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Antithrombotic Management and Thrombosis Rates in Children Post-Liver Transplantation: A Case Series and Literature Review

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Abbreviations

HAT – hepatic artery thrombosis; HVT – hepatic vein thrombosis; IVC- inferior vena cava; LMWH – low molecular weight heparin; OLT – orthotopic liver transplant; PVT – portal vein thrombosis

Abstract

Thrombosis is a major postoperative complication in pediatric liver transplantation. There is marked heterogeneity in prophylactic antithrombotic therapies used, without established guidelines. This review summarizes current worldwide incidence of thrombotic events and compares antithrombotic therapies in children post-liver transplant, with comparison to our institution's experience. Of the twenty-three articles with sufficient detail to compare antithrombotic regimens, the overall incidence of thrombosis ranged from 2.4-17.3%. Incidence of hepatic artery thrombosis (HAT) ranged from 0-28.1%, 0-4.7% for hepatic vein thrombosis (HVT), 1.5-11.2% for portal vein thrombosis (PVT), and 0-2.8% for inferior vena cava (IVC) thrombosis. Re-transplantation due to thrombosis ranged from 0-4.8%. Prophylactic antithrombotic therapies varied between studies and bleeding complications were infrequently reported. Since 2010, 96 children underwent 100 liver transplants at our institution with thrombosis incidence comparable to international literature (HAT 6%, PVT 5%, IVC 1%, HVT 0%). Re-transplantation due to thrombosis occurred in 2% and major bleeding occurred in 10%. The prophylactic antithrombotic therapies used post-liver transplantation in children remains varied. Low rates of thrombosis have been reported with antiplatelet use both with and without anticoagulation. Standard definitions and consistent reporting of bleeding complications is required, in addition to thrombosis rates, so that true risk-benefit assessment of reported regimes can be understood.

1. Introduction

Orthotopic liver transplantation (OLT) is an established therapy for children with acute or chronic liver failure, including biliary atresia and metabolic diseases. Pediatric OLT accounts for approximately 17% of all liver transplants in Australia, and increasing numbers of children are undergoing successful OLT as definitive therapy[1]. Graft and patient survival has improved

significantly in the past two decades by targeting medical management, surgical technique, donor availability and procurement, immunosuppressive regimens, and postoperative complications[2].

Thrombosis, a common postoperative complication, is a major source of morbidity and mortality, especially in pediatric patients. Vascular complications are life-threatening events with a high rate of graft failure, often requiring a replacement liver transplant[3,4]. Thrombosis post pediatric OLT occurs due to the changes in flow due to difficulties in anastomosis, smaller vessel calibre, anatomical variations, and hypercoagulable states due to acquired protein S, protein C and antithrombin deficiency[5-9]. The incidence of hepatic artery thrombosis (HAT), hepatic vein thrombosis (HVT), portal vein thrombosis (PVT) and inferior vena cava (IVC) thrombosis has varied worldwide, with HAT more common in pediatric patients than in adults[10]. Currently, despite the significant consequences of thrombotic complications in pediatric OLT patients, there is no standardized protocol for thromboprophylaxis post OLT.

This study aims to summarize the worldwide incidences of thrombosis post-liver transplant in children and to provide a perspective on the current anticoagulation protocols utilized post-transplant. We will also describe our institution's (the Royal Children's Hospital, Melbourne) collective experience, thrombosis rates and anticoagulation protocol. We aim to synthesize and compare the current worldwide experiences/outcomes of anticoagulation post liver transplant in children to further refine thromboprophylaxis protocols and improve clinical outcomes.

2. Methods

2.1 Literature search Strategy

The Ovid MEDLINE and PubMed databases were searched in order to identify all publications reporting the thrombosis outcomes in pediatric liver transplantation patients between 2000 and March 19, 2018. The following search strategy was employed using "Liver Transplant*" AND (thrombosis OR venous thrombosis).

The literature search inclusion criteria were:

- Any study design, including trials, cohort studies, retrospective studies and cross over studies examining outcomes with an inception cohort of ≥50 patients with liver transplantation
- Studies performed in children (0–18 years) or reporting the incidence of thrombosis in children separate to adults
- Studies published during or after 2000 in the "English language"

Articles were excluded if:

- They reported findings from animal studies or adult studies without description of pediatric incidence isolated. Adult studies were excluded from this review, as they did not support this study's purpose of reviewing the use of antithrombotic agents in pediatric liver transplant patients.
- Thrombosis outcomes were not described. A thrombosis outcome for our search was defined as PVT, HAT, HVT and IVC thrombosis. Other thrombotic events or peripheral venous thromboembolism were not included in the search. Thrombosis event rates were only included for post-liver transplantation, and did not include intra-operative thrombotic events.
- No antithrombotic therapy was reported (either antiplatelet OR anticoagulation). When reporting their anticoagulation protocol either a) the agent and dose must be reported or b) the monitoring strategy. Any papers with the incidences of thrombosis were included for an initial broad worldwide understanding of the current rates of thrombosis and then papers without any description of the antithrombotic therapy post liver transplantation were subsequently eliminated from further analysis.

Review articles were included in the search strategy for examination of the references to find suitable original studies and were subsequently excluded from further analysis.

The reference lists of all included papers were subsequently reviewed to identify eligible papers that were not identified in the initial search strategy. Identified manuscripts were categorized according to the geographical region and the antithrombotic therapies described. Duplicated cohorts between studies were removed for calculations, except when reporting thrombosis outcomes in different vessels, with the most recent cohort included in the final analysis when possible.

2.2 Retrospective cohort

Children who underwent OLT between January 2010 and January 2018 in Melbourne, Australia were retrospectively identified from the Victoria Liver Transplant Unit database. Patient demographics, indication for transplant, graft type, postoperative vascular complications and graft outcomes were identified. Doppler ultrasound was the diagnostic imaging method used and all children had routine doppler ultrasounds immediately postoperatively and then daily for three days. After this point doppler ultrasound was performed if there was clinical suspicion of vascular thrombosis.

All patients followed a standardised haemostatic replacement protocol. Plasma antithrombin levels were measured daily from the first postoperative day for 7-10 days. Antithrombin (Thrombotrol®-VF

1000 units) was administered to maintain antithrombin levels between 75% and 100%. Daily fresh frozen plasma (15ml/kg) was given for the first five days post transplant until patients were able to maintain their native protein C without replacement, as per our previous publication[11]. Dextran 40 was given for five days post transplant routinely (<10kg: 2.5ml/hr, >10kg: 5ml/hr intravenously). Intravenous unfractionated heparin 10unit/kg/hr was commenced once the APTT and INR were less than 1.5 times normal. The heparin rate was then titrated to maintain an anti-factor Xa between 0.1 and 0.3unit/mL. Heparin was continued for two weeks postoperatively or until aspirin was commenced. Aspirin 5mg/kg/d (maximum dose 100mg) was commenced when the patient was both tolerating enteral feeds and it was thought unlikely that they would require further invasive procedures, such as a liver biopsy. Aspirin was continued for 6 months in uncomplicated patients, 12 months in patients with a vascular stent and indefinitely in patients with a cardiac device in situ. Major bleeding was defined as bleeding that required surgical intervention, transfusion or resulted in functional end organ damage[11].

Ethics approval was not obtained for this study. At our institution authorisation by an ethics board is not required for quality control audits.

2.3 Statistical analyses

All statistical analyses were performed on Microsoft® Excel® for Mac [computer program] Version 14.4.3. For descriptive statistics, discrete variables were reported as numbers (%) for proportions. Continuous data were described as median (range) for non-normally distributed data.

3. Results

3.1 Worldwide incidence of thrombosis post-liver transplantation

The database interrogation identified a total of 742 publications on the incidence of thrombosis post-liver transplant (See Figure 1). There were 64 articles that reported the incidence of thrombosis post liver transplant in children. There was a broad range in incidence of thrombosis reported, from 0-40.6% for PVT, 0-33.4% for HAT, 0-6.4% for HVT and 0-2.9% for IVC thrombosis. Overall incidence ranged from to 2.4% to 17.3%. Of these articles 41 did not include adequate details about their anticoagulation protocol and so were excluded. There were 23 articles remaining that reported the incidence of thrombosis post liver transplantation in children and included adequate detail about their antithrombotic protocol to allow comparisons between protocols to be made.

3.2 Studies Describing Antithrombotic Strategies

The full-text of the 23 manuscripts describing antithrombotic strategies was reviewed, with Table 1 describing the different study characteristics for each manuscript including year, country, follow-up duration, number of transplants, survival, re-transplantation due to thrombosis and incidences of

thrombosis and major bleeding in percent. Two of the identified manuscripts were prospective cohort study design [12,13], 18 were retrospective cohort study design, and 3 studies were mix of prospective and retrospective cohorts [11,14,15]. The mean or median age at liver transplantation in the included studies ranged from 6.9 months to 6.9 years, and the mean or median follow-up for thrombosis ranged between 15 days and 12 years. Four studies had a longer overall study follow-up but only reported incidences of thrombosis in the first 30 to 31 days post-liver transplantation [16-19] and the incidences of HAT were limited to the first 15 days for Ackermann et al[20].

The incidence of overall thrombosis in the included studies range from 2.4% to 17.3%. The incidence of HAT ranged from 0% to 28.1%, 0% to 4.7% for HVT, 1.5% to 11.2% for PVT, and 0% to 2.8% for IVC thrombosis. Re-transplantation rates due to thrombosis ranged from 0% to 4.8%.

3.3 Major Bleeding Incidence

Overall major bleeding rates while on antithrombotic therapy were only reported in 5/23 (22%) included studies, with incidences ranging from 0 to 28%. The definitions and follow-up for major bleeding varied in each study, for example, the bleeding incidence reported by Uchida et al. is based on suspected bleeding and required transfusion in 4 of the 5 cases[19]. Other than major bleeding, Ziaziaris et al. reported minor bleeding rates of 11.5% in patients managed with heparin and aspirin and 24.6% in patients managed with heparin, aspirin and replacement of haemostatic proteins[21].

3.4 Thrombosis Timing

Studies indicate that thrombosis complications occur most frequently in the first 30 days postoperatively [12,15,16,21,22]. Variations between different thrombotic complications were reported with the timing of HAT more likely to be reported as occurring within 30 days. Neto et al. reported a higher incidence of late PVT (>30 days postoperatively) compared with early PVT (< 30 days postoperatively) (late 4.5% vs. early 2.7%), although this study excluded 6 patients who had concurrent HAT complications[14]. Additionally, Broniszczak et al. reported a wider range in timing of PVT of 1-22 days compared to HAT of 5-8 days[22]. Fifteen of the 23 articles reported the duration of follow up of their cohort, however few studies reported the timing of the thrombotic events (Table 1). It was therefore difficult to ascertain in many cases whether late thrombotic events were included.

3.5 Monitoring & Diagnosis of Thrombosis

Monitoring and diagnosis for thrombotic complications was described in 19/23 articles, with all describing monitoring or screening conducted by Doppler colour ultrasound [11-29]. Ultrasound monitoring of hepatic vessel flow was utilized daily or twice daily for a range of 1 to 10 days postoperatively and then when clinically indicated after the initial post-operative period [12-18,22-26,29]. Ultrasound monitoring was followed by arteriography, surgery or computed tomography scan for

confirmation [11, 14,15,17,20,21,25,29]. Two studies reported utilizing lab findings as a method of monitoring for vascular complications[22,27]. Uchida et al. reported monitoring for HAT by ultrasound hepatic artery pulsatility index less than 0.6 as a warning sign[19].

3.6 Anticoagulation & Antiplatelet protocol post-liver transplantation

Table 2 illustrates the different anticoagulation protocols utilized post OLT in the included manuscripts. Use of aspirin postoperatively without use of anticoagulants was reported in 9/23 manuscripts (39%) and the use of aspirin overall was reported in 17/23 (74%) manuscripts. Heparin was used post-operatively in 13/23 studies (57%), with a target aPTT range from 50 to 70 seconds in 2 studies, Activated Clotting Time of 150 to 200 seconds in two studies or Anti-Xa of 0.1-0.3 U/mL in one study. Several studies had conditional use of heparin including if the patient had Budd-Chiari, intraoperative thrombosis or technically difficult anastomosis. There were 8/23 (35%) studies that described the use of unfractionated heparin postoperatively with a transition to aspirin when oral intake was tolerated. Dipyridamole was described in 8/23 studies (35%). Dextran infusion was described in 2/23 (9%) studies. Fresh frozen plasma was used in 5/23 (22%) manuscripts. Antithrombin was utilized in 3/23 (13%) studies with a target antithrombin range greater than 65 to 70% in two studies, and no target range in Ziaziaris et al. Haematocrit was kept around 30% in 3 studies [21,22,30]. Broering et al. aimed to maintain platelets above 80,000/μLfor the first 24 hours then >50,000/μL [23]. Ooi et al. withheld anticoagulation and antiplatelet therapy prior to liver biopsy, aiming to withhold aspirin for 3-5 days prior where possible[16]. No other study reported their protocol for antithrombotic therapy in the event of invasive procedures.

3.7 Retrospective cohort

Ninety-six children aged 18 years or less underwent 100 liver transplants at the Royal Children's Hospital, Melbourne between January 2010 and January 2018. Five children received a combined transplant (liver and either intestine, pancreas or kidney transplant). The median age of recipients was 33 months (range 5 months to 18 years) and median weight 13kg (range 5.5-75kg). Fifty-four patients received a split graft (54%), 37 received a whole graft (37%) and nine patients received a reduced graft (9%). As illustrated in Table 3, PVT occurred in five patients (5%), HAT in six patients (6%) and IVC thrombosis in one patient (1%). There were no cases of HVT. Vascular complications occurred more frequently in younger patients, with a median age of 18 months (7 months to 11 years) and median weight 10kg (6-44.7). Thromboses were more common in reduced and split grafts compared to whole grafts (22%, 13% and 8% respectively). Four patients required re-transplantation, two due to HAT on day 20 and 50 and two for non-haematological indications on day 7 and 601. Three patients died over the follow up period, one patient had gram-negative sepsis and HAT and another was commenced on ECMO for a pulmonary hypertensive crisis, which was complicated by

severe intra-abdominal bleeding and multi-organ failure. The third patient had acute cellular rejection and multi-organ failure.

There were 10 patients (10%) with major bleeding postoperatively, six of which were intra-abdominal with an unknown bleeding point, two were from the arterial anastomosis and two were from the cut surface of a split graft. Nine patients with major bleeding required repeat laparotomy and one was managed conservatively but required a red cell transfusion. In the majority of patients with major bleeding the heparin was transiently ceased until the bleeding had resolved. The median age of the patients with major bleeding was 19.5 months (8 months to 192 months). Major bleeding was more common in reduced grafts compared to split and whole grafts (22%, 9% and 8% respectively). One patient experienced both major bleeding and thrombosis and required re-transplantation for HAT. Of the patients who received combined organ transplants none had thrombosis or major bleeding.

4. Discussion

The development of vascular thrombosis post liver transplantation in children results from the interplay of factors that impact the degree of endothelial injury, the quality of blood flow to the graft and the intercurrent haemostatic balance in the patient. The factors affecting endothelial injury and blood flow have been well-documented, such as surgical techniques, graft types, size of the recipient and the graft-to-recipient weight ratio, and their impact on the incidence of vascular thrombosis[27,31-35]. Thromboprophylaxis post liver transplant has been demonstrated to reduce regional thrombotic complications in adult patients[37-39]. Children have been identified as a high-risk group for thrombosis post liver transplant, however, thromboprophylaxis is widely used despite an absence of prospective or randomised trials to prove its benefit[40]. Antithrombotic management varies considerably and although individual centres have reported their local protocols and rates of thrombosis, the optimal thromboprophylaxis post liver transplant in children is unknown.

There were 23 articles that reported their antithrombotic protocols and thrombosis rates in the literature. The antithrombotic protocols were heterogeneous, with some centres using anticoagulation, antiplatelet therapy, or a combination of both with or without replacement of haemostatic proteins. The antithrombotic protocol used in our institution is more intensive than many reported, and the incidence rates from our centre fell within the ranges reported in these articles. The articles that reported lower thrombosis rates than our centre were examined in more detail. Broniszczak et al., Kanmaz et al. and Mali et al. reported improved rates of HAT compared to our centre (5.6%, 3.9% and 4.9% respectively) though had higher rates of PVT (11.2%, 6.8% and 11.1% respectively) [22,26,30]. Neto et al. reported lower HAT rates than our centre (3.2%) though in a separate paper with a slightly smaller patient cohort and the same antithrombotic regimen Neto et al. reported higher rates of PVT (7.0%)[14 15]. Broering et al. and Ziaziaris et al. (group 3) only reported thrombosis

rates in one vessel though these reported rates were lower than our centre (PVT 1.5%, HAT 1.7% respectively) [21,23]. Both of these centres used a similar regimen to ours with heparin, aspirin and replacement of haemostatic proteins with antithrombin and fresh frozen plasma. Broering et al. reported a major bleeding rate of 5%[23].

There were four centres that reported lower thrombosis rates across multiple vessels and had varied thromboprophylaxis protocols [11,16,25,36]. Millar et al. described a cohort of 71 patients that were managed with aspirin alone on alternate days with low rates of HAT, PVT and IVC thrombosis (HAT 1.4%, PVT 4.2%, IVC 2.8%) and also a low rate of major bleeding (4%)[36]. Heffron et al. reported a cohort of 271 transplants managed with aspirin alone from the first postoperative day for three months, with a PVT incidence of 1.5% and no HVT[25]. The HAT incidence of 2.7% was published in a separate paper from a smaller but presumably overlapping patient cohort using the same antiplatelet protocol[13]. Ooi et al. managed patients with heparin and dipyridamole immediately postoperatively, and transitioned to dual antiplatelet cover with aspirin and dipyridamole. Thrombosis incidence was globally low in this cohort of 88 patients with HAT in 3.4%, HVT 3.4%, PVT 2.3% and IVC thrombosis 1.1% and no episodes of major bleeding[16]. However this cohort were only screened for thrombosis on the first postoperative day[16].

Hardikar et al. described two patient cohorts managed with different antithrombotic regimens at our centre from 1992-2002[11]. The first cohort were managed with unfractionated heparin for 24 hours and reported a HAT, PVT and IVC thrombosis incidence of 2.3% and HVT incidence of 4.7%. The rate of major bleeding in this group was 28%. The second patient cohort used the same antithrombotic regimen currently used in our centre and had low rates of thrombosis across multiple vessels (PVT 2.3% and no HAT, HVT or IVC thrombosis) and a decrease in bleeding rate compared to the first cohort (15%)[11]. The improvement in thrombosis rates between the two cohorts reported by Hardikar et al. was attributed to the changes in the antithrombotic protocol and possibly improvement in surgical techniques over that time frame. The decrease in the major bleeding rate despite the addition of antiplatelet therapy and a more protracted time on anticoagulation was thought to be due to the replacement of haemostatic proteins. Interestingly, when comparing Hardikar et al.'s findings to the patients transplanted between 2010 and 2018 there has been an increase in thrombosis rates (PVT 5%, HAT 6%, IVC thrombosis 1% and no HVT) and a further reduction in the major bleeding rate (10%). The bleeding rates at other centres varied from 0-5%, however this may be a result of reporting bias as only 5 out of 23 articles commented on bleeding rates.

The variability in thrombosis rates between centres and eras cannot be attributed to thromboprophylaxis alone. Significant variation exists between centres in patient selection, patient age and size, graft selection, as well as surgical techniques and experience which all impact greatly on

the development of thrombosis. This is most notably demonstrated in the population of infants ≤10kg with the highest reported rates of thrombosis of the cohort (HAT and PVT incidence of 28% and 41% respectively)[28]. The impact of these and other factors on the incidence of thrombosis have been discussed in previous articles[15,27,28,31-35]. The difficulty in determining the optimal thromboprophylaxis protocol is limited by an inability to control for these variables across centres, under-reporting of relevant data where comparisons could be made, and nuanced factors that are difficult to quantify such as surgical skill or patient complexity.

In identifying the optimal thromboprophylaxis protocol a low incidence of both thrombosis and major bleeding is desired. Direct comparison of these rates is limited by variation between papers in the definition of thrombosis and major bleeding. In many instances it is difficult to differentiate between stenosis and thrombosis based on the information provided. Bleeding complications were reported in less than a quarter of articles and even fewer defined bleeding. This is further complicated by the fact that different protocols have different sensitivity for the detection of thrombosis. Variation in ultrasound quality, experience of the sonographer and radiologist and also the frequency of screening would impact on the ability to diagnose thrombosis. There is also large variation in the duration of follow up, with one study reporting follow up for only 15 days post transplant while many articles reported thrombosis events occurring after this time point.

One limitation in this paper is that it in order to compare thromboprophylaxis protocols, articles were excluded that did not include thromboprophylaxis in adequate detail (either antiplatelet OR anticoagulation). In theory this would result in the exclusion of articles that opted not to use antithrombotic therapy however, in reality, the majority of articles were excluded due to insufficient information about the thromboprophylaxis that they used, rather than routinely not instituting any. Only one article reported that they routinely used no thromboprophylaxis (either antiplatelet or anticoagulation) in patients with standard anastomoses but did not report the thrombosis incidence in this group[41]. Therefore the exclusion of papers that do not use thromboprophylaxis had no impact on the outcome of our findings.

All regimens with low rates of thrombosis did include an antiplatelet agent, though there were favourable outcomes both with and without the use of anticoagulation. Our centre had comparable rates of thrombosis and major bleeding, although not the lowest of the series and was more intensive and costly than other protocols that use antiplatelet therapy in isolation or with simple anticoagulation. The question of the optimal antithrombotic protocol is difficult to answer without more homogenous reporting of each centre's experience. In order to make comparisons between centres there needs to be standard definitions of thrombosis, major bleeding and an adequate description of the patient cohort as well as antithrombotic protocol used including agent, doses and monitoring strategy. There

should also be a description of the screening process for diagnosis of thrombosis and a clearly defined end point. Given the morbidity associated with major bleeding in this patient cohort, the intensity of the antithrombotic regimen needs to be balanced with bleeding risk and therefore bleeding rates must always be reported.

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Tables

Table 1. Included Studies.

Author & Year	Where	Study Years	Duration of follow-up (median[1]/mean[2]/whole cohort[3]/range)	*N*	Mean/median age (range)	HAT (%)	HVT (%)	PVT (%)	IVC (%)	Overall (%)	Major Bleeding (%)	Survival (%)	Retransplantation due to thrombosis (%)
Ackermann, 2012[20]	France	1988-2007	15 d[3]	590	23 m[1]	7.60	NR	NR	NR	NR	NR	20 y - 80	4.2
Broering, 2004[23]	Germany	2001-2003	6 m minimum	132	1 y[1] (0.02–15y)	NR	NR	1.52	NR	NR	5	6 m - 100	3
Broniszczak, 2006[22]	Poland	1999-2004	7-60 m	71	(6m-10y)	5.6	NR	11.2	NR	16.9	NR	NR	NR
Corno, 2005[24]	Italy	1997-2004	399 d[1] (3-2129d)	260	2.0 y[2] (0.08-12.6y)	NR	NR	5.38	NR	NR	NR	1 yr - 72	1.5
Hardikar, 2010*[11]	Australia	1992-2002	A: NR B: NR	A: 43 B: 41	A: 4.7y[1] (0.7 – 17.7y) B: 5.25y[1] (7m - 16.2y)	A: 2.33 B: 0	4.65	A: 2.33 B: 2.44	A: 2.33 B: 0	A: 11.63 B: 2.44	A: 28 B: 15	A: 92.5 B: 93	A: 2.33 B: 0
Heffron, 2005[13]	USA	1997-2003	NR	150	NR	2.70	NR	NR	NR	NR	NR	1 yr - 91.8	0.66
Heffron, 2010[25]	USA	1997-2008	1856 d[1]	271	Whole: 9.7y[2] Partial: 3.1 y[2]	NR	A: 0 B: 0	1.48	NR	NR	NR	1 yr - 93.1-93.8	0.37
Kanmaz, 2014[26]	Turkey	2006-2012	19.9 m[1]	103	4.7 y[2] (4.4m-17.3y)	3.9	NR	6.8	NR	NR	NR	1 yr - 89.8	2.9

Kilic, 2008[27]	Turkey	1999-2006	2 groups: 52m[1], 14m[1] (8-92m)	61	2 groups: 40m[1], 12m[1] (5-144 m)	NR	1.64	NR	NR	NR	NR	100	NR
Mali, 2012[30]	Singapore	1991-2010	NR	81	2 groups: 12-24 m	4.94	1.23	11.11	NR	17.28	NR	1 yr - 89	1.2
Millar, 2004[36]	South Africa	1985-2003	2 m -12 y	71	5.3 y[2] (6m-14y)	1.41	NR	4.23	2.82	NR	4	74	NR
Neto, 2014[14]	Brazil	1995-2013	NR	486	14 m[1]	NR	NR	7.00	NR	NR	NR	NR	0
Neto, 2016[15]	Brazil	1995-2015	NR	656	13.3 m[1] (8.9-32m)	3.20	NR	NR	NR	NR	NR	2 y - 89.7 (no HAT) - 51.9 (HAT)	2
Ooi, 2010[16]	Canada	2002-2007	31 d[3]	88	4.1 y[1] (0.1-17.3y)	3.41	3.41	2.27	1.14	7.95	0	NR	NR
Schukfeh, 2016[28]	Germany	2004-2014	4.6 y[2]	64	2 groups: 10 m[1] (6-19m) and 11m[1] (3-26m)	28.13	NR	40.63	NR	NR	NR	78.3-90.1	NR
Sevmis, 2011[17]	USA	2001-2011	30 d[3]	123	NR	8.13	NR	NR	NR	NR	NR	NR	0
Shirouzu, 2006[29]	Japan	1990-2005	6.3 y[1]	65	6.9 m[1] (1-16m)	7.7	NR	7.7	NR	NR	NR	1 y - 73	NR
Tannuri, 2004[42]	Brazil	1989-2003	NR	206	3 y 7 m[2] (9m-18y)	12.2	NR	NR	NR	NR	NR	5 y - 70.2	NR
Tannuri,	USA	1998-	NR	121	2 groups: 26 m[1] (7-	10.74	NR	9.09	NR	NR	NR	1 y - 79.7	NR

2011[43]		2010			192m), 81m[1] (11-17m)								
Tiao, 2005[18]	USA	1986-2003	30 days[3]	84	0.63 y[2] (0.08-0.99y)	6.0	NR	9.52	NR	NR	NR	1 y - 77	4.8
Uchida, 2009[19]	Japan	1996-2005	54 m[1] (2d-121m) Thrombosis in first 30 days[3]	403	11 m[1] (HAT) 18 m[1] (non-HAT)	6.70	NR	NR	NR	NR	1	1 y - 78-84	0 (due to HAT)
Yilmaz, 2007[12]	Turkey	1997-2004	45.3 m² (DDLT), 31.5 m² (LRLT)	75	7.6 y[2] (6m-18y)	6.67	1.33	8.00	NR	NR	NR	74	NR
Ziaziaris, 2017**[21]	Sydney	1986-2008	NR	D: 199 E: 61 F: 57	31.7 m[1]	D: 9.55 E: 11.48 F: 1.75	NR	NR	NR	NR	NR	30y - 70	3.5 (for HAT)
Current cohort	Melbourne	2010-2018	1-8 y	100	2.8 y[2] (0.4-18)	6	0	5	1	12	10	97	2

HAT = hepatic artery thrombosis; HVT = hepatic vein thrombosis; IVC = inferior vena cava; PVT = portal vein thrombosis ; NR = not reported

LT = Liver Transplant; WO = whole organs; RS = reduced-size liver transplantation; LR = living-related liver transplantation; SL = split-liver transplantation; DD = deceased donor

d = day, m = month, y = year

*Grouped according to time period: A = 1992-2002; B =2003-2008

**Grouped according to time period: D=1986-2016; E= 2008-2012; F= 2012-2016

[1] = Median follow up; [2] = mean follow up; [3] = thrombosis events included from a defined period for whole cohort

Table 2. Anticoagulation protocol post-liver transplantation.

Author	Anticoagulation (dose)	Timing post-transplant	Monitoring Target

Ackermann, 2012[20]	A	For 1 m	NR
Broering, 2004[23]	H (100-300IE/kg/d) A (5mg/kg 3 times per wk) FFP or AT	Initial post-op When oral intake possible If AT <65%	APTT: 50-70 Nil AT >65%
Brolese, 2007[44]	H (10 U/kg/hr) A	Initial post-op When oral intake possible	NR NR
Broniszczak, 2006[22]	N (40 to 50 IU/kg/d) Dextran 40,000 infusion A FFP	For 7-10 d For 5-7 d For 6 m When INR >1.7	NR NR NR
Corno, 2005[24]	A	When platelet count >50	NR
Hardikar, 2010*[11]	*A:* H (10 U/kg/hr)	For 24 hrs	aPTT

	B: H (10 U/kg/hr) AT FFP (15mL/kg)	24 hrs postop for 2 wk or until A commenced NR Commencing d1	Anti-Xa 0.1-0.3 U/mL AT level 70-100% Aim to reach native protein C levels for several days
Heffron, 2005[13]	A (41mg/d)	Day 1 post op for 3 m	NR
Heffron, 2010[25]	A (41mg/d)	Day 1 post op for 3 m	NR
Kanmaz, 2014[26]	A (1mg/kg/d)	Day 1 post op, when platelets >100, INR <2	NR
Kilic, 2008[27]	A (50mg daily)	Day 3-4 post op for 6 m	"Depending on platelet count"
Mali, 2012[30]	If technically difficult vascular anastomoses, poor quality vessels, or PT<17 within first week: H A or D	 For 1 wk For 12 m	 APTT: 50-70 NR

Millar, 2004[36]	A (3mg/kg alternate days)	NR	NR
Neto, 2014[14]	D (1mg/kg/d) If intraoperative thrombosis or Budd Chiari: H (10unit/kg/hr) If Budd Chiari: PO anticoagulation	For 3 m NR After H	If platelets >50 x 10^3/mm^3 APTT 2-3 times normal INR 2-3
Neto, 2016[15]	If intraoperative thrombosis or Budd-Chiari: H (10 units/kg/hr) If Budd-Chiari: PO anticoagulation D (1 mg/kg/d)	NR NR For 3 m	APTT 2-3 times normal INR 2-3 If platelets >50
Ooi, 2010[16]	H (2.5-10unit/kg/hr if weight <20kg, 2.5-5unit/kg/hr if weight >20kg)	Immediately post op	NR

	A (3-5mg/kg/d; max 101mg daily) D (30mg/d)	Once on full diet Immediately post op	NR NR
Schukfeh, 2017[28]	H (50IE/kg) A (50mg 3x/wk)	Immediately post op for 7d From d7	NR NR
Sevmis, 2011[17]	H A (80mg/d) D (4mg/kg/d)	From d0 for 1 wk From 1 wk From 1 wk	ACT: 150-200 sec NR NR
Shirouzu, 2006[29]	H FFP D (4mg/kg/d)	Until d8 NR From d 8 for 3 m	ACT: 150-200 sec Maintain PT 15-20 sec NR
Tannuri, 2004[42]	Dextran 40 OR	Depending on INR <3.0	NR

	D with H (150 U/kg/d)		
Tannuri, 2011[43]	H (150unit/kg/d) Oral antiplatelets	For 2 wk For 6 m	NR NR
Tiao, 2005[18]	A	When PT < 14 or INR < 2	NR
Uchida, 2009[19]	H (120unit/kg/d) D 4mg/kg/d	For 1 wk From 1 wk	NR NR
Yilmaz, 2007[12]	A (80mg daily)	For 3-6 m	NR
Ziaziaris, 2017**[21]	*D & E*: H (5unit/kg/hr) A (40mg/d) *F*: H (10U/kg/h initially, max dose 20U/kg/h) A	Day 3-4 post op for 4-5 d Once oral diet tolerated, for 6 m Commence when INR <2, D1-3 and up to 3 weeks or until A commenced Once tolerated	When INR <1.5 NR No target anti-Xa, roughly targeted TEG 1.5-3x greater length on citrated kaolin heparinase curve NR

	AT (daily dose 1,000 U for 0-30kg bodyweight; 2,000 U for 30-60kg; 3,000 U for >60kg)	D1-3	Regardless of serum levels, AT levels measured daily
	FFP (10-20mL/kg/d)	D1-3	Protein S and C measured daily, additional given if ascitic losses significant

Hr = hours; d= days; m = months H = unfractionated heparin, A = aspirin; FFP = Fresh Frozen Plasma; AT = Antithrombin III; D = dipyridamole; N= Nadroparine; INR = international normalized ratio; TEG = thromboelastography; ACT = activated clotting time; PT = prothrombin time; aPTT = activated partial thromboplastin time

*Grouped according to time period: A = 1992-2002; B =2003-2008

**Grouped according to time period: D=1986-2016; E= 2008-2012; F= 2012-2016

Table 3. Vascular complications post liver transplantation

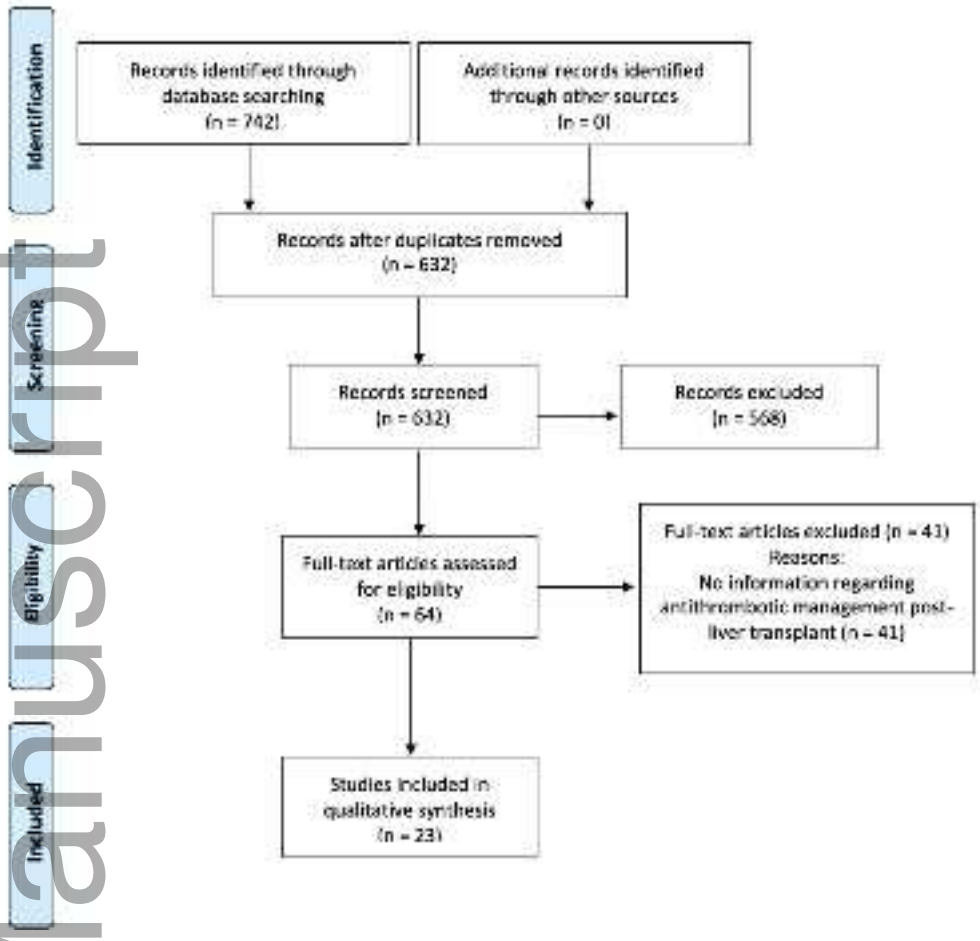
Patient	Age	Weight (kg)	Graft Type	Thrombosis	Diagnosis of thrombosis (post	Outcome

					operative day)	
1	9 months	6.4	Split	PVT	1	Thrombectomy
2	12 months	6	Reduced	PVT	3	Thrombectomy
3	14 months	10.3	Split	PVT	2	Thrombectomy
4	7 months	6.5	Split	PVT	5	Thrombectomy
5	11 years	44.7	Whole	PVT	1	Thrombectomy
6	8 months	7.9	Reduced	HAT	2	Deceased
7	3 years	15	Split	HAT	3	Two HA at transplant, adequate graft perfusion with remaining HA
8	2 years	12.5	Split	HAT	36	Re-transplanted day 50
9	15 months	7.4	Whole	HAT	2	Re-transplanted day 20

10	4 years	17.4	Split	HAT	112	Collaterals evident on angiogram, remains on aspirin
11	20 months	10	Whole	HAT	4	Listed for re-transplant
12	2 years	12.8	Split	IVC	4	3 months of LMWH, resolution of thrombus on US

Figure legend

Figure 1. Preferred reporting items of systematic reviews and meta-analysis study selection diagram.



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