**Name of Journal:** *World Journal of Hepatology*

**Manuscript NO:** 39627

**Manuscript Type:** SYSTEMATIC REVIEW

**Thrombosis prophylaxis in pediatric liver transplantation: A systematic review**

Nacoti M *et al*. Thrombosis in PLT

Mirco Nacoti, Giulia Maria Ruggeri, Giovanna Colombo, Ezio Bonanomi, Federico Lussana

**Mirco Nacoti, Giulia Maria Ruggeri, Giovanna Colombo, Ezio Bonanomi,** Department of Anesthesia and Intensive Care, Pediatric Intensive Care Unit, Papa Giovanni XXIII Hospital, Bergamo 24127, Italy

**Federico Lussana,** Hematology and Bone Marrow Transplant Unit, Papa Giovanni XXIII Hospital, Bergamo 24127, Italy

**ORCID number:** Mirco Nacoti (0000-0002-8737-9812); Giulia Maria Ruggeri (0000-0003-2699-9599); Giovanna Colombo (0000-0002-4190-4976); Ezio Bonanomi (0000-0001-6477-6965); Federico Lussana (0000-0002-6510-8616).

**Author contribution:** Nacoti M was responsible for the concept, design, analysis of data and drafting; Ruggeri GM and Colombo G were responsible for selection of the papers and variables and drafting; Bonanomi E was responsible for concept and critical revision; Lussana F was responsible for the concept, design, searching strategy, drafting and critical revision.

**Conflict-of-interest statement:** The authors of this manuscript have no conflicts of interest to disclose.

**PRISMA 2009 Checklist statement:** The manuscript was prepared and revised according to the PRISMA 2009 Checklist.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Manuscript source:** Invited manuscript

**Correspondence to: Mirco Nacoti, MD, Staff Physician,** Department of Anesthesia and Intensive Care, Pediatric Intensive Care Unit, Papa Giovanni XXIII Hospital, Via Piazza OMS 1, Bergamo 24127, Italy. mnacoti@asst-pg23.it

**Telephone:** +39-35-2675150

**Fax:** +39-35-2674989

**Received:** May 2, 2018

**Peer-review started:** May 4, 2018

**First decision:** May 23, 2018

**Revised:** July 13, 2018

**Accepted:** August 1, 2018

**Article in press:**

**Published online:**

**Abstract**

***AIM***

To review current literature of thrombosis prophylaxis in pediatric liver transplantation (PLT) as thrombosis remains a critical complication.

***METHODS***

Studies were identified by electronic search of MEDLINE, EMBASE and Cochrane Library (CENTRAL) databases until March 2018. The search was supplemented by manually reviewing the references of included studies and the references of the main published systematic reviews on thrombosis and PLT. We excluded from this review case report, small case series, commentaries, conference abstracts, papers which describing less than 10 pediatric liver transplants/year and articles published before 1990. Two reviewers performed study selection independently, with disagreements solved through discussion and by the opinion of a third reviewer when necessary.

***RESULTS***

Nine retrospective studies were included in this review. The overall quality of studies was poor. A pooled analysis of results from studies was not possible due to the retrospective design and heterogeneity of included studies. We found an incidence of portal vein thrombosis (PVT) ranging from 2% to 10% in pediatric living donor liver transplantation (LDLT) and from 4% to 33% in pediatric deceased donor liver transplantation (DDLT). Hepatic artery thrombosis (HAT) was observed mostly in mixed LDLT and DDLT pediatric population with an incidence ranging from 0% to 29%. In most of the studies Doppler ultrasonography was used as a first line diagnostic screening for thrombosis. Four different surgical techniques for portal vein anastomosis were reported with similar efficacy in terms of PVT reduction. Reduced size liver transplant was associated with a low risk of both PVT (incidence 4%) and HAT (incidence 0%, *P* < 0.05). Similarly, aortic arterial anastomosis without graft interposition and microsurgical hepatic arterial reconstruction were associated with a significant reduced HAT incidence (6% and 0%, respectively). According to our inclusion and exclusion criteria, we did not find eligible studies that evaluated pharmacological prevention of thrombosis.

***CONCLUSION***

Poor quality retrospective studies show the use of tailored surgical strategies might be useful to reduce HAT and PVT after PLT; prospective studies are urgently needed.

**Key words**: Pediatric liver transplantation; Hepatic artery thrombosis; Portal vein thrombosis; Prophylaxis; Surgical technique

**© The Author(s) 2018.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** Graft loss and patient death after pediatric liver transplantation (PLT) are most frequently caused by hepatic artery thrombosis and portal vein thrombosis. For this reason, the prevention of hepatic artery and vein thrombosis represents a primary interest for clinicians and researchers, considering the scarcity of hepatic allografts. In our systematic review, we found only nine poor quality retrospective studies showing that tailored surgical strategies might be useful to reduce thrombosis. We did not find eligible studies evaluating pharmacological prevention strategies. Prospective studies are urgently needed to standardize thrombosis prevention in PLT.

Nacoti M, Ruggeri GM, Colombo G, Bonanomi E, Lussana F. Thrombosis prophylaxis in pediatric liver transplantation: A systematic review. *World J Hepatol* 2018; In press

**INTRODUCTION**

Vascular complications are relevant causes of poor outcome for patient and allograft after pediatric liver transplantation (PLT)[1-5]. Among vascular complications of PLT hepatic artery thrombosis (HAT) and portal vein thrombosis (PVT) are one of the most frequent[1-7] and serious causes of graft loss and also patient death[1,2,6-9]. In particular HAT is an extremely serious complication resulting in bile duct necrosis and often requiring retransplantation[10,11]. Thrombosis of other intra-abdominal vessels, such as the hepatic vein and inferior vena cava occurs less frequently[6,11,12]. In the first years of PLT the observed incidence of thrombosis was very high, up to 42%[13-15]. In the last years, an improvement of perioperative care has significantly decreased the thrombosis incidence[1-3]. More recently, an incidence rate of HAT ranging from 2% to 10% after liver transplantation in the pediatric population has been reported[1,6,7,11]; likewise, the incidence rate of PVT ranged from 2% to 10%[1,6,7,9].

In this context, the prevention of HAT and PVT remains very important for PLT outcome and it should be a matter of primary interest for clinicians and researchers, considering the ongoing scarcity of hepatic allografts[1,2,11,12,16-18]. In clinical practice, there is not a standardized approach for thrombosis prevention in PLT. Different surgical techniques and pharmacological prophylaxis have been purposed in several studies[1,5,6,12,14,19-27]. Therefore, we performed a systematic review of current literature about surgical and pharmacological prophylaxis for prevention of thrombosis after PLT to evaluate the current evidence available.

**MATERIALS AND METHODS**

***Search strategy***

The publications were selected through an electronic search of the MEDLINE and EMBASE and Cochrane Library (CENTRAL) databases up to March 2018. The search strategy used the following Medical Subject Headings (MeSH) and EMTREE terms and text words: (“liver transplantation”/exp OR “liver transplantation”) AND (“thromboembolism”/exp OR “thromboembolism” OR “ischemia”/exp OR “ischemia’ OR “vascular disease”/exp OR “vascular disease”) AND (“prophylaxis”/exp OR “prophylaxis’ OR “prevention”/exp OR “prevention”) AND ([newborn]/lim OR [infant]/lim OR [child]/lim OR [preschool]/lim OR [school]/lim OR [adolescent]/lim). In addition the references of the selected studies and two systematic reviews on thrombosis and PLT[11,17] were screened to identify further relevant studies.

Two reviewers (Giulia Maria Ruggeri and Giovanna Colombo) performed an independent study selection, solving any disagreements through discussion and the opinion of a third reviewer (Mirco Nacoti). They obtained study characteristics like year of publication, design, study centre, patients’ characteristics like number, mean age and gender, treatments and number of arterial and venous thrombotic complications.

The following criteria were needed in order to be considered potentially eligible for this systematic review: (1) phase III randomized clinical trials or cohorts including case series with more than 10 patients undergoing elective PLT (age ranged from 0 to 18 years); and (2) reporting arterial and venous thrombosis as primary or secondary events in all different groups according to the used prophylaxis strategy. If data from a study were reported in several publications, data from the most recent paper were used. Studiesdescribing less than 10 PLT/year were excluded as significant high mortality is associated with low volume center[28,29]. Articles published before 1990 were also excluded because new developments in perioperative PLT have dramatically improved the survival[1-3].

***Risk of bias assessment***

Although the evaluation of quality for observational studies is controversial[30], Giulia Maria Ruggeri and Giovanna Colombo assessed the risk of bias using the following items for cohort studies: Type of study (prospective or retrospective); selection of the patients (consecutive or not); thrombosis as pre-specified outcome; quality of measurements (studies in which thrombotic events were measured in an objective way were considered higher quality than studies without these characteristics). A scoring system was put in place to identify the following two quality categories: Studies at low-risk of bias (4 points) and studies at high-risk of bias (≤ 3 points).

**RESULTS**

***Results of the search strategy***

The study process is presented in Figure 1. A total of 560 publications (550 retrieved with the electronic search strategy and 10 by manually reviewing the reference lists of all retrieved articles) were identified. After reading their titles and abstracts 525 were excluded, according to inclusion and exclusion criteria. The remaining 35 publications were analyzed in full for detailed evaluation. Twenty-six papers were eliminated for the following reasons: Publication date before 1990 (*n* = 2), only abstract (*n* = 4), studies without a comparator group (*n* = 13) and studies (*n* = 7) which did not contain explicit data about pediatric thrombotic events.

Nine manuscripts[31-39], which included a total of 1034 PLT in 991 subjects, were included in this systematic review (Table 1). None of the all included studies were at high risk of bias according to pre-defined requirements (Table 2). In particular, no study were prospective, only 7 studies reported thrombosis as a pre-defined outcome, and 8 studies detailed how the diagnosis of thrombosis had been made. The poor quality and the heterogeneity of included studies did not allow us to perform a pooled analysis of results.

***Incidence of the artery and PVT***

Table 1 shows detailed incidence of artery and PVT as reported in the included studies. Most studies reported a total incidence (early and late) of thrombosis. The incidence of PVT varies from 2% to 10% in pediatric living donor liver transplantation (LDLT)[37,39] and from 4% to 33% in pediatric deceased donor liver transplantation (DDLT)[33]. HAT is presented mostly in mixed LDLT and DDLT pediatric population; incidence of HAT varies from 0% to 29%[31,32,34,35,36,38].

***Screening protocol for thrombosis detection***

Most of the studies used Doppler ultrasonography (US) as a first line diagnostic screening for thrombosis[33,35-39}; frequency and duration of the screening is quite variable. Confirmation of the thrombosis detected by a second level diagnostic test, such as computer CT angiography, surgery or other methods is rarely specified[34-37,39].

***Intraoperative surgical prophylaxis***

Table 1 summarizes the main results of the studies analyzed. In LDLT there are four different modalities to perform portal vein anastomosis: (1) standard reconstruction with end to end anastomosis[37,39]; (2) reconstruction with anastomosis to the bifurcation of the recipient left and right vein[39]; (3) reconstruction with anastomosis to the confluence of the recipient mesenteric vein[39]; and (4) reconstruction with an interposition of vein graft[33,37,39]. The overall results of different techniques were similar. The choice of the type of reconstruction depended on the size (length and diameter) and quality of the portal vein and size mismatch between donor and recipient portal vein[33,37,39]. Millis *et al*[33] showed a low PVT incidence with reduced size liver transplant (RLT) [4% *vs* 33% with whole liver transplant (WLT) and native reconstructed vein, *P* < 0.005]; RLT was developed in attempt to resolve the mismatch size liver between donor and recipient and was applied to split liver transplantation and LDLT.

Three different surgical procedures seemed to reduce HAT incidence: RLT with cadaveric left lobe [incidence 0% *vs* 29% with WLT, *P* < 0.05[34]]; aortic arterial anastomosis without graft interposition [incidence 6% *vs* celiac-hepatic artery anastomosis, *P* = 0.02[36]] and microsurgical hepatic arterial reconstruction (MHR) [incidence 0% *vs* conventional artery reconstruction, *P* = 0.006[31]].

Santamaria *et al*[32] and Yandza *et al*[35] did not find significant HAT difference between end-to-end anastomosis and aortohepatic interposition graft; Julka *et al*[38] showed that single hepatic artery reconstruction did not increase the HAT incidence in pediatric LDLT having dual hepatic arterial stump in the liver graft.

***Post-operative pharmacological prophylaxis***

No studies on pharmacological prophylaxis compared clinical outcomes according to different treatments used[1,9,11-13,17,22-24,27].

**DISCUSSION**

Vascular thrombotic complications were a serious life-threatening complication in the first year of PLT with an incidence up to 42% associated with mortality up to 50%[13–15]. Although factors causing thrombotic complications are not fully understood[15], a global improvement of perioperative care has significantly decreased the thrombosis incidence in the last 20 years[1-3,6,7,9,11]. Several retrospective studies without control group tried to identify factors for thrombosis; among them should be mentioned medical factors, such as administration of fresh frozen plasma, elevated hematocrit, protein C deficiency[1,14,40,41] and surgical factors, such as cold ischemia time, technique of anastomosis, small vessel diameter, the use of aortic grafts, donor arterial anatomy and reconstruction[1,7,14,31,36], but without any definitive conclusions.

Accordingly, the aim of this systematic review was to identify evidence based methods both surgical and pharmacological for the prevention of thrombosis after PLT. In this systematic review, we found no prospective studies and only 9 retrospective studies with a control group referred to surgical prevention.

RLT (with left lobe or segment of left lobe)[34] direct aortic anastomosis and MHR[31] seem the best surgical options for reducing thrombotic complications in PLT, but the impact of RLT and aortic anastomosis on HAT were not confirmed by Stevens[36] and Santamari-Yandza[32,33] respectively. MHR is an arterial reconstruction performed with an operating microscope; it was introduced by the Kyoto group for the fine graft arteries (less than 2 mm in diameter) in LDLT[42]. The amazing results of MHR (0 HAT in 28 PLT)[31] need to be confirmed in a larger clinical trial. It is worth noting that one of the most extensive studies about incidence and risk factors for vascular complication in liver transplantation was excluded from this systematic review because it included a mixed adult and pediatric population, without an appropriate control group[1].

Pharmacological prophylaxis is a relevant topic in PLT. Several studies[1,9,11-13,17,22-24,26] reported their experience using different drugs, such as unfractionated heparin, low molecular weight heparin, vitamin K antagonist fresh frozen plasma, aspirin, dipyridamole, antithrombin concentrate, dextran 40, thrombin inhibitor, prostaglandin. Unfortunately, in these studies there was not a comparator group, necessary in order to achieve formal proof of efficacy and safety and according to the inclusion criteria of this systematic review. In this regard, for example, aspirin is one of the most extensive drugs used for HAT prevention[11,14,17], but without formal evidence derived from prospective clinical trials.

The careful search of the literature and the inclusion of different types of studies are the main strengths of this review. Nevertheless, our study presents some weaknesses. First, the risk of thrombosis might have been underestimated because we assumed not all authors systematically reported thrombotic events. Second, the description of methods for preventing vascular thromboses may be incomplete because only studies reporting the outcome were considered.

Although, HAT and PVT incidence has decreased in the last decades[1-3,6,7,9,11], they remain one of the more frequent and serious complications causing a poor outcome after PLT[1,2]. Furthermore, the old question “thrombosis after PLT - a medical or surgical event?“[14] remains an unresolved issue. Concerning this, our systematic review of studies, in which different prophylaxis strategies were tested for the prevention of HAT and PVT failed to provide enough evidence for a definitive conclusion due to the poor quality of studies found[31-39]. However, our analysis emphasizes the need of developing well-designed clinical studies in order to correctly determine PLT-associated thrombosis risk and to define an evidence-based antithrombotic prophylactic strategy. The recent “single ventricle trial”[43] showed that randomized clinical trials are possible also in the pediatric surgery area.

**ARTICLE HIGHLIGHTS**

***Research background***

Hepatic artery thrombosis (HAT) and portal vein thrombosis (PVT) commonly occur after pediatric liver transplantation (PLT) that may cause graft loss and patient death. Different surgical techniques and pharmacological prophylaxis have been purposed in several studies; nevertheless, there is not a standardized approach for thrombosis prevention in PLT.

***Research motivation***

Prevention of HAT and PVT remains very important for PLT outcome and it should be a matter of primary interest for clinicians and researchers, considering the ongoing scarcity of hepatic allografts.

***Research objective***

We performed a systematic review of current literature about surgical and pharmacological prophylaxis for prevention of thrombosis after PLT to evaluate the current evidence available.

***Research methods***

Studies were identified by electronic search of MEDLINE, EMBASE and Cochrane Library (CENTRAL) databases until March 2018. We excluded from this review case report, small case series, commentaries, conference abstracts, papers which describe less than 10 pediatric liver transplants/year and articles published before 1990. Two reviewers performed an independent study selection, solving any disagreements through discussion and the opinion of a third reviewer.

***Research results***

Nine retrospective studies were included in this review. They showed the use of tailored surgical strategies might be useful to reduce thrombosis. We did not find eligible studies evaluating pharmacological prevention strategies. The overall quality of studies was poor. A pooled analysis of results from studies was not possible due to the retrospective design and heterogeneity of included studies.

***Research conclusions***

This systematic review in which different prophylaxis strategies were tested for the prevention of HAT and PVT failed to provide enough evidence for a definitive conclusion due to the poor quality of studies found.

***Research perspective***

This systematic review showed there is no evidence based strategy for thrombosis prevention in PLT. Prospective studies are urgently needed. The recent “single ventricle trial” showed that randomized clinical trials are possible also in the pediatric surgery area.

**ACKNOWLEDGMENTS**

The authors acknowledge Dr. Squizzato A for his help in developing the search strategy and Ms. Anne Brown for language revision.

**REFERENCES**

1 **Duffy JP**, Hong JC, Farmer DG, Ghobrial RM, Yersiz H, Hiatt JR, Busuttil RW. Vascular complications of orthotopic liver transplantation: experience in more than 4,200 patients. *J Am Coll Surg* 2009; **208**: 896-903; discussion 903-905 [PMID: 19476857 DOI: 10.1016/j.jamcollsurg.2008.12.032]

2 **Kamath BM**, Olthoff KM. Liver transplantation in children: update 2010. *Pediatr Clin North Am* 2010; **57**: 401-414, table of contents [PMID: 20371044 DOI: 10.1016/j.pcl.2010.01.012]

3 **Goss JA**, Shackleton CR, McDiarmid SV, Maggard M, Swenson K, Seu P, Vargas J, Martin M, Ament M, Brill J, Harrison R, Busuttil RW. Long-term results of pediatric liver transplantation: an analysis of 569 transplants. *Ann Surg* 1998; **228**: 411-420 [PMID: 9742924 DOI: 10.1097/00000658-199809000-00014]

4 **Yilmaz A**, Arikan C, Tumgor G, Kilic M, Aydogdu S. Vascular complications in living-related and deceased donation pediatric liver transplantation: single center's experience from Turkey. *Pediatr Transplant* 2007; **11**: 160-164 [PMID: 17300495 DOI: 10.1111/j.1399-3046.2006.00601.x]

5 **Orlandini M**, Feier FH, Jaeger B, Kieling C, Vieira SG, Zanotelli ML. Frequency of and factors associated with vascular complications after pediatric liver transplantation. *J Pediatr* (Rio J) 2014; **90**: 169-175 [PMID: 24370174 DOI: 10.1016/j.jped.2013.08.010]

6 **Ooi CY**, Brandão LR, Zolpys L, De Angelis M, Drew W, Jones N, Ling SC, Fecteau A, Ng VL. Thrombotic events after pediatric liver transplantation. *Pediatr Transplant* 2010; **14**: 476-482 [PMID: 19849808 DOI: 10.1111/j.1399-3046.2009.01252.x]

7 **Spada M**, Riva S, Maggiore G, Cintorino D, Gridelli B. Pediatric liver transplantation. *World J Gastroenterol* 2009; **15**: 648-674 [PMID: 19222089 DOI: 10.3748/wjg.15.648]

8 **Unal B**, Gonultas F, Aydin C, Otan E, Kayaalp C, Yilmaz S. Hepatic artery thrombosis-related risk factors after living donor liver transplantation: single-center experience from Turkey. *Transplant Proc* 2013; **45**: 974-977 [PMID: 23622602 DOI: 10.1016/j.transproceed.2013.02.070]

9 **Corno V**, Torri E, Bertani A, Guizzetti M, Lucianetti A, Maldini G, Pinelli D, Zambelli M, Aluffi A, Alberti D, Spada M, Gridelli B, Torre G, Colledan M. Early portal vein thrombosis after pediatric split liver transplantation with left lateral segment graft. *Transplant Proc* 2005; **37**: 1141-1142 [PMID: 15848649 DOI: 10.1016/j.transproceed.2004.11.034]

10 **Heffron TG**, Emond JC, Whitington PF, Thistlethwaite JR Jr, Stevens L, Piper J, Whitington S, Broelsch CE. Biliary complications in pediatric liver transplantation. A comparison of reduced-size and whole grafts. *Transplantation* 1992; **53**: 391-395 [PMID: 1738934 DOI: 10.1097/00007890-199202010-00024]

11 **Bekker J**, Ploem S, de Jong KP. Early hepatic artery thrombosis after liver transplantation: a systematic review of the incidence, outcome and risk factors. *Am J Transplant* 2009; **9**: 746-757 [PMID: 19298450 DOI: 10.1111/j.1600-6143.2008.02541.x]

12 **Sieders E**, Peeters PM, TenVergert EM, de Jong KP, Porte RJ, Zwaveling JH, Bijleveld CM, Slooff MJ. Early vascular complications after pediatric liver transplantation. *Liver Transpl* 2000; **6**: 326-332 [PMID: 10827234 DOI: 10.1053/lv.2000.6146]

13 **Wozney P**, Zajko AB, Bron KM, Point S, Starzl TE. Vascular complications after liver transplantation: a 5-year experience. *AJR Am J Roentgenol* 1986; **147**: 657-663 [PMID: 3529892 DOI: 10.2214/ajr.147.4.657]

14 **Mazzaferro V**, Esquivel CO, Makowka L, Belle S, Kahn D, Koneru B, Scantlebury VP, Stieber AC, Todo S, Tzakis AG. Hepatic artery thrombosis after pediatric liver transplantation--a medical or surgical event? *Transplantation* 1989; **47**: 971-977 [PMID: 2472028 DOI: 10.1097/00007890-198906000-00011]

15 **Mazzaferro V**, Esquivel CO, Makowka L, Kahn D, Belle S, Kahn D, Scantlebury VP, Ferla G, Koneru B, Scotti-Foglieni CL. Factors responsible for hepatic artery thrombosis after pediatric liver transplantation. *Transplant Proc* 1989; **21**: 2466-2467 [PMID: 2652807]

16 **Warnaar N**, Polak WG, de Jong KP, de Boer MT, Verkade HJ, Sieders E, Peeters PM, Porte RJ. Long-term results of urgent revascularization for hepatic artery thrombosis after pediatric liver transplantation. *Liver Transpl* 2010; **16**: 847-855 [PMID: 20583091 DOI: 10.1002/lt.22063]

17 **Robertson JD**. Pediatric transplantation: preventing thrombosis. *J Thromb Haemost* 2015; **13** Suppl 1: S351-S361 [PMID: 26149047 DOI: 10.1111/jth.12968]

18 **Nacoti M**, Cazzaniga S, Colombo G, Corbella D, Fazzi F, Fochi O, Gattoni C, Zambelli M, Colledan M, Bonanomi E. Postoperative complications in cirrhotic pediatric deceased donor liver transplantation: Focus on transfusion therapy. *Pediatr Transplant* 2017; **21** [PMID: 28681471 DOI: 10.1111/petr.13020]

19 **Neto JS**, Pugliese R, Fonseca EA, Vincenzi R, Pugliese V, Candido H, Stein AB, Benavides M, Ketzer B, Teng H, Porta G, Miura IK, Baggio V, Guimaraes T, Porta A, Rodrigues CA, Carnevale FC, Carone E, Kondo M, Chapchap P. Four hundred thirty consecutive pediatric living donor liver transplants: variables associated with posttransplant patient and graft survival. *Liver Transpl* 2012; **18**: 577-584 [PMID: 22271646 DOI: 10.1002/lt.23393]

20 **Englesbe MJ**, Kelly B, Goss J, Fecteau A, Mitchell J, Andrews W, Krapohl G, Magee JC, Mazariegos G, Horslen S, Bucuvalas J. Reducing pediatric liver transplant complications: a potential roadmap for transplant quality improvement initiatives within North America. *Am J Transplant* 2012; **12**: 2301-2306 [PMID: 22883313 DOI: 10.1111/j.1600-6143.2012.04204.x]

21 **Nacoti M**, Corbella D, Fazzi F, Rapido F, Bonanomi E. Coagulopathy and transfusion therapy in pediatric liver transplantation. *World J Gastroenterol* 2016; **22**: 2005-2023 [PMID: 26877606 DOI: 10.3748/wjg.v22.i6.2005]

22 **McLin VA**, Rimensberger P, Belli DC, Wildhaber BE. Anticoagulation following pediatric liver transplantation reduces early thrombotic events. *Pediatr Transplant* 2011; **15**: 117-118 [PMID: 21159111 DOI: 10.1111/j.1399-3046.2010.01426.x]

23 **Quintero J**, Ortega J, Miserachs M, Bueno J, Bilbao I, Charco R. Low plasma levels of antithrombin III in the early post-operative period following pediatric liver transplantation: should they be replaced? A single-center pilot study. *Pediatr Transplant* 2014; **18**: 185-189 [PMID: 24438318 DOI: 10.1111/petr.12217]

24 **Hardikar W**, Poddar U, Chamberlain J, Teo S, Bhat R, Jones B, Ignjatovic V, Campbell J, Newall F, Monagle P. Evaluation of a post-operative thrombin inhibitor replacement protocol to reduce haemorrhagic and thrombotic complications after paediatric liver transplantation. *Thromb Res* 2010; **126**: 191-194 [PMID: 20541794 DOI: 10.1016/j.thromres.2010.05.015]

25 **Uchida Y**, Sakamoto S, Egawa H, Ogawa K, Ogura Y, Taira K, Kasahara M, Uryuhara K, Takada Y, Kamiyama Y, Tanaka K, Uemoto S. The impact of meticulous management for hepatic artery thrombosis on long-term outcome after pediatric living donor liver transplantation. *Clin Transplant* 2009; **23**: 392-399 [PMID: 19191812 DOI: 10.1111/j.1399-0012.2008.00924.x]

26 **Borst AJ**, Sudan DL, Wang LA, Neuss MJ, Rothman JA, Ortel TL. Bleeding and thrombotic complications of pediatric liver transplant. *Pediatr Blood Cancer* 2018; **65**: e26955 [PMID: 29350493 DOI: 10.1002/pbc.26955]

27 **Haberal M**, Sevmis S, Karakayali H, Moray G, Ozcay F, Torgay A, Arslan G. Outcome of pediatric liver transplant in grafts with multiple arteries. *Pediatr Transplant* 2008; **12**: 407-411 [PMID: 18266797 DOI: 10.1111/j.1399-3046.2008.00888.x]

28 **Burroughs AK**, Sabin CA, Rolles K, Delvart V, Karam V, Buckels J, O'Grady JG, Castaing D, Klempnauer J, Jamieson N, Neuhaus P, Lerut J, de Ville de Goyet J, Pollard S, Salizzoni M, Rogiers X, Muhlbacher F, Garcia Valdecasas JC, Broelsch C, Jaeck D, Berenguer J, Gonzalez EM, Adam R; European Liver Transplant Association. 3-month and 12-month mortality after first liver transplant in adults in Europe: predictive models for outcome. *Lancet* 2006; **367**: 225-232 [PMID: 16427491 DOI: 10.1016/S0140-6736(06)68033-1]

29 **Rana A**, Pallister Z, Halazun K, Cotton R, Guiteau J, Nalty CC, O'Mahony CA, Goss JA. Pediatric Liver Transplant Center Volume and the Likelihood of Transplantation. *Pediatrics* 2015; **136**: e99-e107 [PMID: 26077479 DOI: 10.1542/peds.2014-3016]

30 **Stroup DF**, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000; **283**: 2008-2012 [PMID: 10789670 DOI: 10.1001/jama.283.15.2008]

31 **Shackleton CR**, Goss JA, Swenson K, Colquhoun SD, Seu P, Kinkhabwala MM, Rudich SM, Markowitz JS, McDiarmid SV, Busuttil RW. The impact of microsurgical hepatic arterial reconstruction on the outcome of liver transplantation for congenital biliary atresia. *Am J Surg* 1997; **173**: 431-435 [PMID: 9168083 DOI: 10.1016/S0002-9610(97)00066-4]

32 **López Santamaria M**, Vazquez J, Gamez M, Murcia J, Bueno J, Martinez L, Paz Cruz JA, Reinoso F, Bourgeois P, Diaz MC, Hierro L, Camarena C, de la Vega A, Frauca E, Jara P, Tovar JA. Donor vascular grafts for arterial reconstruction in pediatric liver transplantation. *J Pediatr Surg* 1996; **31**: 600-603 [PMID: 8801323 DOI: 10.1016/S0022-3468(96)90506-0]

33 **Millis JM**, Seaman DS, Piper JB, Alonso EM, Kelly S, Hackworth CA, Newell KA, Bruce DS, Woodle ES, Thistlethwaite JR, Whitington PF. Portal vein thrombosis and stenosis in pediatric liver transplantation. *Transplantation* 1996; **62**: 748-754 [PMID: 8824471 DOI: 10.1097/00007890-199609270-00008]

34 **Jurim O**, Csete M, Gelabert HA, Millis JM, Olthoff K, Imagawa D, Shaked A, McDiarmid SV, Busuttil RW. Reduced-size grafts--the solution for hepatic artery thrombosis after pediatric liver transplantation? *J Pediatr Surg* 1995; **30**: 53-55 [PMID: 7722830 DOI: 10.1016/0022-3468(95)90609-6]

35 **Yandza T**, Hamada H, Gauthier F, Pariente D, Lababidi A, de Dreuzy O, Valayer J. Pediatric liver transplantation: effect of the site of arterial inflow on the incidence of hepatic artery thrombosis according to recipient weight. *Transplant Proc* 1994; **26**: 169-170 [PMID: 8108923]

36 **Stevens LH**, Emond JC, Piper JB, Heffron TG, Thistlethwaite JR Jr, Whitington PF, Broelsch CE. Hepatic artery thrombosis in infants. A comparison of whole livers, reduced-size grafts, and grafts from living-related donors. *Transplantation* 1992; **53**: 396-399 [PMID: 1738935 DOI: 10.1097/00007890-199202010-00025]

37 **Sabra TA**, Okajima H, Yoshizawa A, Okamoto T, Anazawa T, Ygi S, Hata K, Yasuchika K, Taura K, Hatano E, Kaido T, Uemoto S. Portal vein reconstruction using vein grafts in pediatric living donor liver transplantation: Current status. *Pediatr Transplant* 2017; **21** [PMID: 28111865 DOI: 10.1111/petr.12888]

38 **Julka KD**, Lin TS, Chen CL, Wang CC, Komorowski AL. Reconstructing single hepatic artery with two arterial stumps: biliary complications in pediatric living donor liver transplantation. *Pediatr Surg Int* 2014; **30**: 39-46 [PMID: 24292409 DOI: 10.1007/s00383-013-3436-z]

39 **Saad S**, Tanaka K, Inomata Y, Uemoto S, Ozaki N, Okajima H, Egawa H, Yamaoka Y. Portal vein reconstruction in pediatric liver transplantation from living donors. *Ann Surg* 1998; **227**: 275-281 [PMID: 9488527 DOI: 10.1097/00000658-199802000-00018]

40 **Harper PL**, Edgar PF, Luddington RJ, Seaman MJ, Carrell RW, Salt AT, Barnes N, Rolles K, Calne RY. Protein C deficiency and portal thrombosis in liver transplantation in children. *Lancet* 1988; **2**: 924-927 [PMID: 2902380 DOI: 10.1016/S0140-6736(88)92597-4]

41 **Hesselink EJ**, Klompmaker IJ, Grond J, Gouw AS, van Schilfgaarde R, Sloof MJ. Hepatic artery thrombosis (HAT) after orthotopic transplantation (OLT)--the influence of technical factors and rejection episodes. *Transplant Proc* 1989; **21**: 2468 [PMID: 2652808]

42 **Inomoto T**, Nishizawa F, Sasaki H, Terajima H, Shirakata Y, Miyamoto S, Nagata I, Fujimoto M, Moriyasu F, Tanaka K, Yamaoka Y. Experiences of 120 microsurgical reconstructions of hepatic artery in living related liver transplantation. *Surgery* 1996; **119**: 20-26 [PMID: 8560381 DOI: 10.1016/S0039-6060(96)80208-X]

43 **Ohye RG**, Sleeper LA, Mahony L, Newburger JW, Pearson GD, Lu M, Goldberg CS, Tabbutt S, Frommelt PC, Ghanayem NS, Laussen PC, Rhodes JF, Lewis AB, Mital S, Ravishankar C, Williams IA, Dunbar-Masterson C, Atz AM, Colan S, Minich LL, Pizarro C, Kanter KR, Jaggers J, Jacobs JP, Krawczeski CD, Pike N, McCrindle BW, Virzi L, Gaynor JW; Pediatric Heart Network Investigators. Comparison of shunt types in the Norwood procedure for single-ventricle lesions. *N Engl J Med* 2010; **362**: 1980-1992 [PMID: 20505177 DOI: 10.1056/NEJMoa0912461]

**P-Reviewer:** Mikulic D, Morimatsu H, Tchilikidi KY **S-Editor:** Ji FF **L-Editor: E-Editor:**

**Specialty type:** Gastroenterology and hepatology

**Country of origin:** Italy

**Peer-review report classification**

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): C, C

Grade D (Fair): D

Grade E (Poor): 0

**Figure 1 Flow-chart of study selection process.**

Studies excluded after articles screening

Publication date before 1990 (*n* = 2)

Only abstract (*n* = 4)

Studies without a comparator group (*n* = 13)

Studies without data about thrombotic events (*n* = 7)

Potentially relevant studies identified and screened for retrieval (*n* = 560)

Records identified from database = searching (*n* = 550)

Additional records identified through manually reviewing the references lists of all retrieved articles and of two published systematic reviews (*n* = 10)

Studies included in the systematic review (*n* = 9)

Studies excluded after screening of

Their titles and abstracts, based on inclusion criteria

(*n* = 525)

Studies retrieved for detailed evaluation (*n* = 35)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Table 1 Summary of findings of the nine included studies** | | | | | | | |
| **Reference** | **Country** | **Population (*n*)** | **Study design** | **Method used for diagnosis and follow-up duration** | **Intervention** | **Outcome** | **Main results** |
| Sabra *et al*[37] | Japan | 113 pediatric LDLT | Retrospective | Doppler US twice daily till 1st week. If any PV complications were found, specific  tests such as angiography were performed  1 yr of follow-up | PV reconstruction with VG (31 pts)  PV reconstruction with EEA (82 pts) | Preoperative recipient factors  PVT incidence  Pt survival  Graft survival | Global incidence PVT (2.6%) in the first 3 mo after OLT  1 PVT in 31 VGs *vs*  2 PVT in 82 without VGs  No significant difference for PVT, Pt survival,  Graft survival  In the two groups |
| Julka *et al*[38] | Taiwan | 87 pediatric LDLT | Retrospective | Routine doppler US post LT; CT angiography for HAT confirmation  5 yr of follow-up | HA reconstruction with two arterial stumps.  2 HA stumps with 2 HA reconstruction = 20 pts  2 HA stumps with 1 HA reconstruction = 22 pts  1 HA stump with 1 HA reconstruction  = 45 pts | HAT Incidence  BC incidence | Overall HAT incidence 6.9%  The incidence of HA thrombosis and biliary complications was similar in the three groups |
| Saad *et al*[39] | Japan | 110 LDLT in pediatric pts | Retrospective  LDLT | Doppler US, performed routinely before, during and after surgery  Follow-up not defined | Different types of  portal vein reconstructions  Type 1: End- to- end anastomosis = 36 pts  Type 2: Branch patch anastomosis = 27 pts  -Type 3: Anastomosis  to the confluence  (superior mesenteric vein-splenic  vein) = 16 pts  Type 4: Vein graft = 32 pts  Chosen according to the surgical evaluation | C  TC  SC  Survival rate | Type 1: 1 SC / 36 pts  Type 2: 2 TC / 27 pts  Type 3: 0 / 16 pts  Type 4: 1 TC / 32 pts  Overall survival rate 86% |
| Shackleton *et al*[31] | California | 194 pediatric OLT for biliary atresia (mixed LDLT and DDLT) | Retrospective | Clinical suspect confirmed by angiography and/or surgical exploration.  3 yr of follow-up | Gr1: Conventional artery reconstruction (*n* = 166)  Gr 2: MHR ( *n* = 28) | Risk factors for HAT  Impact of MHR on incidence of HAT, need of re-OLT, patient and graft survival | Impact of MHR  HAT incidence: Gr1 32/166 (19%) *vs* Gr2 0/28 (0%), *P* = 0.006  Re-OLT: Gr1 31/166 (19%) *vs* Gr2 1/28 (4%),  *P* = 0.05  1 yr actuarial survival: Gr1 81% *vs* Gr2 100%,  *P* = 0.02 (univariate analysis)  BUT  *P* = 0.076 in step wise Cox regression for patient survival |
| Santamaria  *et al*[32] | Spain | 104 OLT in 82 pediatric pts (mixed LDLT and DDLT) | Retrospective | Doppler US routinely and selective arteriography for confirmation.  3 yr of follow-up | Arterial revascularization technique:  Gr 1 (*n* = 48) AhG  Gr 2 (*n* = 56) EEA  Chosen according to the surgical evaluation | HAT incidence  Survival rate | HAT incidence  Gr 1. (AhG): 6.25%  Gr 2. (EEA): 8.92%  (*P* not significant)  Graft Survival rate (1 yr)  61.5% (AhG) *vs* 60% (EEA) (*P* < 0.05)  Graft survival rate (5 yr): 77.5% (AhG) *vs* 75.1% (EEA) (*P* < 0.05) |
| Millis *et al*[33] | Illinois | 66 pediatric LDLT  and  48 pediatric RLT | Retrospective | Doppler US every day for the first 3 d and at 1, 3, 6, 12, 18, and 24 mo after transplantation + angiography for confirmation  5 yr of follow-up | Portal anastomosis with venous graft conduit in LDLT  Gr1 (*n* = 18): Native reconstructed vein  Gr2 (*n* = 37): Cryopreserved iliac vein;  Gr3 (*n* = 11): Cryopreserved femoral vein | Incidence of PVC  Graft survival  Patient survival | Incidence PVC  LDLT 33/66 (50%) *vs*  RLT 4/48 (8%) *P* < 0.0001  Early PVT  LDLT Gr1: 6 (33%)a  LDLT Gr2: 3 (8%)  LDLT Gr3: 1 (9%)  RLT : 2 (4%)  a*P* < 0.005 *vs* RLT  Late PVC  LDLT Gr1: 3 (16%)  LDLT Gr2: 19 (51%)a  LDLT Gr3: 1 (9%)  RLT: 2 (4%)  a*P* < 0.005 *vs* RLT; *P* < 0.02 *vs* Gr1 and Gr3  Graft survival  PVC: 61%  No PVC:67%, *P* = NS  Patient survival:  PVC: 67%  No PVC: 71%, *P* = NS |
| Jurim *et al*[34] | California | 35 pediatric OLT  Emergency transplants only (type of donor not specified) | Retrospective | Not reported.  Follow-up not defined | Gr1: RLT = 7 pts  Gr2: Whole graft = 18 pts | HAT incidence  Incidence of other complications: Biliary; bleeding; chronic rejection | HAT:  Gr1:0 (0%)/Gr2:5 (29%) (*P* < 0.05)  The incidence of biliary complications, bleeding  (requiring surgical exploration) and chronic rejection were similar between the groups |
| Yandza *et al*[35] | France | 143 DDLT in 122 pediatric pts | Retrospective | Doppler US daily the first 15 d, twice/wk until discharge  Follow-up not defined | Gr1 (*n* = 41 pts,  *n* = 50 grafts) children < 10Kg  Gr2 (*n* = 81 pts,  *n* = 93 grafts) children > 10 kg  Surgical technique: EEA *vs* AhG | Effect of the site of liver graft arterial inflow on HAT incidence according to the recipient weight | Overall HAT incidence: 14/143 (10%)  HAT incidence between the 2 groups: Gr1: 6/50 (12%) *vs* Gr2: 8/93 (9%), p not significant; Gr1 EEA 5/31 (16%) *vs* Gr1 AhG 1/19 (5%); *P* not significant  Gr2 EEA 4/60 (6%) *vs* Gr2 AhG 4/32 (12%)  *P* not significant |
| Stevens *et al*[36] | Chicago | 134 OLT in 100 pediatric pts < 2 yr: mixed LDLT and DDLT | Retrospective | Doppler US, frequency not defined  Follow-up | 60 standard whole liver *vs* 74 RLT (13 LDLT)  -Surgical technique: Arterial inflow with 83 hepatic artery *vs* 32 celiac artery *vs* 5 supraceliac aorta *vs* 27 infrarenal aorta *vs* 7 unusual reconstruction | Effect of the graft type and site of arterial inflow on the Incidence of HAT | HAT incidence in 25% whole liver transplant *vs* 23% in LDLT *vs* 15% RLT (*P* = 0.06)  Aortic anastomosis (supraceliac and infrarenal) reduces incidence of HAT (6% *vs* 24%, *P* = 0.02) |

BA: Biliary atresia; BW: Body weight; CTA: CT angiography; Gr: Group; GRWR: Graft-to-recipient weight ratio; HAG: Hepatic artery graft; LT: Liver transplantation; OLT: Orthotopic liver transplantation; Pt: Patient; RLT: Reduced size liver transplantation; re-OLT: Re-transplantation; SC: Stenotic complication; TC: Thrombosis complication; US: Ultrasonography; LDLT: Living donor liver transplantation; PV: Portal vein; VG: Vein graft; EEA: End-to-end anastomosis; PVT: Portal vein thrombosis; HAT: Hepatic artery thrombosis; HA: Hepatic artery; BC: Biliary complications; C: Complications; MHR: Microsurgical hepatic arterial reconstruction; AhG: Aortohepatic interposition graft; PVC: Portal vein complications; DDLT: Deceased donor liver transplantation.

**Table 2 Risk of bias and quality of the studies**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Reference** | **Study design** | **Consecutive enrolment** | **Thrombosis as pre-defined outcome** | **Methods use to the diagnosis of thrombosis** |
| **Shackleton *et al*[31]** | Retrospective | Yes | Yes, HAT | Clinical grounds and angiography and/or surgical exploration for confirmation |
| **Santamaria *et al*[32]** | Retrospective | Yes | No | Doppler US and angiography for confirmation, post mortem second confirmation |
| **Millis *et al*[33]** | Retrospective | Yes | Yes, PVT | Doppler US and angiography for confirmation |
| **Jurim *et al*[34]** | Retrospective | Yes | Yes, HAT | Not reported |
| **Yandza *et al*[35]** | Retrospective | Yes | Yes, HAT | Doppler US |
| **Stevens *et al*[36]** | Retrospective | Yes | Yes, HAT | Doppler US |
| **Sabra *et al*[37]** | Retrospective | Yes | Yes, PVT | Doppler US |
| **Julka *et al*[38]** | Retrospective | Yes | No | Doppler US and angiography for confirmation |
| **Saad *et al*[39]** | Retrospective | Yes | Yes, PVT | Doppler US |

PVT: Portal vein thrombosis; HAT: Hepatic artery thrombosis; US: Ultrasonography.