUS can be used to detect and predict the outcome of the graft even before patients develop symptoms or present abnormal laboratorial findings [76, 133]. Treatment of these pre-symptomatic or asymptomatic patients further improves long-term outcomes. For example, treatment of hepatic artery thrombosis (HAT) in asymptomatic patients showed better graft salvage compared to symptomatic patients (81.4 vs 40%) [135].

However, in children, the exact prognostic value of each DUS parameter is less understood and varies among studies in relation to the type of population, outcome, and timing of assessment. Studies have reported different thresholds, different degrees of diagnostic accuracy, and have analysed diverse complications. For example, one study showed that a resistive index (RI) <0.5 or >0.8 predicted vascular complications [53], another study reported that a RI ≤0.57 to predict biliary complications [87], while another used a RI <0.6 to be predictive for HAT only [110].

Furthermore, most of the studies analyzing the prognostic value of DUS do not adjust for other known clinical risk factors for complications, such as patient's characteristics (e.g. young age [136, 137], weight [138-140], portal vein diameter [92, 138], arterial variants [141], liver disease [116], history of previous thrombosis [137, 142]), donor's characteristics (e.g. living vs death donor [143], donor's age [144], CMV status [39 139, 145],

graft-to-spleen ratio [146]), or surgery-related factors (e.g. type of graft [147], type of vascular anastomosis [148] [147], cold ischemia time [149] operation time [144], volume centers [39]). Another important risk factor to consider in pediatric liver transplantation is the vascular size discrepancies. The DUS parameters obtained in these two sites (either in the native or transplanted vessel) might differ, in addition to the potential decrease in caliber cause by the anastomosis itself [59, 97].

Finally, many studies analyse the DUS value of just one vessel or only include one type of complications in their analyses (either arterial, venous or portal). This approach might be inappropriate since the portal and arterial systems are interrelated though a regulatory system commonly known as the "buffer response", a mechanism mediated by adenosine washout in the portal triad [150-152] that produces dilatation of the HA to regulate blood flow, according to the portal flow [128] [129]. This regulation, is independent of the hepatic oxygen supply [153], and it has been studied with DUS by proving changes in the resistive index (RI) in cirrhotic patients with hepatopetal flow after TIPS [128], and in pediatric liver transplant recipients, with high hepatic artery velocities and lower RIs after a decrease in the portal flow [57, 126].

There is an increasing demand for DUS assessment immediately after skin closure to provide an important anchoring baseline to ensure vessel patency, and to help interpret subsequent perturbations in measurement parameters. Our goal was to determine if any DUS parameter from this immediate post-operative assessment could predict future complications that require invasive management (e.g. surgery or endovascular procedures) in the following five years after LT. This could potentially identify patients that would benefit from more frequent DUS assessment to detect these complications promptly.

Methods

We recruited all patients younger than 18 years old that received a primary liver transplant at the Stollery Children's Hospital from 2000 to 2019 and had a DUS assessment within 12 hours after transplant. The end of follow-up date was December 2019. Multiorgan recipients and cases of re-transplantation were excluded.

Our sample size included all liver transplant recipients since 2000, because prior to 2000 no electronic record of DUS images were available. Our data, including demographics and clinical information, were extracted from a local access-restricted pediatric transplant database. Missing information was obtained from the University Hospital's Organ Transplant Tracking Record (OTTR®) software. Data included recipient's age, sex, weight, indication for transplant, history of previous abdominal surgery, or portal vein thrombosis, creatinine, dialysis status, ePELD at transplantation, UNOS MELD/PELD, CMV status, donor's age, ABO compatibility, liver volume. Surgical characteristics such as time and day of the transplant, if arterial micro-anastomosis was performed, operation time, cold ischemia time, rewarm time, arterialization minutes, spleen length and volume (when a cross sectional image study was available).

Doppler parameters were extracted from local PACS. We included DUS assessment within the first 12 hours after liver transplantation. Most DUS assessments were done in the ICU. using a (iU22 units, Philips Health- care) with probes including C8-5, L12–5, C9–4, and C5-1 MHz) performed by ultrasound technicians with experience in pediatric ultrasound. Images were revised by pediatric radiologists who corroborated DUS parameters directly when needed. The parameters extracted were time and date of the DUS assessment, resistive index (RI), peak systolic velocity (PSV), end diastolic velocity (EDV) in the arteries, main velocity in portal (PVV) and hepatic veins (HVV), and hepatic vein pattern, presence of splenomegaly, defined if splenic length greater than 90th percentile upper limit by age, measured with DUS it was considered splenomegaly [154, 155]. Velocity measurements

were angle corrected. If values were not measured at the time of examination, we calculated them manually from saved imaged when possible. If multiple measurements were taken, the best technically or the one with the highest velocity was selected. We did not include parameters if measured inappropriately, either by lack of angle-correction or site of measurement. Investigators were not blinded to patients' characteristics or clinical outcomes.

Our primary outcome was development of any complications related to the graft including vascular and non-vascular, that required invasive management up to five years after liver transplantation. Procedures categorized as invasive management included: diagnostic angiographic procedures, angioplasties, vascular stent placements, surgical revisions, open biliary repairs, closed biliary repairs (endoprosthesis placement) or re-transplantation (either surgical, endovascular or endobiliary procedures). Our comparator group were uncomplicated patients, and patients that developed complications treated conservatively defined as the absence of any of the previously mentioned invasive procedures.

Grafts with vascular complications commonly manifest different DUS parameters compared to uncomplicated grafts [53, 54, 82, 89, 91, 92, 94]. Similarly, when non-vascular complications are present, DUS parameters may also change. A case-control study demonstrated that the RI was lower in patients that developed biliary complications including strictures and one biliary leak [87]. These changes are the result of the relationship between inadequate arterial supply and biliary complications, which include strictures [156 157], and biliary leaks [59 157 158].

Moreover, acute rejection has also been associated with the development of biliary complications in pediatric LT [157], and DUS parameters also change in this setting [63]. This has been studied extensively in renal transplant recipients, where Doppler ultrasound has proven to be useful to predict and detect graft rejection [159-161]. Furthermore, studies have reported abnormal RI (<0.55 or >0.8) in children with early hepatic graft failure [102], and changes in the hepatic vein wave pattern in children with acute graft rejection [61].

To build the model for the multivariate regression analysis we included variables that were known risk factors for complications, in addition to considering the relevant results of our univariate analysis. We included the following independent variables: age, sex, pre-operative diagnosis (biliary atresia vs other), dialysis before LT, prior portal vein thrombosis, operation time, portal vein velocity and common hepatic artery peak systolic velocity measured within the first 12 hours after LT at the size of the anastomosis and distally.

We selected only the previously known clinical predictors with the highest reported effect size to avoid overfitting. We did not correlate highly interdependent variables to reduce risk of multicollinearity because it difficults the interpretation of the results from the regression analysis. Associations between potential predictor variables and outcomes were determined using univariate and multiple logistic [odds ratio (OR); 95%CI] or linear (effect size, ES; 95%CI) regressions. Descriptive statistics are presented in absolute values, percentages, means and standard deviations (SD). Associations between potential predictor variables and outcomes were determined using univariate and multiple logistic regression [odds ratio (OR); 95%CI]. We present data as mean ± SD, median and 25 and 75 interquartile range (IQR). Univariate and multivariate analysis comparison with p-values <0.05 were considered significant. We used a complete-case approach in the multivariate logistic regression analysis to manage missing data.

Statistical analysis was performed by using the STATA 12.0 (StataCorp. 2011. *Stata Statistical Software: Release 12*. College Station, TX: StataCorp LP) or SPSS (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp).

Results

From 1990 to 2019, 275 pediatric liver transplants have been performed at the Stollery Children's Hospital, 235 were primary liver transplantations (40 retransplantation were not included). Of these 235 patients, 63 did not have an electronic imaging file (implemented since 2000) and were excluded as the lack of an electronic version precluded our ability to obtain various Doppler measurements. Of the remaining 172 patients, only 81 had a DUS assessment within 12 hours after surgery. One patient had a PVT and required retransplantation, another had PVT and required surgical thrombectomy, they were not included in the final analysis resulting in our final included sample size.

Our sample of 79 liver recipients had a median age of 1.26 years (0.7 – 7.2), 25 (44%) were females and 45 (57%) had a living donor. The median interval between LT and DUS assessment was 1.8 hrs (1.1 – 3.9); 42 (53%) with DUS done within the first 2 hrs after surgery, 61 (77%) in the first 4 hours, and 69 (87%) in the first 8 hours post-surgery.

It is noteworthy to mention that there was a change in the practice of our institution. After December 2013; plastic surgeons performed most of the microvascular anastomoses, since then, the immediate post-surgical DUS assessment in the pediatric intensive care unit was implemented, before December 1^{st,} 2013 the average DUS assessment was 24.7 hours, after that, it was 3.97 hours.

Four patients had complications immediately after LT detected by the post-operative DUS assessment. One had an IVC stenosis managed conservatively, another had simultaneous hepatic artery and portal vein thrombosis that required retransplantation, another had an IVC occlusion that required surgery, and another a portal vein thrombosis that required surgical thrombectomy.

Twenty-eight (35.4%) patients required invasive management (our outcome), 11 (13.9%) patients had mild complications managed with conservative treatment, and 40 (31.6%) patients that did not develop any complication during follow-up Figure 16.

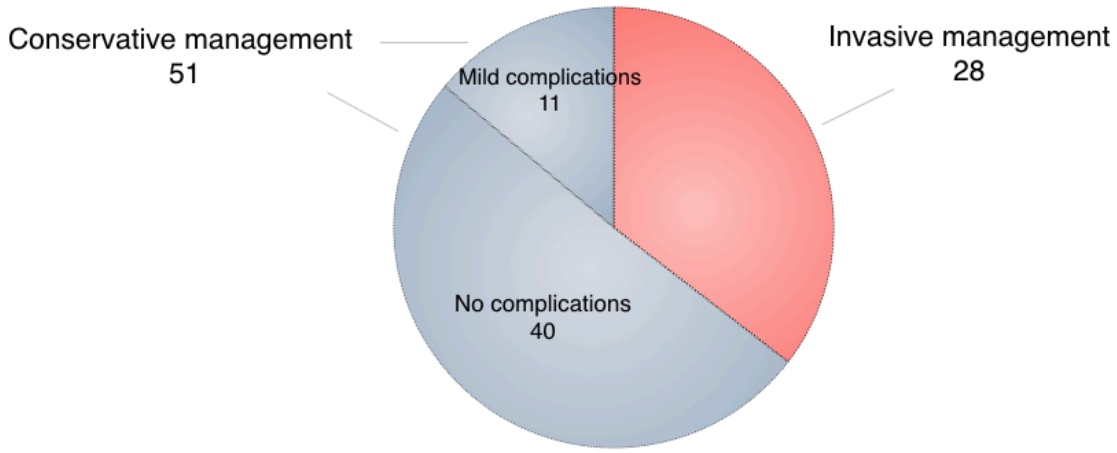

Figure 16. Pie-chart of included participants by outcome.

They were 52 complications; 13 presented in the conservative management groups, 40 in the invasive management group. The most common types of complication were hepatic artery stenosis (9, 17%), portal vein thrombosis (8, 15%), and biliary leak (8, 15%) Table 7, Figure 17.

Table 7. Number of complications by group.

Complication	Conservative management		Invasive management		Total	
	n	%	n	%	n	%
Hepatic artery thrombosis	1	1.9	6	11.5	7	13.2
Hepatic artery stenosis	4	7.5	5	9.6	9	17.0
Portal vein thrombosis	1	1.9	7	13.5	8	15.1
Portal vein stenosis	3	5.7	4	7.7	7	13.2
Biliary stricture	1	1.9	6	11.5	7	13.2
Biliary leak	0	0.0	8	15.4	8	15.1
IVC stenosis	2	3.8	2	3.8	4	7.5
IVC or HV occlusion	0	0.0	2	3.8	2	3.8
Other vascular including AV fistula	1	1.9	0	0.0	1	1.9
Total	13	24.5	40	76.9	53	100.0

AV, arterio-venous; IVC, inferior vena cava; HV, hepatic vein.

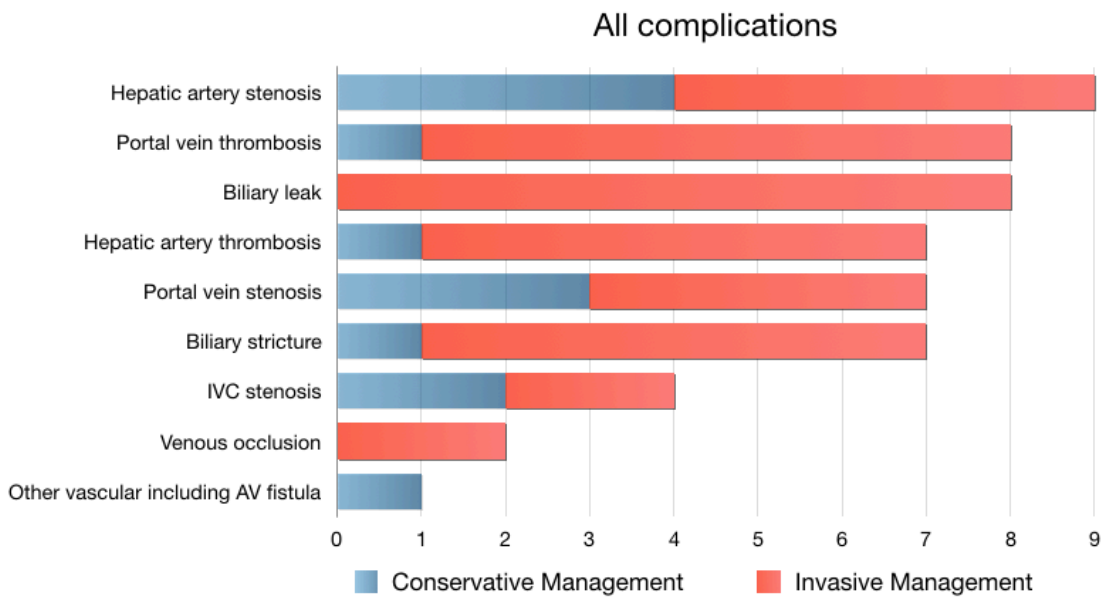

Figure 17. Bar chart of all complications by group.

Median days to develop a complication was 11.5 (4 - 49 days), range from 0 to 1728 days. The mean follow-up time was 4.5 years (SD 3.89). The median follow-up graft survival was 3.0 years (1.4 – 6.0), range from 0.01 to 16.71 years) (Figure 18), and the median patient survival time was 3.2 years (1.7 – 7.0), range from 0.01 to 16.71 years (Figure 19). Most events where observed in the first 2 years after LT. There were no statistically significant differences between patient and graft survival between the invasive management vs conservative management group (graft failure: HR=1.71, 95%CI: 0.52 - 5.61, p=0.38, patient death: HR=1.21, 95%CI: 0.29 - 5.08, p=0.79).

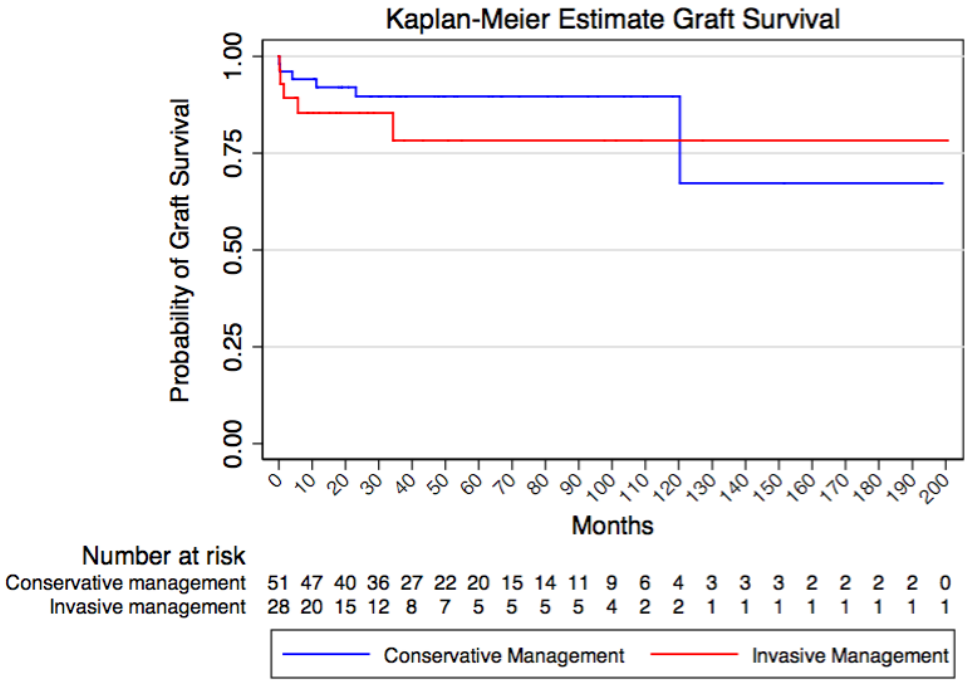

Figure 18. Kaplan-Meier Estimate Graft Survival.

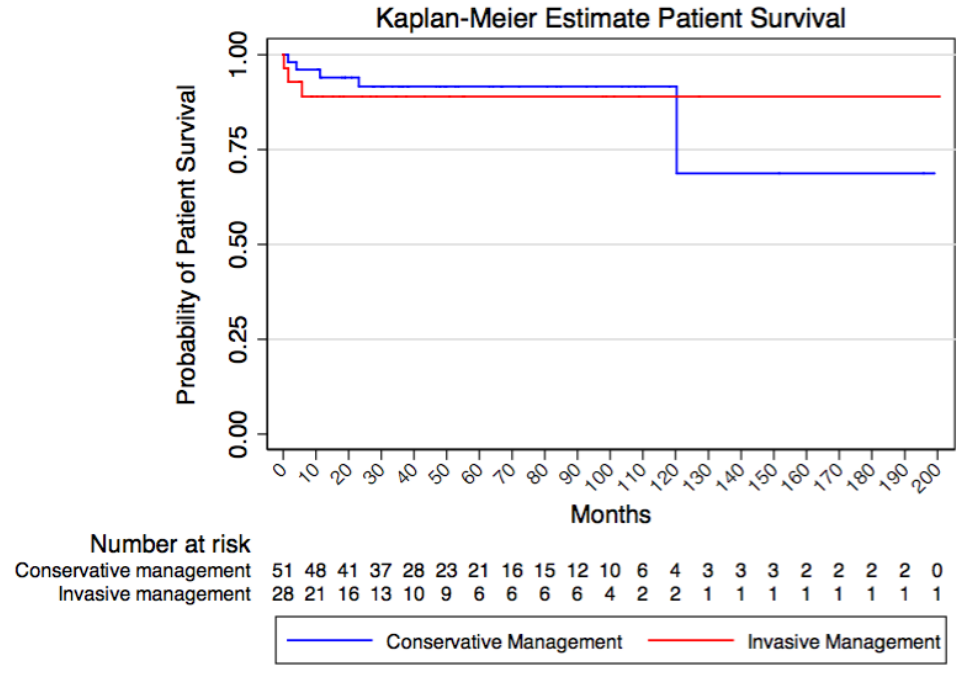

Figure 19. Kaplan-Meier Estimate Patient Survival.

The mean hours between surgery and DUS assessment were significantly lower in patients that required invasive management compared with conservative management [1.35 (1 - 2.43 vs 2.48 (1.17 - 6.58), *p*=0.009].

Univariate Analysis

Results from the univariate analysis (Table 8) showed that the main portal vein velocity (PVV) measured distal to the anastomosis was the only value that showed a statistically significant difference between invasive management vs conservative management [42.5 (20 - 59) vs 60 (40 - 93.5), *p*=0.015]. The main PVV had an AUC = 0.687 95%CI; 0.559 - 0.816) (Figure 20).

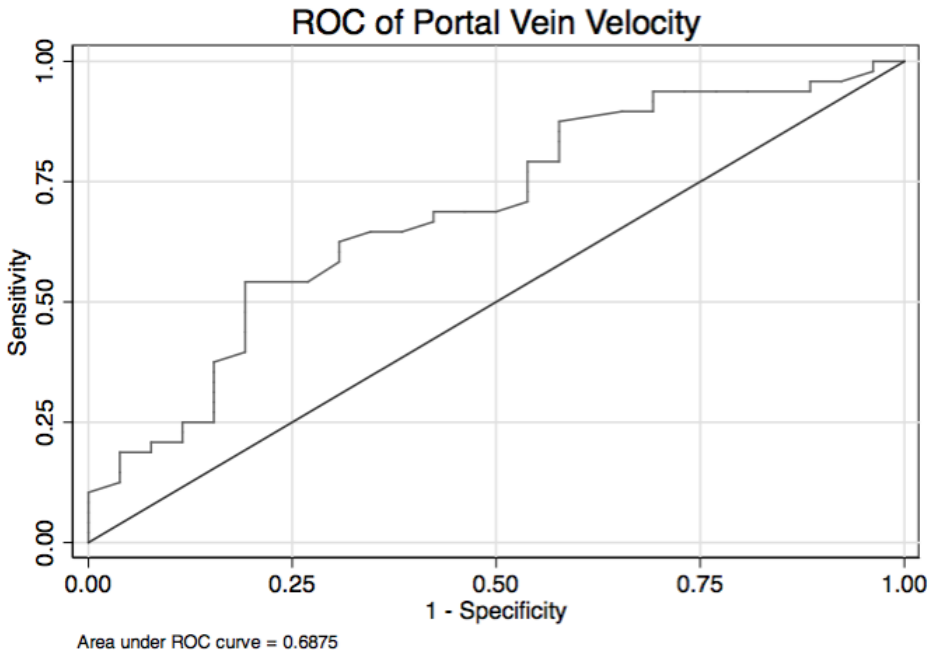

Figure 20. ROC of the portal vein velocity accuracy to predict complications that will require an intervention.

We performed a Youden J statistical analysis to determine the Youden index which is defined as the maximum of sensitivity + specificity -1. This test is used to determine the maximum total diagnostic accuracy a biomarker can achieve, and it mirrors the maximum vertical distance between a receiver operating characteristic (ROC) curve and the chance line [162]. The results of this analysis showed that

the optimal cut-off value was achieved when at 60 cm/s (sensitivity=80.8%, specificity=54.1%, PPV=49, NPV=84, AUC=0.687, 95% CI: 0.569 - 0.816, *p*=0.006).

No other clinical or DUS parameter showed statistically significant differences. In the complicated group, there was a greater proportion of females (57.1 vs 42.9%, p=0.089), higher HA peak systolic and end diastolic velocities, lower resistive indexes and lower hepatic veins velocities, however, these differences were not statistically significant (Table 8).

Table 8. Results from univariate analysis; risk factors in complicated and uncomplicated or mildly complicated patients.

	Conservative Management	**Invasive Management**	
Risk factor	**Median (25 - 75 IQR) n (%)**	**Median (25 - 75 IQR) n (%)**	***P* value**
Age (years)	1.4 (0.68 - 7.65)	1.24 (0.74 - 5.58)	0.494
Sex (female)	19 (37)	16 (57.1)	0.089
Weight (kg)	9.93 (7.75 - 27)	9.6 (7.4 - 20.1)	0.346
Diagnosis (Biliary atresia vs other)	17 (33)	11 (39.3)	0.751
Previous abdominal surgery	26 (51)	16 (57.1)	0.602
Previous venous thrombosis	2 (3.9)	1 (3.6)	0.938
Dialysis prior to transplant	2 (3.9)	4 (14.8)	0.086
Splenomegaly	28 (56.0)	15 (53.6)	0.836
Donor's age	28 (19 - 38)	30.5 (12 - 42)	0.782
Type of graft (partial vs other)	11 (25)	8 (30.8)	0.6
Micro anastomosis (artery)	31 (60.8)	17 (60.7)	0.995
Cold ischemia time (min)	69.5 (48 - 351)	101 (47.5 - 305)	0.779
Operation time (min)	450 (372 - 515)	448 (319 - 526)	0.669
Time between surgery and DUS (hr)*	2.48 (1.17 - 6.58)	1.35 (1 - 2.435)	0.009
CHA at the anastomosis PSV (cm/s)	152.65 (113 - 209)	157.5 (124 - 215)	0.391
CHA at the anastomosis RI	0.85 (0.7 - 0.89)	0.76 (0.56 - 0.84)	0.13
CHA distal to the anastomosis PSV (cm/s)	76 (55.9 - 125)	90.35 (60.5 - 145.5)	0.385
CHA distal to the anastomosis RI	0.78 (0.68 - 0.88)	0.795 (0.62 - 0.87)	0.411
MPV vel at the anastomosis (cm/s)	104 (82 - 136)	96.7 (40 - 150)	0.511
MPV vel distal to anastomosis (cm/s)*	60 (40 - 93.5)	42.5 (20 - 59)	0.015
Hepatic vein velocity (cm/s)	31 (16 - 43)	22.16 (20 - 33)	0.183
Hepatic vein pattern (monophasic)	6 (3.06)	3 (0.84)	0.897
Graft survival (months)	48.12 (27.39 - 84.92)	27.595 (9.62 - 55.2)	0.113
Patient survival (months)	47.84 (23.13 - 83.61)	25.43 (8.72 - 47.065)	0.164

*Positive prediction with a p-value <0.05. CHA; Common hepatic artery, DUS; Doppler ultrasound, MPV; Main portal vein, PVS; Peak Systolic Velocity, RI; Resistive index.

Multivariate Analysis

The multivariate regression analysis showed a 6.4 times increase in the odds of requiring invasive management with a PVV<60 cm/s, compared with PVV≥60 cm/s, after adjusting for age, sex, diagnosis, dialysis pre-transplant, operation time and common hepatic artery peak systolic velocity (aOR=6.37; 95%CI: 1.71-23.72, *p*=0.006) Table 9.

This analysis was calculated with 72 patients and was statistically significant, with a p-value of 0.007, with an AUC = 0.818. Figure 21.

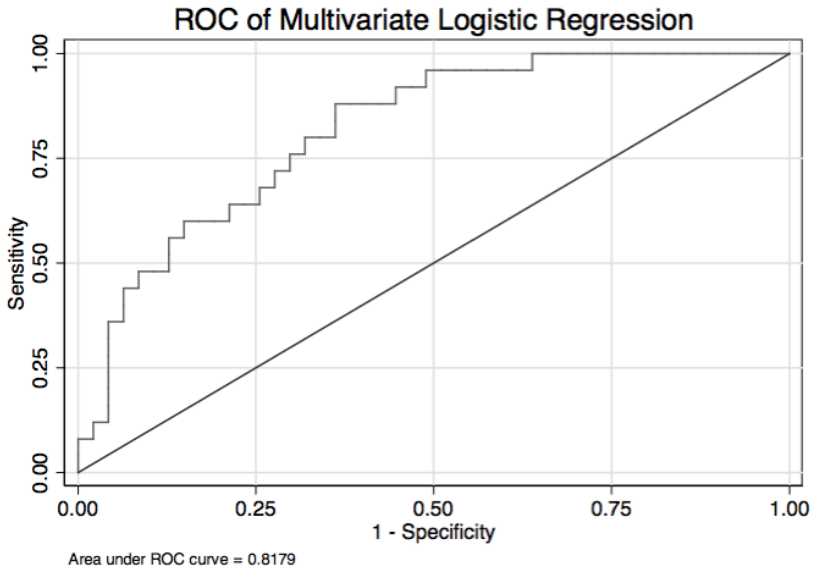

Figure 21. ROC of Multivariate Logistic Regression.

Table 9. Results from Multivariate Logistic Regression.

Variables	**Odds Ratio**	**St.Err.**	**p-value**	**95%CI**
Age (yr)	0.979	0.071	0.772	0.85 - 1.13
Sex (female)	0.867	0.502	0.806	0.28 - 2.70
Diagnosis (BA vs other)	2.069	1.412	0.287	0.54 - 7.89
Dialysis**	11.003	13.193	0.046	1.05 - 115.39
Prior thrombosis	1.542	2.163	0.758	0.10 - 24.12
Operation Time (min)	0.997	0.003	0.287	0.99 - 1.00
Time between LT and DUS**	0.674	0.127	0.037	0.46 – 0.98
PVV <60 cm/s***	6.376	4.274	0.006	1.71 - 23.72
CHA PSV	1.008	0.006	0.159	0.99 - 1.02
Constant	0.207	0.366	0.373	0.006 - 6.64

Mean dependent var	0.347	SD dependent var	0.479
Pseudo r-squared	0.242	Number of observations	72
Chi-square	22.47	p-value	0.007

*** $p<0.01$, ** $p<0.05$, * $p<0.1$

BA; Biliary atresia, CHA; Common Hepatic Artery, DUS; Doppler Ultrasound, LT; Liver transplantation, PSV; Peak Systolic Velocity, PVV: Portal Vein Velocity measured distal to the anastomosis.

Discussion

In children, the exact prognostic value of DUS assessment immediately after LT is unclear. Although some studies exist, they rarely consider confounding patient-, donor- and surgery-related risk factors, or analyze only one vessel or one type of complication. In our study, we included multiple clinical and surgical previously reported risk factors, and multiple DUS parameters.

Patient that developed complications and required invasive management had an earlier postoperative DUS assessment compared to conservative [1.35 (1 - 2.43 vs 2.48 (1.17 - 6.58), p=0.009]. This is likely related to a more urgent request by the operating surgeon due to greater concern related to clinical suspicion or a specific patient risk, rather than complications as consequences of the earlier DUS assessment.

The only DUS parameter that showed statistical differences was the portal vein velocity measured distal to the anastomosis. Previously published studies, including a multicentric study including our institution, have showed similar findings, with lower PVV in patients that developed vascular complications (30 ± 44 vs 72 ± 46 cm/s. p=0.073) [54]. The reported normal values of the portal flow include mean peak velocity of 55.1 ± 31.8 cm/s [82].

The cut-off value of <60 cm/s showed the best diagnostic accuracy with a relatively high sensitivity=80.8%, but low specificity=54.1%. This low specificity reflects that there were patients with a PVV <60 cm/s who did not require invasive management. This limited accuracy is possibly related to two main reason: Firstly, we included all graft-related complications, some of which might not be related with portal flow. Secondly, the decision for invasive management is not based on one isolated DUS parameter. Other studies in children that have reported a cut-off value of <10 cm/s in the immediate postoperative period with a sensitivity of 87% and specificity of 99% p=0.003 for portal vein thrombosis [57].

The PVV measured at the anastomosis was also lower in complicated grafts, but this difference was not statistically significant (106 ± 65 vs 120 ± 65, p=0.51). Multiple studies have analyzed this parameter to predict portal vein stenosis, reporting cut-off values of >180 cm/s (sensitivity=83%, specificity=71%, p=0.002) during the first week post-transplant [84], >49.6 cm/s in the first 6 months post LT (sensitivity=83.3%, specificity=81.2%, p=0.007) [85], and >106 cm/s (sensitivity=100%, specificity=79.6%, p<0.001) from day 1 to 12 years (mean 15 months) after LT [92]. It is noteworthy that in our cohort, the most common complication was portal vein thrombosis (21.3%), while other complications had a low incidence. This could be the reason why the PVV distal to the anastomosis was the only significant DUS parameter predictor of invasive management, and other arterial or venous DUS parameters had no statistically significant differences.

A low RI in the common hepatic artery in the early post-operative period is a known predictor of adverse outcome. The normal proposed values range 0.78 ± 0.11 in uncomplicated living donor pediatric recipients [82]. In adults, a RI cut-off of ≤0.6 reported a sensitivity of 85% and specificity of 80% (p<0.005) for vascular complications compared with uncomplicated grafts developed between day 1 and 12 months post LT [163]. In children <3 years, the same RI cut-off of <0.6 had similar diagnostic accuracy (sensitivity of 81.8% and specificity of 95.2%) for predicting early HAT [93]. In our study, although the HA RI was lower in the complicated group in both sites of measurement (at the anastomosis and distally), this difference was not statistically significant, similar to what other studies with combined population have reported in cases of HAT [158]. Moreover, in the immediate post-operative period, the mean (±SD) hepatic artery PSV and RI were 49.6 (±30.3) and 0.78 (±0.11) cm/s, in uncomplicated living donor pediatric recipients [82].

In our study, the common hepatic artery peak systolic velocity was higher in the complicated group but not statistically significant, this is similar to what has been reported by Jamieson et. al. where the common hepatic artery (CHA) PSV was lower in patients with arterial complications (50 vs 107 cm/s, p=0.03), and velocities > 200 cm/s presented in complicated cases such as venous thrombosis or

pancreatitis [54]. We obtained higher CHA peak systolic velocities compared to what has been reported in uncomplicated living donor pediatric recipients (49.6 ± 30.3 cm/s) [82], this could be related to the immediate post-operative state. While one studies reported an optimal PSV cut-off of ≤37 cm/s in combination with RI <0.6 (sensitivity of 63.6% and a specificity of 76.5%) for the prediction of early HAT [93], another study showed no correlation of PSV with complications, AUC=0.05, not even in combination with RI [53].

No clinical or surgical risk factors showed a statistically significant predictive value. However, in contrast to those studies, we did not compare complicated against uncomplicated patients, we classified our groups according to the type of management, either invasive or conservative. Also, those studies analysed specific outcomes such as development of HAT [142], vascular complications [163], graft and patient survival [144], development of post-transplant lymphoproliferative liver disease (PTLD)[164].

Limitations

Although patient and graft survival were worst in the severe complication management group, the lack of statistical significance could be explained by the small sample size.

The first postoperative DUS assessment is technically difficult due to multiple factors including mechanical ventilation, wound dressings, pain, and residual intraabdominal gas. Another concern is the potential variability in the measurements. Some studies have reported high inter and intraobserver variation in measurements of portal and arterial velocities [130]. While generally reassuring for the transplant team, confirmation of adequate flow on the initial posttransplant Doppler provides reassurance and helps to direct the optimal aggressive anticoagulation management in the perioperative period. Further a change in parameters can more effectively trigger additional corrective interventional events including rapid confirmatory CT or angiography, or straight to further surgical exploration. On at least two occasions we have returned to surgery in children when an acute absence

of arterial flow was reported, but at surgery found a bounding arterial pulse with pleasingly no concern. We recognize that this happens occasionally.

Another possible limitation of our study is that we did not analyse other known risk factors for portal vein complications, such as graft to recipient weight ratio (GRWR) [136, 165], and a portal vein diameter <3.5 [92], retrograde portal flow [166], and presence of collaterals [166]. Finally, although statistical adjustment was done for the multivariate analysis, since this is a retrospective cohort study, residual confounding might be present.

Conclusion

The immediate post-operative DUS assessment provides valuable information by detecting immediate complications and by identifying high-risk patients through the PVV distal to the anastomosis. No other DUS parameter showed statistically significant differences in patients that required invasive management compared with conservative management.

CHAPTER 4

Conclusion

Doppler Ultrasound is a safe and widely available procedure that allows practical and timely follow-up in patients undergoing a liver transplant, especially in children, who benefit from a radiation-free assessment.

Interpretation of obvious findings such as parenchymal hematomas, perihepatic collections, biliary dilatation, absent intravascular flow, direct observation of intravascular thrombi or areas of vessel stenosis is relatively straightforward [24] [76]. However, interpretation of other specific DUS parameters is sometimes challenging (such as a high hepatic artery peak systolic velocity), especially in the immediate post-operative period.

Additionally, there is a lack of standardization of the protocol of DUS post-liver transplant (e.g. timing, frequency, areas/structures of interest, equipment) and no consensus on what is considered normal. These issues are particularly prevalent in children, which hampers the identification of high-risk patients that should benefit from prompt invasive management and increases the misclassification of low-risk or normal patients who might not benefit or develop a problem, resulting from unnecessary testing.

Early post-operative DUS assessment is done universally. This first assessment is essential not only to diagnose and predict complications, but also serves as a baseline study for further comparison. However, it can be technically challenging and sometimes difficult to interpret.

Systematic reviews in radiology

Our systematic review revealed that all of the published literature involving DUS assessment in pediatric liver recipients consist of observational studies. This is directly related to the nature of the DUS assessment which is unfeasible to randomize as it is part of the routine post-surgical follow-up.

Systematic reviews of diagnostic tests are considered high-grade evidence by the GRADE system, however, systematic reviews of observational studies have a lower grade of evidence compared with systematic reviews of randomized controlled trials (RCT), considering that judging the quality of evidence of the alternative diagnostic strategy is challenging [56]. Systematic reviews of diagnostic studies are less common that systematic reviews with RCTs, particularly in radiology, and included studies can have a smaller sample size and limited methodological quality. Nevertheless, they can map the current published literature, and provide valuable information for clinical practice and potential future research areas [55 78].

In systematic reviews of diagnostic imaging studies, the results can be presented as dichotomous, categorical or continuous variables. In the case of dichotomous outcomes, sometimes authors report the diagnostic accuracy of the test and the raw data. However, if they report only sensitivities and specificities without the denominators, their results cannot be included in the meta-analysis and end-up being excluded [55].

The models to analyze meta-analysis for diagnostic studies include univariate pooling methods (random or fixed effects), summary receiver operating characteristic regression (SROC) curve or hierarchical models [78]. Moreover, as we observed, heterogeneity is common in test-accuracy studies. Therefore, a random effects model is needed because, as opposed to the fixed model approach, it accounts for between-study variability beyond chance [55]. Nevertheless, when significant heterogeneity is present, these methods are not that effective when few studies are included [167].

We identified that a vast amount of studies do not report specific DUS parameters, they rather use cut-off values proposed from other studies done in adults to categorize the DUS assessment into normal or abnormal [51]. However, using this approach in children may be inaccurate as mentioned earlier, DUS values in children differ from adults, which reflects the differences between adult and pediatric liver transplantation [53, 54, 63, 82, 84, 85, 87, 91-93, 103, 108, 110].

After a thorough analysis, we gleaned that the quality of the published studies was affected by three main aspects: 1) selection bias, 2) confounders, and 3) work-up bias:

Selection bias: Some of the included studies did not include a control group, consequently we could not include them in the meta-analysis and were only analyzed individually in the narrative synthesis. A comparator group is essential in research studies about diagnostic tests; and by not having a comparator group, the diagnostic accuracy cannot be estimated. Although the information obtained from some of these studies is valuable, its true utility in clinical practice is unknown [82].

Other forms of selection bias were also observed in some studies. For example, one retrospective study analysed the performance of DUS assessment in children that had Percutaneous Transhepatic Portal Venography (PTPV) for suspicion of portal hypertension [84], then they compared the values of children that had a stenosis >50% by venography with the children whose venography revealed a stenosis <50% or no complication. The results of this study reflect the performance of the DUS in this particular setting of children with suspicion of portal hypertension. It is important to remember that these DUS values do not reflect the actual diagnostic or prognostic value of DUS assessment in all pediatric liver recipients. Another study analyzed the use of DUS intraoperatively as well as for follow-up. The intraoperative assessment resulted in some patients undergoing a surgical revision of the anastomosis. This intervention might have changed the management in some patients, for example by redoing the anastomosis or changing the site of the graft, probably decreasing the incidence of post-surgical complications. Therefore, these post-surgical patients are not comparable with patients that do not have an intraoperative assessment. All of these factors related to selection bias gravely affected the quality of multiple studies.

Confounders: Although some studies perform a multivariate analysis including patient, donor and surgical variables [57], most studies did not. The lack of adjustment for confounders could distort the true effect of an intervention. This is concerning because the parameters of DUS assessment are a manifestation, rather than an actual biological risk factor for complications. Furthermore, the

development of complications is the result of multiple variables, rather than only one or just few risk factors. Some of these variables are interrelated (e.g. type of donor and time of cold ischemia), and some others produce an effect only in the presence of another variable (e.g. splenomegaly only in the setting of portal hypertension). Multiple factors, including patient's, donor's, and surgical characteristics, can be present simultaneously, therefore their effect should be examined by a multivariate analysis.

Work-up bias: Many of these studies are retrospective, thus it is likely some form of differential work-up (also known as verification bias) might have occurred. For example, a patient with an abnormal ultrasound is more likely to have a confirmatory test or invasive management, compared to a patient with normal DUS values. This can introduce differential work-up bias and make groups of complicated vs uncomplicated patients less comparable.

Finally, publication bias is particularly concerning in diagnostic and prognostic studies because these types of studies commonly include population at high-risk of presenting the outcome. Evidently, a diagnostic test has a better performance in people that have a higher preclinical probability. Therefore, it is common for the performance of these studies to be overestimated, particularly in observational studies. Due to the heterogeneity of our DUS parameters and outcomes in our systematic review, we did not have enough similar studies to build an accurate funnel plot to objectively assess publication bias.

Synthesis

To summarize, in general, the number of published studies grew exponentially in the last decades, reflecting the evolution of surgical techniques, liver transplantation policies, and the development of DUS technology. A lot of the research in this field came from Asia, especially from Taiwan, and Japan.

We obtained some statistically significant values from our meta-analysis, the use of these results clinically should be done with caution for clinical decisions, as they were calculated from observational studies.

For example, from the hepatic artery (HA) we can obtain the resistive index (RI), the peak systolic velocity (PSV), the acceleration time (AT) among others, but multiple complications not only arterial, but portal and biliary, are related to changes in the flow of the HA. Another source of heterogeneity was the time of DUS assessment. The DUS follow-up protocol differ in multiple centres; while some studies analyzed just the immediate postoperative period, others follow their patients up to 17 years [99].

In view of these limitation we decided to carry out a cohort study analyzing the DUS assessment performed in the first 12 hours after LT, and its correlation with the development of complications that required invasive management.

Hepatic artery

In our meta-analysis with studies of early and late post LT periods, a RI cut-off value of <0.6, had a sensitivity of 83% and a specificity of 87% for HAT. In contrast, in our cohort study in the immediate post-operative period, the RI did not show statistically significant differences between invasive and conservative management. This discrepancy could be explained by the timing of assessment. High RI are frequent in the immediate post-operative period. In one study, a RI >0.8 was seen in up to 45.6% in both adults and children in the first 72 hours post LT, and had no clinical repercussion or prognostic value [118].

The role of the hepatic artery peak systolic velocity is less well understood. Results from the studies included in our systematic review were either non-significant or contradictory. A low HA PSV distally to the anastomosis in combination with RI have been proposed for HAT but with relatively low sensitivity 63.6% [93], while a higher PSV, especially >200 cm/s are associated with complications [53] [54]. In our study, the invasive management group had a higher PSV compared with conservative

management, however, these differences were not statistically significant. This lack of statistical significance could be explained by the low incidence of arterial complications in our cohort.

Portal vein

The PVV distal to the anastomosis was the only DUS parameter that had a statistically significant difference. It was lower in complicated grafts with an optimal cut-off value of <60 cm/s, (sensitivity=80.8%, specificity=54.1%, AUC=0.687, 95% CI: 0.569 - 0.816) to predict severe complications after LT. Furthermore, the multivariate analysis showed that this value increases 6.4 times the odds of requiring invasive management, compared with patients with PVV≥60 cm/s, after adjusting for age, sex, diagnosis, dialysis pre-transplant, operation time and common hepatic artery peak systolic velocity (aOR=6.37; 95%CI: 1.71-23.72, *p*=0.006).

In our cohort study, the PVV at the level of the anastomosis was also lower in complicated patients but had no statistically significant prognostic value. In contrast, our review showed that high velocities were related with portal vein stenosis.

Hepatic vein

Our meta-analysis showed that the HVV was higher in cases of hepatic vein obstruction [54, 91, 94], a velocity >126 cm/s showed a sensitivity of 75% and specificity of 62% for hepatic vein obstruction [91, 94]. Moreover, a monophasic flow pattern was associated with complications (sensitivity 80%, specificity=78%, p<0.001). In contrast, in our cohort study in the immediate post-operative period, neither the HVV nor the flow pattern had prognostic value.

Potentially, the differences between the results of our meta-analysis and our cohort study could be the result of choosing a different outcome. While for the systematic review we analyzed complicated vs uncomplicated patients, in our cohort study, we compared patients with complications that required invasive management vs conservative management.

Also, the timing of DUS assessment is different among our two projects. While in our systematic review we included studies with various DUS timing of assessment (as seen in table 2), in our cohort study, we analyze only the immediate post-operative period within the first 12 hours after the surgery.

Another thing to consider is the possible relationship between the hemodynamic changes in the early post-operative state and their correlation with Doppler parameters. Blood pressure and the use of inotropic agents could potentially influence the hepatic flow. For example, adult studies have shown that the splenic resistive index, can correlate with the cardiac responsiveness in post-operative mechanically ventilated patients [168]. This parameter increases in hypotension, hypovolemia and anemia, and its reduction is associated with fluid responsiveness. It is also independent of perfusion pressure and can be used to detect occult hypoperfusion [168].

Other adult study showed that the RI did not change significantly after reperfusion and did not correlate with the change in cardiac output pre-and post-transplant [118]. However, this has not been studied in children yet.

It is presumed that the immediate post-operative period after LT produces a high perfusion state with increased portal vein velocities and high hepatic artery resistance [169]. This is even more pronounced in cases of living donor LT [170]. These changes have been attributed to multiple factors, including the loss of sympathetic graft innervation, and elevated cardiac output. Moreover, in patients with portal hypertension, these changes have been attributed to the persistence of the hyperkinetic splenic circulation, and the regulatory buffer mechanism of the hepatic artery [169, 170].

In adults, it has been proven that these Doppler characteristics change over time; the PPV and the hepatic artery PSV decrease [171] [169]. In pediatric liver recipients with biliary atresia, a study showed a decrease in the PSV and RI, and an increase in the PVV comparing pre and post-operative parameters [103].

Future directions

Doppler imaging and pediatric liver transplant are fields that have evolved exponentially throughout the years and are continuously changing. Advances in ultrasound equipment and new surgical techniques encourage us to pursue ongoing and further research studies. We believe that the following areas of research have the biggest potential.

In terms of DUS parameters, more studies are needed to analyse three main aspects; 1. Studies for commonly assessed parameters, but uncertain significance (e.g. PSV, acceleration time); 2. Studies for other uncommonly assessed parameters (e.g. intrahepatic parameters, arterial collaterals, splenic vein flow and size (graft-to-spleen ratio)); 3. Studies for composite parameters that reflect the perfusion of the graft, which in addition to the arterial and venous flow, include other variables such as vessel diameter, graft volume, cardiac output, body surface, intravascular blood volume, hemoglobin levels, among others. The latter can reflect more accurately the real blood/oxygen supply of the graft, and although we don't know if this can predict the graft or patient outcome, it could be the first step to propose a non-invasive score to estimate graft-perfusion and eventually perform future studies to validate it and estimate its potential prognostic value.

Another promising area of research is related to the fact that parameters change over time. For example, it is known that in adults. the arterial peak systolic velocity increases over time [172], and after the immediate post-operative period, the portal vein velocity, the hepatic artery peak systolic, and end diastolic velocity tend to decrease [173].

The high RI immediately after LT has been attributed to reperfusion injury [118]. This injury and high resistance arterial flow has been described after renal transplantation after a prolonged cold ischemia time producing acute tubular necrosis. In cases of acute kidney rejection, a high resistance flow is seen, and it is attributed to the interstitial edema or endovasculitis. The same mechanism has been

proposed for the high RI in liver grafts [118] and in *tardus parvus* wave pattern due to edema of the anastomosis or vasospasm [174, 175].

Another thing to consider is the possible relationship between inotropic agents and blood pressure. These hemodynamic changes and their DUS manifestation has not been studied that extensively yet. However, adult studies have shown that the splenic resistive index, a not very commonly obtained DUS parameter, can correlate with the cardiac responsiveness and hemodynamics in post-operative mechanically ventilated patients. This parameter increases in hypotension, hypovolemia and anemia, and is independent of perfusion pressure and can be used to detect occult hypoperfusion. This study showed that a reduction of the RI was associated with fluid responsiveness [168]. In contrast, another adult study showed that the hepatic artery RI did not change significantly after reperfusion and did not correlate with the change in cardiac output pre-and post-transplant [118].

These aspects could be important and interesting areas of research, especially in pediatric liver recipients; by knowing the expected changes in the DUS parameters according to the post-operative state we could determine the appropriate clinical decisions to even prevent complications from occurring.

Other potential areas of research include the use of intraoperative DUS assessment for determining graft placement to achieve optimal vascular flow. A study on the use of intraoperative DUS in children showed that it detected complications in 11/68 patients [175]. Also, the use of Paparevine intraoperatively has been proposed to differentiate narrowing from vasospasm [174]. Intraoperative DUS can also help guide de decision in cases of tight abdomen to determine if abdominal closure is feasible without causing vascular compromise [174].

Other novel technologies are also being studied, such as continuous Doppler monitoring implantable devices, and the use of contrast-enhanced ultrasound (CEUS). Doppler monitoring devices are placed intraoperative and provide continuous assessment of the intravascular flow, which in combination with traditional DUS assessment, has proven to decrease the false-positive rate of the conventional

DUS assessment to detect early hepatic artery thrombosis [176]. CEUS has also shown potential to analyze the parenchyma and vessels of liver grafts. A study showed that the velocities tend to increase after administration of ultrasound contrast agents, but these differences were not statistically significant [177]. Moreover, a case series of 10 pediatric liver recipients showed that CEUS is useful to evaluate focal liver lesions after transplantation [178].

For all these potential future research avenues, communication and collaboration with other institutions are paramount. Since pediatric LT is not a common procedure and only performed in a few highly specialized centres, multicentric studies are crucial to obtain sample sizes large enough to support any evidence-based recommendations.

Pediatric liver transplantation has multiple intricacies including the procurement of the organ, the complexity of the surgical procedure and the highly specialized post-operative care required. Many more questions to be answered await, but hopefully, the knowledge obtained from this research is one step forward to decrease those uncertainties.

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APPENDICES

Appendix 1. Search Strategy for Doppler Ultrasound Parameters in Pediatric Liver Recipients. A Systematic Review and Meta-analysis

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to November 29, 2018

1 Liver Transplantation/ (52703)
2 ((allograft* or graft* or transplant*) and (hepatic* or liver*)).tw,kf. (82712)
3 or/1-2 [Combined MeSH & text words for liver Tx] (90331)
4 Graft Rejection/dg [Diagnostic Imaging] (660)
5 Hepatic Artery/dg [Diagnostic Imaging] (3063)
6 Postoperative Complications/dg [Diagnostic Imaging] (15940)
7 Ultrasonography, Doppler/ (14436)
8 doppler*.ti. (31924)
9 doppler*.ab. /freq=2 (30913)
10 (doppler* and (ultraso* or US)).tw,kf. (36624)
11 ((hepatic adj (arter* or venous*)) and (ultraso* or US)).tw,kf. (1969)
12 (flow adj3 (arter* or monophasic* or triphasic* or venous*)).tw,kf. (27051)
13 ((HA or arter* or venous*) adj3 velocity*).tw,kf. (4942)
14 ((post-op* or postop*) and (ultraso* or US)).tw,kf. (25926)
15 or/4-14 [Combined MeSH & text words for doppler US] (136241)
16 Adolescent/ (1897588)
17 exp Child/ (1797821)
18 Hospitals, Pediatric/ (12106)
19 exp Infant/ (1080069)
20 exp Intensive Care Units, Pediatric/ (19295)
21 exp Pediatrics/ (54251)
22 (adolescen* or babies* or baby* or child* or infan* or newborn* or neonat* or teen* or toddler*).tw,kf,jw. (2057822)
23 p?ediatric*.tw,kf,jw. (680920)
24 or/16-23 [Combined MeSH & text words for pediatric patients] (4031500)
25 and/3,15,24 [Combined concepts for liver Tx, doppler US & pediatric patients] (813)
26 exp Animals/ not Humans/ (4519948)
27 (animal* or bovine* or calves or camel* or canine* or cat or cats or chimp* or dog or dogs or equine* or feline* or goat* or hamster* or horse* or llama* or mice* or monkey* or mouse* or pig or piglet* or pigs or porcine* or primate* or rabbit* or rat or rats or rodent* or sheep* or simian* or swine* or veterinar*).ti. (2204602)
28 25 not (26 or 27) [Exclude animal studies] (806)
29 remove duplicates from 28 (806)

Appendix 2. Data extraction form for Doppler Ultrasound Parameters in Pediatric Liver Recipients. A Systematic Review and Meta-analysis

Study identification

Reference ID			
First author		Title	
Publication year		Journal	
Publication type	Fulltext ☐ / Abstract ☐ / Book chapter ☐ / Internal progress report ☐ / other ☐ (please specify).		

Methodological characteristics

Type of study design	RCT ☐ / Cohort ☐ / Case control ☐ / Cross-sectional ☐ / Case series ☐ / Case report ☐ / NR ☐ / Other ☐ (specify): _____				
Funding source	Industry ☐/ Public ☐/ Mixed ☐ (industry supported: drug ☐ / data management ☐/ travel ☐/ salary ☐) / Other ☐ / Unclear ☐ / NR ☐				
Conflict of interest statement	Yes ☐ / No ☐ / NR ☐				
Recruitment method	Consecutive inclusion ☐ / Other ☐ / NR ☐				
Number of participants (total)		Number of groups		Group categories / sample size on each group	
Length of follow-up	From _____ till _____ Median (range): _____ Mean: _____				
Completeness of trial	Yes ☐ / No ☐ / NA ☐				
Missing data	Number of participants with any missing value (Exposure or Outcome)				
	Number of missing data for each value				
	How did authors handle missing data?	☐ Complete-case analysis ☐ Imputation ☐ Last observation carried forward ☐ NR ☐ Other (specify): _____			
Randomization	Yes ☐ / No ☐ / NR ☐				
	If yes, what method of randomization was used? Central ☐ / Block ☐ / Stratified ☐ / NR ☐ / Other ☐ (specify)				
	What Method of concealment of allocation was used? (specify): _____, was it adequate ☐/ Inadequate ☐ / Done + unclear ☐ / Not done ☐ ?				
	Blinding extent Single ☐ /Double ☐ /Triple ☐ / Not possible ☐ / Unclear ☐ / NR ☐ To which extent unblinding could affect the results:				

Primary study aims/objectives	NR ☐
Secondary study aims/objectives	NR ☐
Outcome definition	Primary: Secondary: Unclear ☐ NR ☐

Assessment of how researchers dealt with confounding	
Method for *identifying* relevant confounders described: yes no If yes, describe the method used:	☐ ☐
Relevant confounders described: yes no List confounders described under	☐ ☐
Method used for controlling for confounding At design stage: At analysis stage: stratification multivariable regression propensity scores (matching) propensity scores (multivariable regression) List confounders controlled for under	☐ ☐ ☐ ☐ ☐

Characteristics of participants
(enter characteristics, tick if considered to be a confounder [Conf], then enter mean and SD, or frequency and percentage for each characteristic, for entire study population and by group. Finally, for each characteristic, tick last column to indicate whether groups were considered different [Diff] by the researchers.)

Characteristic	Conf	Entire study	Exposed	Unexposed	Diff
Number of participants					
Number of excluded participants / losses of follow up					☐
Number of included participants					
Eligibility criteria		Inclusion: Exclusion:			☐

Demographics					
Age (specify days ☐ / months ☐ / years ☐)	☐				☐
Sex (male)	☐				☐
Weight (kg)	☐				☐
Underlying disease					
Cholestatic disease	☐				☐
Metabolic disease	☐				☐
Acute liver failure	☐				☐
Other underlying liver disease (specify): _____	☐				☐
Type of liver transplantation					
Primary transplantation	☐				☐
Re-transplantation	■				☐
Type of graft					
Whole graft	☐				☐
Split graft	■				☐
Of split, what lobe was used?					
Left lobe	☐				☐
Right lobe	☐				☐
Type of donor					
Cadaveric donor	☐				☐
Living donor	☐				☐

Characteristics of the exposure (Doppler assessment)

Characteristics of the method used			
Ultrasound equipment (Brand, model)	☐ NR	Probe type	☐ Lineal ☐ Convex ☐ NR
Ultrasound assessment performed by:	☐ Nurse ☐ Clinician ☐ US technician ☐ Radiologist ☐ Other ☐ NR	Probe mHz	_____mHz ☐ NR

DUS assessment										
Days after liver transplantation	Mean			SD						
Vascular structure analysed	Hepatic artery ☐		Portal vein ☐		Hepatic vein ☐		IVC ☐		Other ☐ (specify):	
Measurement	RI		Flow velocity (cm/s)		Flow velocity (cm/s)		Flow velocity (cm/s)			
	PSV (cm/s)		Pattern: ☐Monophasic /flat ☐Biphasic ☐Triphasic ☐Tetraphasic		Pattern: ☐Monophasic /flat ☐Biphasic ☐Triphasic ☐Tetraphasic		Pattern: ☐Monophasic /flat ☐Biphasic ☐Triphasic ☐Tetraphasic			
	EDV (cm/s)									
	Acceleration time (cm/s)									
	Pulsatility index									
Other measurements (specify)										
Number of measurements performed										

Characteristics of the outcome

Outcome	Graft survival (mean days)	Complication	Time to develop complications (days after liver transplantation)
Uncomplicated grafts	☐ NR	NA	NA
Complicated grafts	☐ NR	Vascular: ☐ HA Stenosis ☐ HA thrombosis ☐ Other HA complications ☐ PV stenosis ☐ PV thrombosis ☐ Other PV complication ☐ HV stenosis ☐ HV thrombosis ☐ Other HV complications Non-vascular: ☐ Graft rejection ☐ Biliary leak	

		☐ Biliary stricture ☐ Other (Specify): _____	