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Review article

Portal vein obstruction after pediatric liver transplantation: A systematic review of current treatment strategies

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ABSTRACT

Introduction: Portal vein obstruction (PVO) is a significant vascular complication after liver transplantation (LT) in pediatric patients. Current treatment strategies include percutaneous transluminal angioplasty (PTA), with or without stent placement, mesorex bypass (MRB), splenorenal shunt, mesocaval shunt, endovascular recanalization (EVR), splenic artery embolization and splenectomy. However, specific characteristics of patients undergoing intervention and selection of individual treatment and its efficacy have remained unclear. This review systematically analyzed biochemical and clinical characteristics, selection of treatment, efficacy, and post-procedural complications.

Methods: We systematically searched PubMed and Embase between January 1995 and March 2021 for studies on the management of PVO after LT. We analyzed the reports for biochemical and clinical characteristics at the timing of the intervention in different patients, selection of treatment, and reported efficacies.

Results: We found 22 cohort studies with 362 patients who had the following characteristics: biliary atresia (83%), living-donor LT (85%), thrombocytopenia (73%), splenomegaly (40%), ascites (16%), or gastrointestinal bleeding (26%). The 3-year primary patency of PTA without stent placement was similar to that with stent placement (70%–80% and 43%–94%, respectively). MRB was used as an initial treatment with a 3-year patency of 75% to 100%. One study showed that 5-year primary patency of EVR was 80%. Secondary patency was 90% to 100% after 3 years in all studies with PTA alone, PTA/stent placement, and stent placement alone.

Conclusion: This is the first review of all treatment protocols in PVO after pediatric LT. We showed that an important group of patients has severe symptoms of portal hypertension. Efficacy of all treatment modalities was high in the included studies which make them important modalities for these patients.

List of abbreviations

EVR	endovascular recanalization
LT	liver transplantation
MRB	mesorex bypass
PTA	percutaneous transluminal angioplasty
PVAS	portal vein anastomosis stenosis
PVO	portal vein obstruction
PVT	portal vein thrombosis

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1. Introduction

Liver transplantation (LT) is the standard care for patients with end-stage liver disease and liver failure [1]. Despite marked improvements in operating techniques, vascular complications, such as portal vein obstruction (PVO), occur frequently in pediatric patients after LT, particularly in young patients with biliary atresia after a living-donor LT [2,3].

Postsurgical obstruction at the portal vein anastomosis in children has an incidence of 3% to 14% after living-donor LT compared with 2% to 3% after a deceased-donor LT [4]. PVO may be asymptomatic or it may present with secondary manifestations of portal hypertension such as splenomegaly, thrombocytopenia, or gastrointestinal bleeding. Active surveillance of clinical and diagnostic parameters, mainly with ultrasonography, is important for the timely detection of PVO [5,6].

Therapeutic strategies to treat PVO include endovascular options as percutaneous transluminal angioplasty (PTA) with or without stent placement, endovascular recanalization (EVR), splenic arterial embolisation and surgical options as mesorex bypass (MRB)/other surgical shunts, and splenectomy. PTA with or without stent placement is the treatment option where the most publications refer to [7–9].

Several studies have evaluated the potential benefit of the individual interventions [6–8,10–17]. However, the efficacy the different treatments protocols and the biochemical and clinical characteristics of patients undergoing interventions remain unclear. This review was conducted to systematically analyze the reported biochemical and clinical characteristics of patients undergoing intervention, the selection of treatment, the efficacy, and the complication rate after different treatment protocols for pediatric patients with PVO after LT.

2. Materials and methods

2.1. Search strategy

This systematic review was conducted in accordance to the preferred reporting items for systematic review and meta-analysis guidelines. PubMed and Embase databases were searched for eligible studies on the management of PVO (endovascular or surgical interventions, or both). The full search strategy is available in Supplementary Table 1. We also identified additional studies by reviewing reference lists of studies found in the reviewed reports.

2.2. Study selection

We included studies published between January 1995 and March 2021 that investigated treatment for PVO, which included portal vein anastomosis stenosis (PVAS) and portal vein thrombosis (PVT) after LT (PTA, stent placement, shunt surgery, endovascular recanalization, splenic artery embolization or splenectomy) in pediatric patients (aged $\leq$18 years). We considered all types of studies (randomized control trials, nonrandomized prospective, or retrospective cohort studies). Studies were excluded if they met 1 or more of the following criteria: non-pediatric patients, no post-LT intervention, non-English publication, mixed population of adult and pediatric patients, case reports, fewer than 5 patients in total or unavailable full-texts. Moreover, studies with incomplete efficacy data (primary and secondary patency) were also excluded. Primary LT and repeat LT were both included.

Titles and abstracts of the articles were independently reviewed by 2 authors (B.A., R.B.). After screening, the full text of the articles was independently reviewed by 2 authors. The 2 screeners discussed items in which there was disagreement. If consensus could not be reached, third-party adjudication was sought (H.D.).

2.3. Data extraction

We collected data by using the Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia; available at www.covidence.org). Study details were extracted from the articles using a predefined extraction form containing the following items: study information (first author's surname, year, and number of patients included), clinical results including procedural details, technical success, primary/secondary patency, post-interventional anticoagulation, and complications.

2.4. Assessment of risk of bias and quality

We used the Cochrane tool for assessing risk of bias. The items considered included patient selection, comparability, and outcome. The methodological quality of the included studies was assessed with the use of the Methodological Index for Non-Randomized Studies (MINORS). Studies scoring lower than 11 on the MINORS score were deemed of insufficient quality and were excluded from further analysis [18].

2.5. Outcome measures

The biochemical and clinical characteristics of patients undergoing intervention, efficacy, post-procedural anticoagulation therapy and complications were evaluated.

We analyzed the provided biochemical and clinical characteristics of patients undergoing intervention and specifically assessed the following parameters that were included at the first intervention for PVO: general characteristics (age, primary disease, and type of liver donor), mild signs of portal hypertension (thrombocytopenia or persistent splenomegaly, or both), or severe form of portal hypertension (gastrointestinal bleeding or ascites, or both).

Technical success was defined as success of the intervention during the procedure (reestablishment of portal flow). Primary patency was defined as the patency of the portal vein anastomosis or MRB/other surgical shunt (without stenosis or thrombosis) after 1 intervention. Secondary patency was defined as the patency of the portal vein anastomosis or MRB/other surgical shunt (without stenosis or thrombosis) after more than 1 intervention.

Post-procedural anticoagulation therapy was defined as the anticoagulation regimen in the preprocedural, intraprocedural, and post-procedural setting. Complications were defined as the presence of post-procedural complications, including infection, bleeding, and thrombosis.

3. Results

The search resulted in 135 studies after duplicates were removed (Fig. 1). After titles and abstracts were screened, 86 studies remained, of which 64 were excluded during the full-text assessment based on the inclusion and exclusion criteria.

There were 22 studies eligible for analysis [1–17,19–23]. Three articles described the results of PTA alone [5–7], 11 described the results of PTA and stent placement [1–4,8,9,19–23], 2 described the results of stent placement alone [10,11], 1 study described the results of EVR [12], and 5 studies described the results of MRB [13–17]. Overall, our systematic review included 362 children with an intervention for PVO after LT from 22 retrospective cohort studies reported between 1995 and 2021 without overlapping publications. Of these cohort studies, 8 studies (156 children) reported treatment in patients with a PVAS without thrombosis [2,5,6,8–10,19,21], 6 studies (76 children) reported treatment in patients with a PVT [12–17] and 8 studies (130 children) reported treatment in both type of patients [1,3,4,7,11,20,22,23].

Supplementary Table 2 shows the bias and methodological quality scores of the included studies. The Cochrane risk of bias tool assessment ranged from unclear to high per domain of quality assessment. The MINORS score of each study was higher than 11, and therefore, no study was excluded.

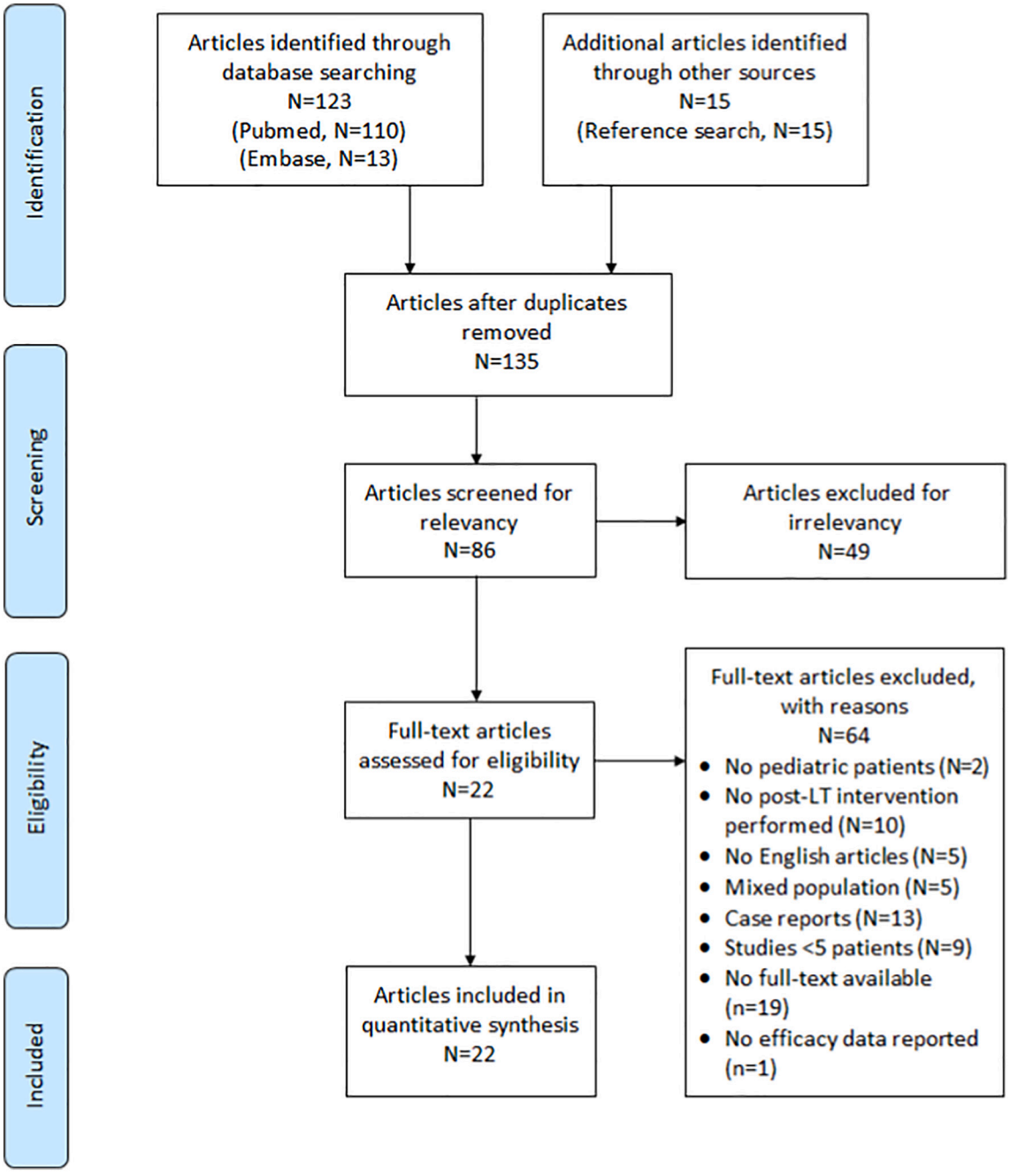

Fig. 1. PRISMA flow diagram of primary studies.

3.1. Biochemical and clinical characteristics of patients undergoing intervention

At the time of the intervention, 250 of 300 patients (83%) had biliary atresia as the original indication for LT, and 308 of 361 patients (85%) had undergone living-donor LT. Ten studies reported an age of transplantation in 170 patients, with a median age of 1.6 years (mean, 1.9 years) (Table 1).

In general, the biochemical and clinical characteristics of patients undergoing intervention and the selection of individual treatment modalities were poorly described. Yet, of all treated PVAS patients, 73% had thrombocytes levels of $<150 \times 10^9$/L, 40% had splenomegaly, 16% had ascites, and 26% had gastrointestinal bleeding (Table 2). Hepatopulmonary syndrome was only reported in 2 patients [7,16] and hepatic encephalopathy [16] in 1 patient.

3.2. Types of intervention

The numbers of the different interventions described in the 22 studies had a total of 213 PTAs, 74 stent placements, 48 MRBs, and 28 EVRs. Of the 8 studies with only PVAS patients [2,5,6,8–10,19,21], the following treatments were described: 2 studies included only PTA [5,6], 5 studies included PTA and stent placement [2,8,9,19,21], and 1 study included only stent placement [10]. Of the 8 studies with PVAS and PVT combined [1,3,4,7,11,20,22,23], the following treatments were described: 1 study included only PTA [7], 6 studies included PTA and stent placement [1,3,4,20,22,23], and 1 study included only stent placement [11]. Of the 6 studies with only PVT patients [12–17], the following treatments were described: 5 studies included only MRB [13–17], and 1 study included only EVR [12]. Other treatment modalities were not reported in the included studies.

Table 1
Basic characteristics.[1]

Studies	N	Intervention	Type PVO	Age at transplantation[2]	Age at 1st intervention[2]	Gender	Primary disease	Type liver donor
Ueda 2005	39	PTA	PVAS/PVT	1.9 yr^{x} (R 29d-17 yr)	N.r.	N.r.	87% BA (n = 34) 13% non-BA (n = 5)	100% LD (n = 39)
Naik 2018	19	PTA	PVAS	2.4 yr^{x} (IQR 1.1 yr–3.8 yr)	12 yr^{x} (IQR 7y-15y)	63% M (n = 12)	57% BA (n = 11) 43% non-BA (n = 8)	31% LD (n = 6) 69% DD (n = 13)
Tannuri 2004	5	PTA	PVAS	3.7 yr$^{\#}$ (R 9 m-18 yr)	N.r.	N.r.	100% BA (n = 5)	100% LD (n = 5)
Yabuta 2014	43	PTA/Stent	PVAS	N.r.	4.1 yr$^{\#}$ (R 7 m-19y)	44% M (n = 19)	83% BA (n = 36) 17% non-BA (n = 7)	100% LD (n = 43)
Gao 2017	30	PTA/Stent	PVAS/PVT	2.4 yr$^{\#}$ (R 5 m-12 yr)	N.r.	53% M (n = 16)	86% BA (n = 26) 14% non-BA (n = 4)	60% LD (n = 18) 40% DD (n = 12)
Funaki 1997	22	PTA/Stent	PVAS	N.r.	3.5 yr$^{\#}$ (R 9 m-17y)	36% M (n = 8)	100% BA (n = 22)	100% LD (n = 22)
Patel 2018	21	PTA/Stent	PVAS/PVT	0.9 yr^{x}	1.7 yr^{x} (R 3 m–16.2y)	47% M (n = 10)	66% BA (n = 14) 34% non-BA (n = 7)	95% LD (n = 20) 5% DD (n = 1)
Ko 2007	12	PTA/Stent	PVAS/PVT	N.r.	4.2 yr$^{\#}$ (R 6 m-9y)	33% M (n = 4)	100% BA (n = 12)	100% LD (n = 12)
Funaki 1995	11	PTA/Stent	PVAS	N.r.	2.1 yr$^{\#}$ (R 1y-3.6y)	36% M (n = 4)	100% BA (n = 11)	100% LD (n = 11)
Czerwonko 2019	7	PTA/Stent	PVAS/PVT	1.3 yr$^{\#}$ (R 6 m-2.1 yr)	N.r.	43% M (n = 3)	100% BA (n = 7)	100% LD (n = 7)
Karakayali 2011	7	PTA/Stent	PVAS	N.r.	5.3 yr$^{\#}$ (R 6 m-13y)	43% M (n = 3)	58% BA (n = 4) 42% non-BA (n = 3)	100% LD (n = 7)
Bueno 2010	5	PTA/Stent	PVAS/PVT	1.1 yr$^{\#}$ (R 7 m-1.4 yr)	N.r.	40% M (n = 2)	100% BA (n = 5)	60% LD (n = 3) 40% DD (n = 2)
Buell 2002	38	PTA/Stent	PVAS	N.r.	1.8 yr$^{\#}$	N.r.	N.r.	100% LD (n = 38)
Cho 2014	6	PTA/Stent	PVAS/PVT	3.5 yr$^{\#}$ (R 4 m-17 yr)	N.r.	67% M (n = 4)	84% BA (n = 5) 16% non-BA (n = 1)	100% LD (n = 6)
Huang 2012	11	Stent	PVAS	N.r.	N.r.	36% M (n = 4)	N.r.	100% LD (n = 11)
Vasavada 2015	10	Stent	PVAS/PVT	1.1 yr^{x}	N.r.	40% M (n = 4)	100% BA (n = 10)	100% LD (n = 10)
Cavalcante 2018	28	EVR	PVT	0.7 yr^{x} (5.9 m − 3.4 yr)	2.7 yr^{x} (8.1 m-11.8 yr)	54% M (n = 15)	97% BA (n = 27) 3% non-BA (n = 1)	93% LD (n = 26) 7% DD (n = 2)
Krebs-Schmitt 2009	14	MRB	PVT	N.r.	4.9 yr^{x} (4 m-13y)	64% M (n = 9)	N.r.	N.r.
Stenger 2001	12	MRB	PVT	N.r.	5.5 yr^{x} (10 m-12y)	N.r.	N.r.	91% LD (n = 11) 8% DD (n = 1)
Chocarro 2016	9	MRB	PVT	N.r.	0.4 yr$^{\#}$	N.r.	100% BA (n = 9)	100% LD (n = 9)
de Ville de Goyet 1996	8	MRB	PVT	N.r.	N.r.	N.r.	88% BA (n = 7) 12% non-BA (n = 1)	13% LD (n = 1) 87% DD (n = 7)
de Ville de Goyet 2013	5	MRB	PVT	N.r.	8.9 yr$^{\#}$ (R 2.5y-14.4y)	N.r.	100% BA (n = 5)	60% LD (n = 3) 40% DD (n = 2)
Total	362					45% M (117/259)	83% BA (250/300) 17% non-BA (37/300)	85% LD (308/361) 15% DD (40/361)

N: number; N.r.: not reported; BA: biliary atresia; DD: deceased donor; LD: living donor; M: male; PTA: percutaneous transluminal angioplasty; MRB: mesorex bypass; EVR: endovascular recanalization; PVO; portal vein obstruction; PVAS: portal vein anastomosis stenosis; PVT: portal vein thrombosis. 2 yr: year; m: month; d: day; #: mean; x: median; R: range; IQR: interquartile range.

[1] There are no specifications per treatment type possible; just for the whole treatment process.

The PTA and EVR techniques were relatively consistent between the studies with respect to type of catheter, type of balloon, and protocol. However, the stent technique (type, diameter) differed between studies: only self-expandable stents were described in 5 studies [2,8,9,19,22] whereas only balloon-expandable was described in 1 study [12], in contrast to both self-expandable and balloon-expandable stents described in 5 other studies [1,3,4,20,23] (Supplementary Table 3). The MRB technique was performed in all studies according to the surgical technique described by De Ville de Goyet et al. [22] MRB was made using a venous graft and anastomosed end-to-side to this terminolateral opening. In all cases, a standard MRB was done using the patient's own jugular or iliac vein as a graft for the bypass.

3.3. Efficacy

Each study determined the technical success by visual inspection and pressure gradients, although no difference in pressure gradient was regarded as threshold for (no) success. The technical success rate directly after the dilatation ranged from 66% to 100% in the different reports (Supplementary Table 3).

The 3-year primary patency of combined approach PTA/stent was 43%–94% [1–4,8,9,19–23], in which 1 study reported lower primary patency of 43% [4] compared with 75% to 94% [1–3,8,9,19–23] in the other studies. PTA alone [5–7] and stent placement alone [10,11] had a 3 years patency of 70%–80% and 95%, respectively. One study reported a 5-year primary patency of EVR which was 80% [12]. MRB was used as an initial treatment, with a patency of 75% to 100% at 3 years [13–17]. Secondary patency was 90% to 100% after 3 years in all studies with PTA alone, PTA/stent placement, and stent placement alone whereas a secondary patency after EVR was 80% after 5 years (Table 3). Patient survival and graft survival were not reported.

3.4. Post-procedural anticoagulation regimen and complications

Intraprocedural heparin was used in 16 of 22 studies that reported their anticoagulation regimen [1–6,8,9,12,15,17,19–23]. Post-

Table 2
Inclusion criteria intervention[1,2].

Studies	N	Intervention	Thrombocytes[3]	Thrombocytopenia[4]	Splenomegaly	Ascites	GI bleeding
Ueda 2005	39	PTA	95	100% (*n* = 39)	95% (*n* = 37)	N.r.	23% (n = 9)
Naik 2018	19	PTA	191	58% (n = 11)	11% (*n* = 2)	N.r.	N.r.
Tannuri 2004	5	PTA	N.r.	N.r.	N.r.	N.r.	N.r.
Yabuta 2014	43	PTA/Stent	137	100% (*n* = 43)	N.r.	N.r.	N.r.
Gao 2017	30	PTA/Stent	70 (35–99)	40% (n = 12)	N.r.	17% (*n* = 5)	10% (n = 3)
Funaki 1997	22	PTA/Stent	N.r.	N.r.	9% (n = 2)	14% (n = 3)	13% (n = 3)
Patel 2018	21	PTA/Stent	191	58% (n = 12)	10% (n = 2)	5% (n = 1)	19% (n = 4)
Ko 2007	12	PTA/Stent	N.r.	N.r.	42% (n = 5)	25% (n = 3)	8% (n = 1)
Funaki 1995	11	PTA/Stent	N.r.	N.r.	9% (n = 1)	18% (n = 2)	27% (n = 3)
Czerwonko 2019	7	PTA/Stent	N.r.	N.r.	N.r.	N.r.	N.r.
Karakayali 2011	7	PTA/Stent	95 (70–120)	57% (n = 4)	57% (n = 4)	29% (n = 2)	N.r.
Bueno 2010	5	PTA/Stent	N.r.	N.r.	N.r.	N.r.	N.r.
Buell 2002	38	PTA/Stent	N.r.	N.r.	13% (n = 5)	16% (n = 6)	45% (*n* = 17)
Cho 2014	6	PTA/Stent	N.r.	50% (n = 3)	50% (n = 3)	N.r.	N.r.
Huang 2012	11	Stent	67	100% (n = 11)	100% (*n* = 11)	N.r.	N.r.
Vasavada 2015	10	Stent	N.r.	N.r.	N.r.	N.r.	N.r.
Cavalcante 2018	28	EVR	N.r.	62% (*n* = 21)	62% (n = 21)	27% (n = 8)	39% (n = 11)
Krebs-Schmitt 2009	14	MRB	115	N.r.	N.r.	N.r.	N.r.
Stenger 2001	12	MRB	139	N.r.	N.r.	N.r.	N.r.
Chocarro 2016	9	MRB	117	N.r.	N.r.	N.r.	N.r.
de Ville de Goyet 1996	8	MRB	122	100% (n = 8)	25% (n = 2)	13% (n = 1)	88% (n = 7)
de Ville de Goyet 2013	5	MRB	N.r.	100% (n = 5)	N.r.	N.r.	N.r.
Total	362			73% (169/230)	40% (95/235)	16% (31/190)	26% (58/222)

[1] There are no specifications per treatment type possible; just for the whole treatment process.

[2] (3) cases had other clinical findings than abovementioned which present <1% of the total number (1 patient with refractory encephalopathy and 2 patients with hepatopulmonary syndrome).

[3] In x10^9/L, only mean is reported, only range is reported.

[4] $<150 \times 10^9$/L.

Table 3
Clinical results intervention.[1]

			Primary patency				*Secondary patency*			
Studies	N	Intervention	1 year	3 years	5 years	10 years	1 year	3 years	5 years	10 years
Ueda 2005	39	PTA	75%	70%	N.r.	N.r.	95%	95%	N.r.	N.r.
Naik 2018	19	PTA	85%	80%	70%	N.r.	100%	100%	100%	N.r.
Tannuri 2004	5	PTA	75%	70%	N.r.	N.r.	95%	95%	N.r.	N.r.
Yabuta 2014	43	PTA/Stent	83%	78%	76%	70%	100%	100%	100%	96%
Gao 2017	30	PTA/Stent	95%	90%	85%	N.r.	100%	100%	100%	N.r.
Funaki 1997	22	PTA/Stent	99%	91%	87%	N.r.	100%	100%	100%	N.r.
Patel 2018	21	PTA/Stent	43%	43%	36%	29%	95%	95%	95%	95%
Ko 2007	12	PTA/Stent	95%	90%	83%	N.r.	100%	100%	95%	N.r.
Funaki 1995	11	PTA/Stent	95%	91%	87%	N.r.	100%	100%	100%	N.r.
Czerwonko 2019	7	PTA/Stent	97%	94%	89%	N.r.	100%	100%	100%	N.r.
Karakayali 2011	7	PTA/Stent	95%	90%	85%	N.r.	100%	100%	100%	N.r.
Bueno 2010	5	PTA/Stent	89%	75%	N.r.	N.r.	95%	95%	N.r.	N.r.
Buell 2002	38	PTA/Stent	88%	73%	69%	N.r.	90%	90%	90%	N.r.
Cho 2014	6	PTA/Stent	85%	70%	65%	N.r.	90%	90%	90%	N.r.
Huang 2012	11	Stent	95%	95%	95%	N.r.	100%	100%	100%	N.r.
Vasavada 2015	10	Stent	95%	95%	95%	N.r.	100%	100%	100%	N.r.
Cavalcante 2018	28	EVR	N.r.	N.r.	80%	N.r.	N.r.	N.r.	80%	N.r.
Krebs-Schmitt 2009	14	MRB	100%	100%	N.r.	N.r.	100%	100%	N.r.	N.r.
Stenger 2001	12	MRB	100%	100%	N.r.	N.r.	100%	100%	N.r.	N.r.
Chocarro 2016	9	MRB	80%	75%	N.r.	N.r.	80%	75%	N.r.	N.r.
de Ville de Goyet 1996	8	MRB	100%	100%	N.r.	N.r.	100%	100%	N.r.	N.r.
de Ville de Goyet 2013	5	MRB	100%	100%	N.r.	N.r.	100%	100%	N.r.	N.r.

[1] There are no specifications per treatment type possible; just for the whole treatment process.

procedural anticoagulation protocols were different within the studies of which it could include heparin, warfarin, or acetylsalicylic acid. Also, different durations of postintervention anticoagulant prophylaxis were applied, varying from stopping upon clinical discharge to post-intervention prophylaxis for 8 months (Supplementary Table 4). No reliable report of complications could be construed due to missing data: only 5 of the 22 studies reported complications [2,7–9,15], which included infections, thrombosis, and bleeding (Supplementary Table 5).

4. Discussion

We report the first systematic review on endovascular or surgical

treatment, or both, for PVO after pediatric LT. We concentrated on the biochemical and clinical characteristics at the intervention and the efficacy of the procedures applied. Our analysis indicates that most of the included patients had thrombocytopenia at the moment of intervention, but other complications of portal hypertension were also quantitatively prominent, such as ascites (16%) and gastrointestinal bleeding (26%).

This wide variation in the biochemical and clinical characteristics, from rather mild (thrombocytopenia and splenomegaly) to severe (ascites and gastrointestinal bleeding) signs of portal hypertension, illustrates that the timing for invasive diagnostics and subsequent treatment of PVO after LT is rather not standardized in the field. Standardization of the indications for treatment would be very helpful for studying the natural history, with or without intervention, in a more structured way.

Our review also indicates once again the unmet diagnostic need of reliable noninvasive markers for portal hypertension. In the literature, persistent splenomegaly and thrombocytopenia have been described as markers for portal hypertension, but either marker has limitations for clinical use, particularly in young patients after LT [24]. Although most of the included patients had thrombocytopenia, 27% of all patients had thrombocyte levels within normal reference ranges ($> 150 \times 10^9$/L), and therefore, excluding portal hypertension solely on normal values for thrombocytes is difficult. Moreover, the percentage of persistent splenomegaly in our systematic review was low (40%). Our experience after transplantation is that it takes some time for the spleen to decrease in size, and therefore, splenomegaly may be a relatively late marker for portal hypertension [25].

Although the present data do not stem from controlled studies, the primary patency results seem to justify PTA without stent placement as a preferred first-choice therapy in PVO patients without portal vein thrombosis. The rationale for this is based on PTA as a less invasive treatment modality, with acceptable primary patency numbers compared with the other treatment modalities. We do realize, however, that the reported patient numbers were low for the primary patency report: 11 of the 22 studies reported primary patency for 1 treatment modality alone (PTA, 3 studies, 63 patients [5–7]; stent placement, 2 studies, 21 patients [10,11]; MRB, 5 studies, 48 patients [13–17]; and EVR, 1 study, 28 patients [12]).

Furthermore, optimal timing of stent placement remains unclear from the studies included in this systematic review, because the studies with PTA with stent placement did not report their treatment protocol, and the studies did not specify the primary patency of a first or second PTA without stent placement. However, 1 single-center study reported adequate long-term patency of 81% after 2 or fewer PTAs without stent placement and recommended a PTA with stent placement after 2 sessions of PTA alone [8].

Although different treatment protocols are reported, secondary patency was highly acceptable in all studies with PTA, with or without stent placement (90%–100% at 3 years). Even though we believe that the current data of secondary patency are presently acceptable, we still need further information to optimize the treatment protocol.

After unsuccessful endovascular interventions, MRB has been recommended as a next treatment modality to restore the portal flow in patients with PVO without thrombosis, although reports are limited [9]. In patients with portal vein thrombosis, MRB is the preferred primary treatment in the majority of the reported patients [13–17]. However, direct comparison between endovascular and surgical treatment was not possible as we could not identify the PVT patients individually in endovascular treatment studies (most of the studies were mixed populations of PVAS and PVT patients). The MRB technique was performed in all studies as described by De Ville de Goyet et al., in which the use of grafts varied between studies [16].

One single study reported EVR as an endovascular treatment for PVT and could be an acceptable option if a MRB is technical not possible [12]. Furthermore, we could not recommend other treatment modalities, like non-MRB shunt surgery, splenic artery embolization or splenectomy, as no articles met our inclusion criteria. Based on our findings, we have made a treatment algorithm for patients with PVO after pediatric LT (Fig. 2).

The use of anticoagulation after different procedures remains controversial, and the current data are not sufficient to recommend any specific anticoagulation prophylaxis regimen over another [17,26]. This is reflected by wide variation in type and duration of the anticoagulant prophylactic protocols.

4.1. Strengths and limitations

This study is the first systematic review of treatment of PVO. We were able to review the data of a large number of patients and pool the data on biochemical and clinical characteristics of patients undergoing intervention.

However, as with most studies in pediatric LT, we could only include small retrospective cohort studies in the absence of larger, prospective controlled studies of which not all treatment modalities were reported. As a result of this, data for several parameters were missing, including the biochemical and clinical characteristics of patients undergoing an intervention. In addition, not all studies reported the definition of PVO and the definition of recurrence of PVO, which might lead to a selection bias (different in patient selection) and difficulty in establishing restenosis. Another limitation was that we were not able to pool the data on the efficacy of the interventions because different treatment protocols were used. Finally, the screening protocol was unknown in all of the studies; therefore, we do not know whether earlier detection of PVO would have resulted in better treatment results.

4.2. Implications for the future

Although current data are promising, this systematic review shows that there is a need for two major factors to improve the clinical care for PVO patients following LT. The first point is that a large multicentre evaluation on all treatment protocols is needed to assess the clinical and imaging characteristics prior to PVO treatment, efficacy of the individual portal vein revascularisation treatments, technical success numbers of all related treatments, complications and post-interventional management. The second point is that a guideline is needed, especially for screening and indications for treatment of PVO after pediatric liver transplantation.

5. Conclusion

We performed the first review of all treatment protocols in pediatric PVO patients after LT. We showed that an important group of patients treated for PVO has severe symptoms of portal hypertension (16% ascites and 26% gastrointestinal bleeding) and attempted to combine the varying protocol into a more uniform one. Secondary patency was high in the included studies which make both an important modalities for our patients. Even though the current outcomes are acceptable, treatment protocols are highly variable and based on retrospective data. Therefore, we need additional studies and guidelines to provide the best care for these pediatric patients .

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Authorship

Alfares: Helped design the work, acquired the data, conducted the analysis, interpreted the results and drafted the manuscript. Bokkers and van der Doef: Conceived and designed the work, revised the acquired data, and played an important role in the interpretation of the results; revised the manuscript, approved the final version. Verkade, Dierckx,

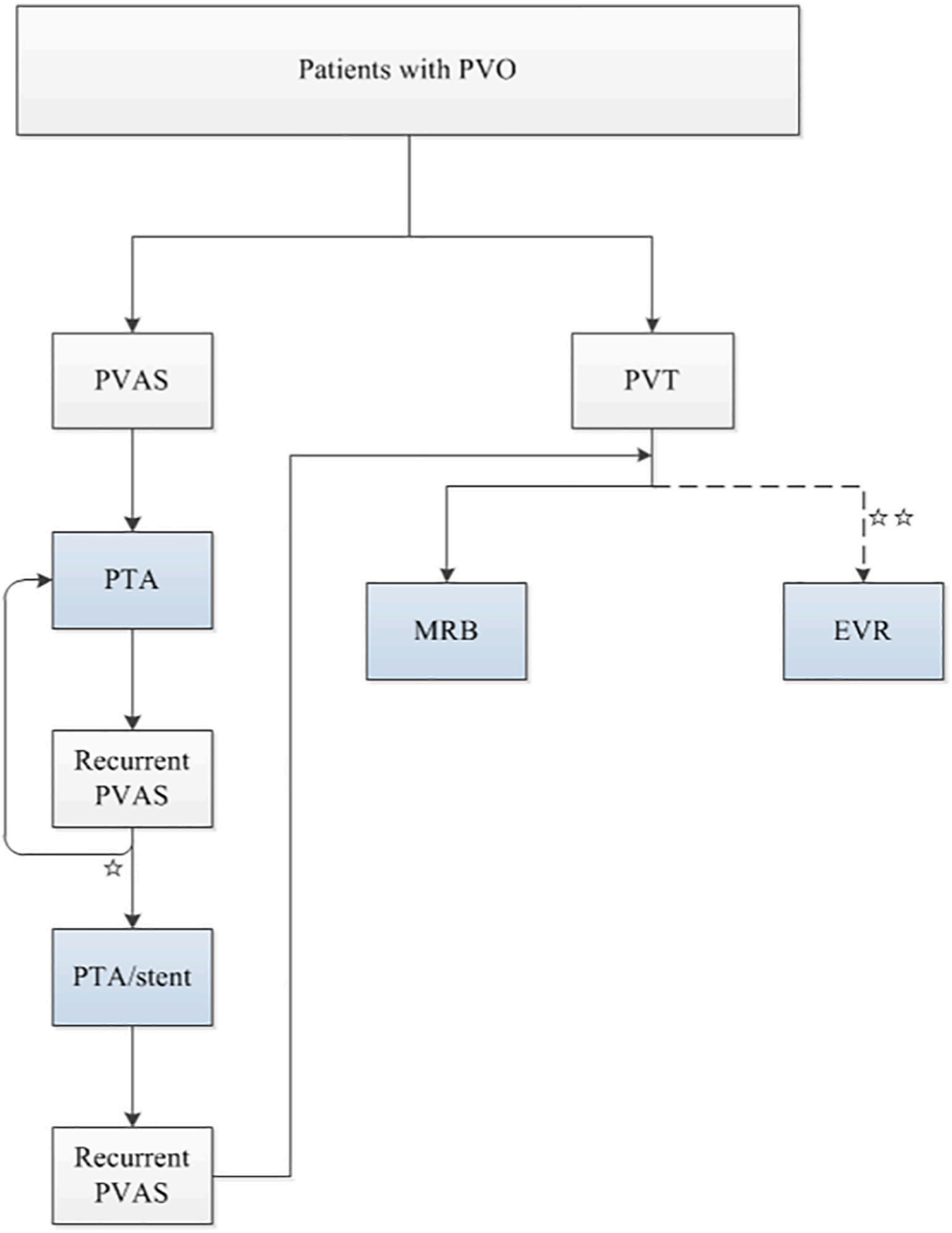

Fig. 2. Treatment algorithm for patients with PVO. *PVO*: portal vein obstruction, *PVAS*: portal vein anastomosis stenosis, *PVT*: portal vein thrombosis, *PTA*: percutaneous transluminal angioplasty, *MRB*: mesorex bypass, *EVR*: endovascular recanalization. ☆ limited data to make a recommendation between a second PTA or a PTA/stent after the first recurrence of PVAS, decisions are made on expertise of the centre. ☆☆ limited data for EVR as first approach in patients with PVT.

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Declaration of Competing Interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.trre.2021.100630.

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