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Inferior Vena Cava Constriction After Liver Transplantation Is a Severe Complication Requiring Individually Adapted Treatment: Report of a Single-Center Experience

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Statistical Analysis C
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Background: Reports on vena cava occlusion after liver transplantation (LT) are rare, but this finding represents a severe complication in the early postoperative period. In the context of the complex presentation of a patient after LT, symptoms are often misinterpreted and can be subtle.

Material/Methods: In our cohort of 138 LTs performed between 2014 and 2017 at our University's Transplantation Department, 117 transplantations were valid for further analysis after exclusion of pediatric transplantations and transplants with primary non-function grafts. In 101 cases (73%), patients received a deceased-donor full-size organ. Living-donor LT was performed in 8 patients (6.4%) and 8 patients (6.4%) received a split graft. We report on 6 patients who had inferior vena cava (IVC) occlusion and summarize the treatment choices.


Results: In our series, patients with positive findings (age 38–70 years) received an orthotopic full-size deceased-donor graft with end-to-end IVC anastomosis. In the subsequent period, imaging revealing IVC occlusion was done on a follow-up basis (n=2), due to dyspnea (n=1), and for progressive ascites (n=2). In 3 cases, a thrombus was found. We give detailed information on our treatment options from interventional treatment to transcatheter thrombus removal and anastomosis augmentation.

Conclusions: IVC constriction and subsequent thrombosis are severe complications after LT that require individually adapted treatment in specialized centers. Since patients often present with subclinical symptoms, vascular diagnosis should be performed early to detect caval anastomosis pathologies. Despite regular ultrasonography, we favor CT and cavography for subsequent quantification. We also review the literature on IVC occlusion after LT.

MeSH Keywords: **Anastomosis, Surgical • Angioplasty, Balloon • Liver Transplantation • Thrombosis • Vena Cava, Inferior**

Abbreviations: **AIH** – autoimmune hepatitis; **CIT** – cold ischemic time; **CMV** – cytomegalovirus; **CT** – computed tomography; **E/E** – end-to-end anastomosis; **HBV** – hepatitis B virus; **HCC** – hepatocellular carcinoma; **HCV** – hepatitis C virus; **IVC** – inferior vena cava; **LDLT** – living-donor liver transplantation; **LT** – liver transplantation; **NASH** – non-alcoholic steatohepatitis; **PTA** – percutaneous transluminal angioplasty; **RA** – right atrium

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Background

Although vascular difficulties following LT are infrequent, they are serious complications with a high incidence of both graft loss and mortality [1]. Their incidence remains around 7% after LT in various series [2,3]. While inferior vena cava (IVC) obstructions are expectable complications after LT, they are rare, as is their scientific assessment. Apart from bleeding complications in the early postoperative setting, stenosis and thrombosis are the main problems. End-to-end caval-cavostomy is a widely accepted standard technique for caval anastomosis. The later-introduced piggyback technique (partial clamping of the cava) has become an accepted alternative and is mandatory in living-donor liver transplantation (LDLT) [4]. In the context of the complex presentation of a patient after LT, symptoms are often misinterpreted and can be subtle – ascites [5,6], early graft dysfunction, reduced portal venous (PV) flow, decreased renal function [7], lower venous congestion, and allograft dysfunction can result. IVC stenoses can be divided into early and late stenoses after LT. Acute stenoses, which are mostly caused by technical complications, occur due to constriction by a swollen anastomosis (e.g., edema), extravascular compression (e.g., hematoma), or kinking by a rotated organ [1,8]. Secondary stenosis can be caused by neointimal hyperplasia, fibrosis [9], thrombosis, or extravascular compression from edema, hematoma, or localized ascites [10,11]. The causes of thrombosis are unclear, although, stasis due to mechanical restriction seems predominant. In the literature, reports on thrombosis are infrequent (Table 1). IVC complications remain a rare finding, diagnosed in less than 1% of the transplanted cases (Table 1) [2, 6]. In the present article, we discuss our insights on a variety of therapeutic options and present our own data on IVC complications after LT, with special emphasis on thrombotic problems.

Material and Methods

Data on patient characteristics and clinical course and transplant-specific data are routinely collected prospectively in a database. Analysis of the sample collection was retrospectively performed from this source. From 2014 to 2017 (4 years), we carried out 138 LT in 125 patients. Pediatric transplantations and transplants with primary non-function grafts were excluded from this study. Finally, 117 transplantations were valid for further analysis. All patients had signed an informed consent for publication of clinical data and the study was approved by the local ethics review board (D 400/19).

Perioperative setup

Caval anastomoses were sewn with an Optilene® 4/0 suture (B. Braun AG, Melsungen, Germany) in evverting end-to-end

technique for full-size grafts or via performing a unification venoplasty for reconstruction of the inferior right hepatic vein in case of right-lobe transplantation.

All patients received standard immunosuppression with tacrolimus taper scheme (tacrolimus through 4–6 ng/ml); cortisone (early postoperative dosage of 20 mg prednisolone daily) and Basiliximab 20 mg at day 0 and day 4 after transplant. Additionally, all patients received anti-infective treatment; standard antibiosis consisted of cefotaxime and metronidazole, with amphotericin B and cotrimoxazole prophylaxis as well as valganciclovir in the case of a CMV-positive donor and CMV-negative recipient.

Imaging procedures

Postoperatively, Doppler ultrasound was performed 3 times daily in the early postoperative period and at any point of the periodically conducted consultation in our outpatient clinic, followed by CT scanning in case of suspicious findings to avoid interobserver variation. IVC constrictions were quantified using cavography. Patients were seen quarterly in the first year after LT. The mean follow-up duration was 21.5 (\pm 15.3) months, with a maximum of 49 months.

Results

We analyzed 117 transplantations for occurrence of vascular complications. Patient age ranged from 17 to 77 years, including 32 women and 85 men. Major indications for LT were alcohol-induced cirrhosis (42.7%), primary sclerosing cholangitis (13.6%), hepatocellular carcinoma (44.4%), chronic viral hepatitis (27.2%), and cryptogenic cirrhosis (4.5%). The patients were listed to Eurotransplant and received an organ within 14 days to 11 years after listing (mean 348 ± 672 days). Mean cold ischemic time was 554.8 min. Re-transplantation within the same hospital stay was done in 8 cases (6.4%), and in 5 other cases (4.0%) within the time of the study, with a total of 16 (12.8%) re-transplantations, respectively. Full-size LT was carried out in 101 cases (73.2%). Living-donor liver transplantation (LDLT) was performed in 8 patients (6.4%, all right-lobe) and 8 patients received a split graft (3 patients: right-lobe, 5 patients: extended right-lobe). The bile duct was connected in end-to-end technique in 105 cases (76.1%) and a biliodigestive anastomosis was performed in 12 cases (10.3%). After 1 and 2 years, 80.3% (94/117) and 74.4% (87/117), respectively, of the patients were alive. Twelve patients (10.3%) died during the hospital stay.

We present detailed information on our patients with IVC abnormalities. Table 2 summarizes the clinical characteristics of our patients with a positive IVC occlusion. In the thorough LT

Table 1. Literature overview of systematic studies comprising thrombosis and stenosis with respective diagnostic tools and treatment options.

#	Author & year	Time of study (yrs)	Thrombosis vs. stenosis	Number of findings/LT (patients)	Children	Method & time of diagnosis	Treatment & outcome (n)
1	Cardella JF et al. 1986 [12]		t+s	5/46	Partly	Angiography (n=18)	PTA (1)
2	Wozney P et al. 1986 [2]	5	t	1/625 (477)	n=204	Angiography (n=104) 1 m	Re-LT
3	Stiglbauer R et al. 1990 [13]		s	12/159		Angiography (n=34) 45 d	Watch & wait or revision
4	Raby N et al. 1991 [14]		s(+t)	4/600		US+angiography 8 m – 4.5 yrs	PTA (3), revision (1); 1 died
5	Brouwers MA et al. 1994 [7]	14	t+s	6/245		US	Revision; thrombectomy transarterial or via cavotomy
6	Kok T et al. 1998 [15]		t+s	9/268		US + angiography	
7	Settmacher U et al. 2000 [8]	10	s	17/1000		US (add. angiography, CT scan, or MRI) 1w – 3.5 yrs	Conservative (1), PTA (3), surgical (4), Denver shunt (3), Re-LT (5); 3 died
8	Buell JF et al. 2002 [16]	12	s	12/600 (325)	Yes	US+angiography 2 m + 10 yrs	PTA (6) or stenting (4); 2 late recurrence
9	Jiang L et al. 2002 [17]		s	6/46		US + angiography	PTA or stenting
10	Jia YP et al. 2007 [18]	7	t	10/286	Partly	US 5–13 d	Drug therapy
11	Yilmaz A et al. 2007 [19]	8	s	6/75	Yes		PTA, stenting; Re-LT
12	Ma Y et al. 2008 [20]	7	s	10/776		US + angiography	PTA (8) or stent, Re-LT (2); 3 died
13	Boraschi C et al. 2016 [21]	4	t	1/170		US + multidetector CT 90 d	Drug therapy
14	Galloux A et al. 2018 [22]	24	s	26/917 (792)	Yes	Day 1–8.75 yrs	Re-LT (3)
15	Gundlach JP et al. 2020	4	t+s	6/138 (125)		US, CT + angiography 1 w – 9 m	Interv. thrombectomy, AV-fistula + PTA (1); transarterial thrombectomy (1); PTA (1) or conservative; 3 died

Systematic studies (>10 patients) with emphasis on vascular complications. The table gives detailed information on covered years within the studies; number of stenotic (s) or thrombotic (t) findings and pediatric transplantations. In addition, diagnostic options are demonstrated (US – ultrasound; CT – computer tomography; MRI – magnetic resonance imaging), the time of postoperative diagnosis (d – days; m – months; yrs – years) period after LT (time), and an overview of the treatment options.

Table 2. Transplantation characteristics.

#	Sex	Age R/D	BMI R/D	Diagnosis	MELD	Re-LT	CIT (min)
1	M	68/63	26.5/38.5	Post-alcoholic liver cirrhosis	29	No	442
2	F	61/34	25.3/20.6	HCC in AIH and NASH	25	No	540
3	M	51/45	23.6/27.8	Post-alcoholic liver cirrhosis	29	Yes (4 d)	360
4	M	68/58	26.5/24.8	Chronic HBV cirrhosis; simultaneous KT	23	No	576
5	M	38/68	28.6/27.1	Post-alcoholic liver cirrhosis	14	Yes (3 d)	375
6	M	70/68	25.1/26.1	HCC in HCV cirrhosis	8	No	630

Recipient (R) sex, donor (D) and recipient age (male vs. female), body mass index (BMI), LT diagnosis, MELD, specification of re-transplantation (re-LT) with stated days (d) after first LT, as well as cold ischemic time (CIT) indicated in minutes (min). HCC – hepatocellular carcinoma; HBV – hepatitis B virus, KT – kidney transplantation; HCV – hepatitis C virus.

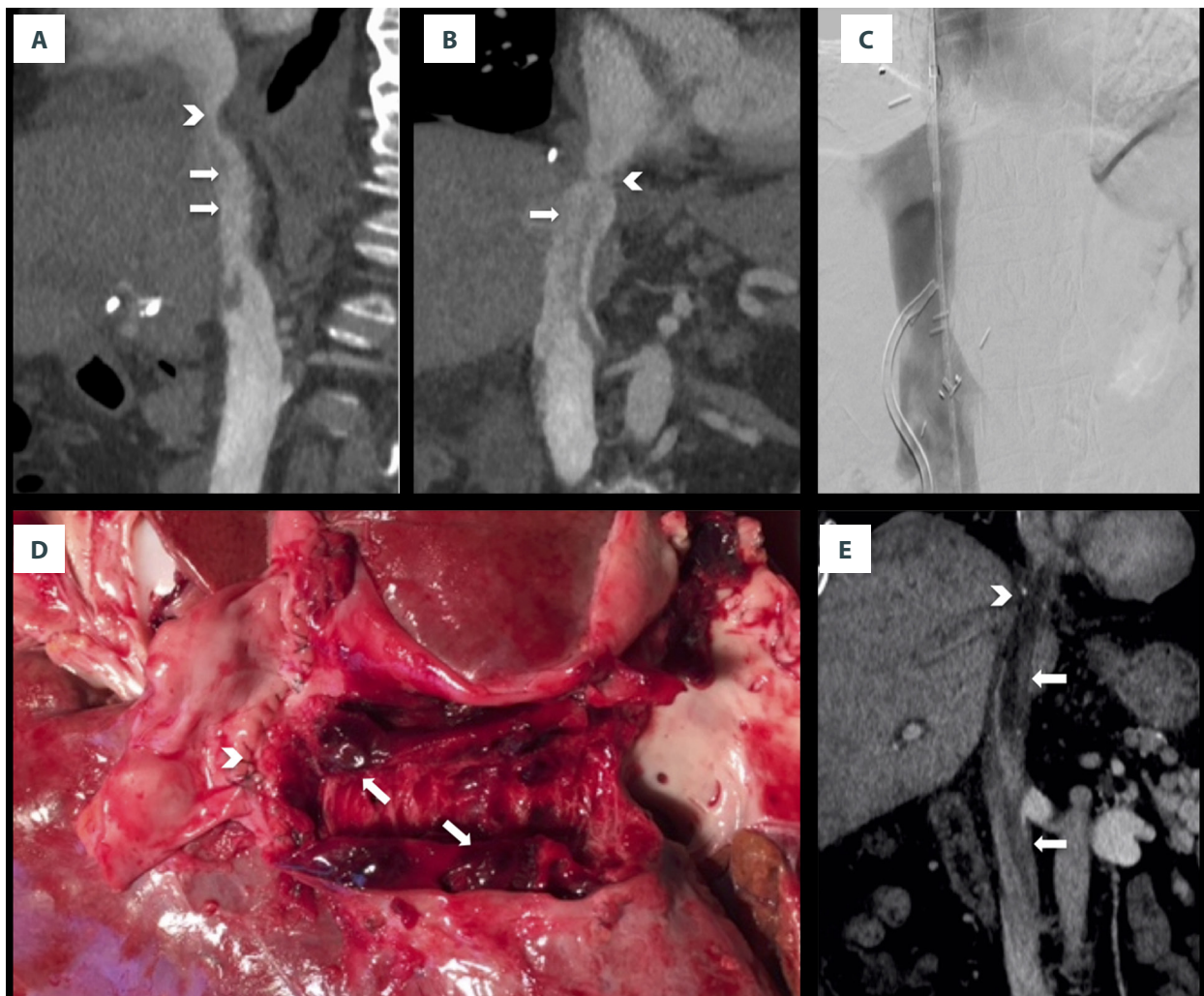


Figure 1. Radiologic and macroscopic finding of IVC thrombosis. (A–C): patient #1: CT scan (A, B) and cavography (C) of thrombus due to fibrotic stenosis (arrow heads) of suprahepatic IVC anastomosis; (D) patient #2 at autopsy with cranio-caudal opened IVC (from left to right); arrow head indicates suprahepatic IVC anastomosis; (E) CT scan showing a massive IVC thrombosis in patient #3 with arrowhead indicating stenotic suprahepatic IVC anastomosis. White arrows indicating thrombosis. Pictures A–C, and E are displayed in coronal view.

Table 3. Diagnostic and therapeutic procedures in case of IVC occlusion.

#	Time	Radiologic finding	ΔP before	ΔP after	treatment option	Specific anticoagulation	follow-up
1	1.5 m	US + cavography: thrombus + fibrotic stenosis of suprahepatic anastomosis	14 mmHg	0 mmHg	Transthoracic thrombectomy, balloon protection, AV fistula + delayed PTA (after 2w)	None LMWH	50 m
2	16 d					LMWH prophylaxis	16 d †
3	4 m	CT: stenosis and thrombus			Transatrial thrombectomy + augmentation	Rivaroxaban	19 m
4	1 m	US + cavography: stenotic IVC due to kinking	5 mmHg		Without intervention	None	6 m †
5	11 d	CT: stenotic IVC anastomosis after 11 d	10 mmHg	3 mmHg	PTA 9 m post LT	None	28 m
6	9 m	CT: slit-shaped stenosis of IVC anastomosis, collaterals + varices	11 mmHg (9 m)	2 mmHg (12 m)	Without intervention	LMWH prophylaxis	13 m †

Time period after LT (time), trans-stenotic pressure gradient before and after intervention (ΔP), time of follow-up as well as the administered postinterventional anticoagulation. d – days; w – weeks; m – month/months; US – ultrasound; ΔP – pressure gradient; LMWH – low-molecular-weight heparin; † – death.

follow-up carried out from 2014 until 2019, we found 3 cases of IVC thrombosis (Table 2, cases # 1–3; Figure 1) as well as 3 cases of manifest or occult (n=1) caval stenosis (Table 2, cases # 4–6). All transplantations were full-size grafts with duct-to-duct biliary anastomoses. Transplantation was successfully performed in all cases, although 2 cases (33%) needed re-transplantation within the same hospital stay due to primary non-function of the transplant. We analyzed whether time of transplantation or surgeon's experience had an influence on the occurrence of undetected stenosis or thrombosis. The procedural quality of LT in Germany is ensured by the independent Institute for Quality Assurance and Transparency in Healthcare (IQTIG). In the recent quality report published in September 2019, in-hospital mortality was reported to be 11.2%, 1-year survival was 82.3%, and 2-year survival with known or unknown status (worst-case analysis) was 72.8% [23]. Accordingly, our 1- and 2-year survival rates (80.3% and 74.4%, respectively) are well above the lower limit.

The first patient (Tables 2 and 3, #1), age 68 years, was listed due to post-alcoholic liver cirrhosis and received a full-size LT with a MELD score of 29. During the in-hospital postoperative period 6 weeks after transplantation, following persisting ascites, ultrasound revealed a thrombus in the IVC, which was confirmed by cavography (Figure 1A–1C). The thrombus was located in the IVC until the pelvic circulation and was caused by a fibrotic stenosis of the suprahepatic IVC anastomosis. Combined surgical and interventional trans-thoracic thrombectomy under balloon protection was performed and

a simultaneous arterio-venous fistula was created to improve caval perfusion. After an angiographic control 2 weeks later demonstrating no remaining thrombosis, an anastomosis dilatation via percutaneous transluminal angioplasty (PTA) was conducted. By the use of regularly-performed imaging procedures, no pathologies have been detected to date.

The second patient (Tables 2 and 3, #2; Figure 1D), aged 61 years, received LT due to autoimmune hepatitis and non-alcoholic steatohepatitis. The early postoperative course was uneventful, but on the day of planned discharge, 16 days after transplantation, the patient suffered a fulminant pulmonary embolism and died during attempted resuscitation. An autopsy revealed a massive IVC thrombosis without deep vein thrombosis.

The last patient with postoperative IVC thrombosis (Tables 2 and 3, #3), aged 51 years, received LT with simultaneous creation of an 8-mm portocaval shunt for post-alcoholic cirrhosis with extensive portal hypertension and grade IV varices. The shunt was implanted to reduce the immediate pressure on the transplant. Due to primary non-function of the transplanted organ, re-transplantation was done 4 days later with simultaneous shunt explantation. After 4 months, CT scanning (Figure 1E) was performed due to acute dyspnea, revealing IVC stenosis with a floating thrombus. Anticoagulation with heparin was induced immediately. Due to the size of the thrombus, the multidisciplinary team decided to use a transatrial approach under cardiac arrest in an on-pump setting

via cannulation of the superior vena cava and arteria femoralis. The thrombus was removed trans-diaphragmally by additional phrenotomy, and an augmentation of the suprahepatic IVC anastomosis was performed. Clinical follow-up 1 year later showed unrestricted general health.

Furthermore, we investigated whether we had a systematic problem with IVC stenosis after transplantation. During thorough clinical and imaging examinations at follow-up, an asymptomatic stenosis was found in a 68-year-old patient (Tables 2 and 3, #4) who received an LT for chronic hepatitis B cirrhosis and simultaneous kidney transplantation for chronic terminal renal failure. After a conspicuous finding in ultrasound, venography revealed a stenosis of the suprahepatic IVC anastomosis due to kinking, with a pressure gradient of 5 mmHg (IVC pressure before stenosis 13 mmHg; right atrium (RA) pressure after stenosis 8 mmHg). Due to the clinical condition, no intervention was performed. The patient died due to multiorgan failure 6 months after transplantation.

However, symptoms of lower venous congestion such as ascites or edemas are more common reasons for initiation of imaging diagnostics. A 38-year-old patient (Tables 2 and 3, #5) received LT for post-alcoholic cirrhosis and 3 days later by primary non-function re-transplantation. An early postoperative abdominal CT revealed an IVC stenosis within the anastomosis 11 days after transplantation. Following progressive hemodynamic relevance, PTA was performed 9 months after transplantation with excellent results – the pressure gradient decreased from 10 mmHg before dilatation (IVC 14 mmHg; RA 4 mmHg) to 3 mmHg (IVC 10 mmHg; RA 13 mmHg). PTA was repeated 1 year after transplantation and the pressure gradient slightly decreased from 9 mmHg to 7 mmHg, presumably because of a rigid stenosis (before PTA: IVC 10 mmHg; RA 1 mmHg, after PTA: IVC 6 mmHg; RA 13 mmHg). Nevertheless, the hemodynamic status remained unaltered without need for stent implantation or surgical intervention.

Another case with symptomatic IVC stenosis was found in a 70-year-old patient (Tables 2 and 3, #6) who received LT due to hepatocellular carcinoma in hepatitis C cirrhosis after listing 1 month ahead. Ascites remained high 9 months after transplantation. CT scanning showed a narrow stenosis of the suprahepatic IVC and subsequent cavography revealed an IVC pressure gradient of 11 mmHg (IVC 23 mmHg; RA 12 mmHg). One year after transplantation, the pressure gradient had nearly vanished (IVC 10 mmHg, RA 8 mmHg), although the clinical condition was significantly restricted. The patient died due to multiorgan failure 13 months after transplantation.

Discussion

IVC obstruction is less common than radiologically indicated, but remains a severe complication with possible fatal outcome [14,20,24]. The clinical significance of radiological findings is only determined by correlation of the imaging with clinical symptoms. In contrast, subtle symptoms in the complex presentation of a patient after LT should be carefully balanced and early diagnostic imaging should be performed.

Anastomosis technique has less influence on IVC stenosis than expected – comparison of end-to-end [25–27] with piggyback [28–31] technique revealed no difference in thrombotic occurrence. Interestingly, the piggyback method [4, 32], which was introduced to reduce venal and cardiac compromise during LT, does not seem to prevent anastomotic stenosis of the venous outflow tract or the IVC [5,33–37]. In particular, torsion is a more frequent finding in this patient cohort; however, therapy was in general satisfactory with PTA and stenting [5,35–37]. Reports on IVC stenosis following LDLT remain rare [38]. In addition, patients after LDLT suffer venous outflow stenosis, although it seemed to be less common than in deceased-donor liver transplantation (DDLT) [10,38–41]. The Korean standardization of right-lobe LDLT suggests preservation of retro-hepatic IVC and unification venoplasty techniques for reconstruction of the inferior right hepatic vein [42], which was likewise performed in our center. Venous augmentation is frequently performed in highly experienced LDLT centers [41,43,44], and PTFE grafts [41,43] or homologous vascular grafts [43,45] can be used. Although remaining a rare complication after LDLT, IVC stenosis can be successfully treated by PTA [44]. In our cohort, 8 patients received an LDLT and 8 received a right-lobe split LT, and we did not experience any stenoses in these groups.

In general, treatment options range from conservative monitoring to re-transplantation. A watch-and-wait approach is reserved for selected cases with special regard to the patient's overall condition. Conservative treatment using anticoagulation should be reserved for partial thrombosis or prophylaxis in patients with subclinical stenosis. Regional thrombolysis is the most common form of therapy for thrombosis [25–27], although local thrombolysis using a catheter technique is also described [31,33]. More recently, interventional thrombectomy via Fogarty catheter and subsequent stenting has been successfully performed [26,27]. PTA and stent placement commonly produce better results than surgical treatment [14,17,46]. Nevertheless, relapse of stenosis after PTA is common, and repeated angioplasties may be necessary [9]. Systemic reviews of interventional vs. surgical treatment options, especially of late complications in adults, are lacking [47]. Early postoperative transabdominal revision of the superior caval anastomosis is often feasible, although it is a technically demanding

procedure due to a large congestive organ, and the need for vascular occlusion, which might cause secondary harm to the liver graft. Hence, cavotomy and outflow tract reconstruction appear to be the final option in surgical procedures for massive thrombosis [29,30]. Shunt placement [48,49], anastomosis augmentation under cardiac arrest [34,50–53], or re-transplantation [8,54,55] are further treatment options in the later period. Moreover, surgery performed under cardiac arrest has been repeatedly reported to have easy access and limited perioperative complications [7]. The trans-atrial approach is preferred to avoid the difficulties and dangers of large collaterals and adhesions in the abdomen. Also, cavotomy for thrombi in the IVC caudal to the liver were reported with simultaneous use of high positive end-expiratory pressure ventilation [7].

We hereby present the possibility of simultaneous trans-diaphragmal anastomosis augmentation after trans-atrial thrombectomy, showing that this approach is suitable for both interventions while avoiding abdominal complications when interventional treatment does not promise acceptable results (case #3). In addition, trans-thoracic thrombectomy was performed in case #1 with secondary PTA after convalescence 2 weeks later without recurring thrombosis. This surgical approach was chosen due to the size of the thrombosis. The time sequence after LT was considered convenient for anastomosis healing and the subsequent stenosis dilatation showed total pressure gradient reduction. In general, operative treatment for thrombectomy was individually chosen depending on the thrombus localization and dimension as well as the time of occurrence after LT.

We decided on a postponed PTA in case #5 due to initially moderate clinical restriction and presumed transitory stenosis caused by edema. Based on appearance of symptoms, PTA was performed 9 months later with satisfying results, although repeated PTA failed, most probably due to fibrotic stenosis. The untreated patients (cases #4 and #6) remained without intervention due to deteriorated general health unlikely to be improved by therapy. IVC obstruction is reported to be more common in cases of re-transplantation [46], resembling our results with 2 out of 8 patients suffering IVC stenosis after

re-transplantation within the same hospital stay. We could not determine the cause in our case with fatal IVC thrombosis (#2), which led to the unfortunate outcome of in-hospital death after LT, but kinking or edema seems likely. In general, we found less mortality in the observational period after 2015 compared to transplantation before 2016 despite routinely performed ultrasound imaging due to implementation of early interventional treatment.

Conclusions

In conclusion, IVC constriction and subsequent thrombosis is a relatively rare complication as indicated in the literature. Among 117 transplantations, we found 3 cases with thrombosis and 3 cases with IVC stenosis. Since patients often present with subclinical symptoms, vascular diagnosis should be performed early to detect caval anastomosis pathologies. Diagnostic tools include easily available Doppler ultrasound routinely performed in the postoperative course as well as CT imaging or angiography. However, pathologies of caval anastomosis are typically diagnosed in a later stage by CT or angiography. IVC constriction after LT requires immediate surgical or interventional treatment in specialized centers. Treatment options in the early course can be conservative (watch-and-wait as well as anticoagulation) or angiographic procedures with PTA and stent placement. Furthermore, surgical intervention seems feasible in the early period after LT, but is more complicated in the later period due to collaterals and adhesions prompting alternative surgical approaches such as a potential trans-atrial access. In that respect, we demonstrated that retrograde IVC thrombectomy in special cases via cardiac arrest is a feasible treatment option. Caval constrictions remain a severe complication, but accurate and diagnosis and early individually adapted treatment can prevent graft failure and the need for re-transplantation.

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