Endovascular Treatment of Hepatic Venous Outflow Obstruction after Liver Transplant

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Abstract

Liver transplantation provides definitive treatment to address acute or chronic end-stage liver disease and its complications. Hepatic venous outflow obstruction is an infrequent complication of liver transplantation that affects graft survival by compromising outflow via transplant hepatic veins or inferior vena cava. It can occur in the early postoperative phase or in a delayed manner, resulting in venous congestion, graft dysfunction, graft failure, and death. This article addresses the pathophysiology of venous outflow obstruction as it relates to different surgical techniques and patient populations, the noninvasive tools for diagnosis, and the endovascular options for treatment along with their safety, efficacy, and durability.

Keywords
- hepatic venous outflow obstruction
- liver transplant
- stent
- stenosis

Chronic liver disease is the 12th leading cause of mortality in the United States, responsible for approximately 40,545 deaths in 2016.1 Liver transplantation provides definitive treatment to address acute or chronic end-stage liver disease and its complications once medical therapy is no longer effective.2 Improvements in immunosuppression and surgical techniques have led to contemporary graft failure rates below 10% at 1 year, and 5-year survival rates for living donors nearing 75%.3 Surgical techniques have also evolved over time to address the rising need for liver transplantation in the setting of a relatively stable deceased donor pool.4 Transplant graft options include whole, partial, or split deceased donor liver transplant (DDLT), and living donor liver transplant (LDLT). Donor type (deceased vs. living), graft type (whole vs. partial), and surgeon/center experience determine the surgical anastomoses of the hepatic venous outflow. The overall rate of hepatic venous outflow dysfunction in adult recipients is between 1 and 4%,5 and the type of anastomosis impacts its prevalence.6 This review specifically addresses the current understanding of posttransplant venous outflow complications, their diagnosis, and management.

Hepatic Venous Outflow Obstruction Pathophysiology

Post liver transplant vascular complications can be categorized based on the location of the lesion within either the inflow or outflow vessels. Inflow lesions affect vascular supply via the transplant hepatic artery or portal vein and impact graft survival via ischemia. Outflow lesions involve the transplant hepatic veins and inferior vena cava (IVC), and affect graft survival via a phenomenon termed hepatic venous outflow obstruction (HVOO).

Patients experiencing HVOO commonly present with congestive symptoms including ascites, pleural effusion, peripheral edema, abdominal pain, elevated liver enzymes, new onset splenomegaly, renal dysfunction, intestinal congestion, and, ultimately, fulminant graft dysfunction, hypotension, and multi-organ failure.6–12 Mortality rates with HVOO have been reported up to 24%.13,14

HVOO can be subdivided by time frame: early and late postoperative. Early postoperative phase HVOO occurs within 28 days of surgery and is typically secondary to surgical technical factors such as tight anastomotic sutures, kinking

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or twisting of the outflow tract, and compression from the graft or adjacent fluid collection.\textsuperscript{5,7,15–18} Unlike the native recipient liver, which has multiple natural points of fixation in the abdomen such as the falciform ligament, the transplanted liver can rotate on its vascular pedicle leading to kinking or twisting of the outflow tract, and may be more common in liver donor or split liver transplants.\textsuperscript{13} Late postoperative phase HVOO likely results from neointimal hyperplasia, fibrosis due to inflammation, or anastomotic compression due to graft maturation.\textsuperscript{10,15,16,19,20}

### Surgical Technique for Hepatic Venous Outflow

Various surgical techniques are used to reconstruct the hepatic venous outflow during liver transplant, with the two most common being conventional orthotopic liver transplant (OLT) and piggyback liver transplant (PBLT).\textsuperscript{21} The choice of surgical technique has implications with respect to venous outflow complications, imaging diagnosis, and endovascular treatment approaches.

Conventional OLT is utilized in the setting of whole liver DDLT. Operative technique involves complete hepatectomy with or without veno-venous bypass, and cross-clamping of the recipient retrohepatic IVC for resection and creation of new end-to-end caval anastomoses\textsuperscript{21,22} (\textsuperscript{Fig. 1}). Hypotension during the anhepatic phase, retroperitoneal bleeding, longer vascular reconstruction times, and complications of veno-venous bypass are classic shortcomings of conventional OLT.\textsuperscript{23,24} These end-to-end drainage pathways tend to be adequately sized; however, outflow complications involving the superior and inferior caval anastomoses may still occur.

The PBLT technique shortens the anhepatic phase and obviates the need for veno-venous bypass by preserving the recipient IVC through the construction of a venous cuff between the recipient hepatic veins and the donor outflow venous tract.\textsuperscript{21,23–26} The most common iterations of this technique include a venous cuff incorporating the right hepatic vein and middle hepatic vein, the middle hepatic vein and left hepatic vein, or all three hepatic veins.\textsuperscript{21,27} This venous cuff is then fashioned into an end-to-end\textsuperscript{26} or side-to-side caval anastomosis\textsuperscript{28,29} (\textsuperscript{Fig. 2}), sometimes with an additional anastomosis-enlarging cavotomy.\textsuperscript{21,30–32} PBLT is commonly performed in LDLT, split or reduced graft placement, and pediatric transplants, as anatomic variations and size mismatch between graft and recipient can make conventional technique difficult\textsuperscript{33,34}. Overall, HVOO is a rare complication of OLT. In adults, recent rates of HVOO vary between 1 and 4\textsuperscript{\%},\textsuperscript{5,35–37} while historical rates vary widely and are reported to be between 0.5 and 13\textsuperscript{\%}.\textsuperscript{4,13,14,23,30,38–48} Comparatively, HVOO occurs with a slightly higher frequency in the pediatric population. Recent rates vary between 0 and 5\textsuperscript{\%},\textsuperscript{49–54} with historical rates reported to be 5 to 27\textsuperscript{\%}.\textsuperscript{55–60} Prospective data on outflow complications for specific combinations of graft types and donor types are challenging to generate given the complexity of transplant interventions, technical factors, operator variability, and evolving center experience. While a recent randomized clinical trial\textsuperscript{61} and prior analysis of randomized clinical trials reported no difference in vascular complications between conventional and piggyback transplantation methods,\textsuperscript{22} retrospective analyses demonstrate that conventional OLT has a lower rate of HVOO compared to PBLT. As PBLT is more often utilized in LDLT, split graft placement, and pediatric transplantation, it has been implicated in higher rates of HVOO in these instances.\textsuperscript{5,23,42,62} For example, a review of 600 pediatric liver transplants revealed HVOO rates of 1\% for whole liver grafts, 2\% for living-related grafts, and 4\% for reduced or split liver grafts.\textsuperscript{5} Discrepant and/or small size of the venous anastomoses and varying drainage patterns to the IVC have been suspected in these settings.\textsuperscript{5,18,49,63,64} Moreover, anatomical variations such as torsion or kinking that coincide with graft maturation may promote physical obstruction.\textsuperscript{4,5,65}

It is important to recognize that there are many variant drainage patterns within the liver. In the setting of DDLT and split liver transplant, these variations can require individualized anastomoses between the donor graft and recipient. For example, a cryopreserved iliac vein conduit and/or polytetrafluoroethylene (PTFE) graft may be necessary with separate segment 5 and 8 tributaries, or a donor accessory inferior right hepatic vein draining separately into the IVC.\textsuperscript{66} While specific anastomotic variants are beyond the scope of this paper, it is essential to understand the anatomy prior to interpreting diagnostic studies or intervening on any patient post liver transplant.

### Noninvasive Diagnosis

Noninvasive modalities, such as Doppler ultrasound (DUS) and computed tomography (CT), play an important role in the detection of posttransplant complications. DUS is an
excellent screening tool in the evaluation of posttransplant liver dysfunction secondary to its widespread availability, portability, lack of ionizing radiation or iodinated contrast, and relative affordability compared to CT and magnetic resonance imaging. Although widely available, DUS is heavily dependent on the operator performing the exam, and evaluation can be limited in obese patients as well as in the setting of overlying bowel gas. CT will frequently be used to confirm DUS findings prior to intervention, or in the setting of a limited DUS evaluation.

The preservation of a biphasic or triphasic waveform on DUS essentially excludes the possibility of HVOO, which can present as a dampened, monophasic waveform with a pulsatility index of 0.45 or less. These findings are nonspecific, however, and often seen in the posttransplant setting. Ancillary findings may include a visible stenosis on grayscale imaging, color aliasing at the stenosis, reduced hepatic venous velocities below 10 cm/s, and reversal of normal antegrade flow within the hepatic and/or portal venous system.

Similar findings are present when the IVC is involved. Velocities may increase up to fourfold in the diseased segment with associated Doppler aliasing artifact. Moreover, associated dilation of the proximal hepatic veins can be observed along with loss of phasicity and dampening of the expected biphasic or triphasic waveform.

CT has a reported sensitivity of 100% with a positive predictive value of 81% in patients with HVOO, which can present as a dampened, monophasic waveform with a pulsatility index of 0.45 or less. These findings are nonspecific, however, and often seen in the posttransplant setting. Ancillary findings may include a visible stenosis on grayscale imaging, color aliasing at the stenosis, reduced hepatic venous velocities below 10 cm/s, and reversal of normal antegrade flow within the hepatic and/or portal venous system.

Venography and Endovascular Intervention

Hepatic Veins

Conventional venography allows for assessment of anastomotic narrowing, relative vascular flow, and measurement of venous pressures. Additionally, therapeutic intervention can then be performed immediately following confirmation of suspected HVOO. Transjugular access is typically utilized to perform venography within the hepatic veins and IVC, although anatomy can occasionally favor a transfemoral approach. If a severe anastomotic stenosis or occlusion precludes transjugular selection of the hepatic veins, ultrasound-guided percutaneous transhepatic puncture of a dilated hepatic vein can be performed to assist with catheterization.

Measurement of a pressure gradient across the anastomosis can support diagnosis of a venographic stenosis; however, a validated threshold gradient remains to be determined. Some authors suggest a more stringent threshold gradient of >10 mm Hg, while others have argued that gradients >3 mm Hg can be symptomatic, reporting clinical improvements with treatment of gradient ranges between 3 and 5 mm Hg.

Treatments for HVOO are primarily endovascular, with surgical revision infrequently performed secondary to the difficult exposure required to reach the outflow anastomosis. Venoplasty is often the initial intervention. Although high rates of initial patency are described, HVOO often recurs following venoplasty, requiring serial dilation or stent placement. After identification of the stenotic segment, prolonged inflation of an angioplasty balloon is performed until the stenotic waist is reduced. The balloon size should be slightly oversized by 1 to 2 mm with respect to the diameter of the hepatic vein. Kubo et al demonstrated...
restenosis in 55% of patients, a primary patency rate of 60% at 5 years, and an assisted patency rate of 100% at the end of the 5 years follow-up period in the patients with restenosis.

Similar assisted patency rates (95–100%) are reported in pediatric patients with HVOO, with 76 to 79% of patients requiring no more than two to three dilations.

Some favor angioplasty over primary stent placement because indwelling stents are inherently thrombogenic, promote neointimal hyperplasia, and their presence may complicate future surgical intervention or retransplantation.

These considerations are particularly important in the pediatric population in which an initially appropriately sized stent may become a fixed stenosis as the child and graft grow. For this reason, stent placement may be deferred in pediatric liver patients until maturity in favor of serial angioplasty.

Emerging data highlight a role for primary stenting in the setting of HVOO with promising long-term stent patency rates at 5 to 10 years. Early postoperative HVOO may provide a unique scenario for primary stent placement as venoplasty can theoretically disrupt the newly created transplant anastomosis. Moreover, the causes of early postoperative HVOO may not respond well to venoplasty alone, given its inability to address kinking, vascular torsion, or ongoing compression. Even with these considerations, Kim et al recently reported lower patency rates after stent placement than other cohorts, attributing their findings to high rates of kinking that were not amenable to stenting.

Comparison between balloon-expandable and self-expanding stents in the setting of HVOO is yet to be performed. Balloon-expandable stents are often utilized to treat hepatic venous outflow obstruction.
Fig. 4 A 59-year-old male 3 months after split liver transplant with piggyback anastomosis presents with rising bilirubin and liver enzymes. (A) Transplant hepatic venous Doppler examination demonstrates a monophasic waveform with decreased velocities and diminished pulsatility indices in the right and middle hepatic veins. (B) Selective venogram with catheter positioned in the hepatic vein demonstrates a high-grade anastomotic stenosis with catheter occlusion across the stenotic segment (arrow). The measured trans-stenotic gradient is 23 mm Hg. (C) After primary stent placement across the anastomotic stenosis with a 14 mm x 4 cm self-expanding nitinol stent, there is improved hepatic venous flow and a significantly reduced gradient now measuring 5 mm Hg. The stent is appropriately oversized with respect to the size of the hepatic vein and is well positioned across the stenosis without excessive protrusion into the inferior vena cava. (D) At 2-year follow-up, a Doppler ultrasound demonstrates stent patency with an improved, biphasic waveform, and a sustained improvement in hepatic vein velocities.

Table 1 Long-term stent patency rates in hepatic venous outlet obstruction

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stenosis given their higher radial strength and ease of precise placement.\textsuperscript{74} Wang et al utilized short balloon-expandable stents in the setting of HVOO and saw high patency rates.\textsuperscript{33} Ko et al and Chu et al demonstrated high patency rates with self-expanding stents\textsuperscript{35,42} with increased stent diameter demonstrating an association with patency.\textsuperscript{42} Reported stent diameters range from 8 to 14 mm within the hepatic veins.\textsuperscript{74} In the pediatric population, utilization of large self-expanding stents may allow the stent to grow with the patient, potentially reducing concern for future stenosis or stent migration.\textsuperscript{62,77} Data on pediatric stent placement is lacking although high rates of clinical success and patency have been previously reported.\textsuperscript{77,78} Recent data show high rates of stent patency up to 13.5 years (median 6 years)\textsuperscript{62} and 17 years (median 7.5 years)\textsuperscript{54} in low-powered studies.

Complications related to hepatic vein angioplasty and stent placement are rare.\textsuperscript{42} While there is a theoretical risk of anastomotic rupture after angioplasty in the early post-transplant setting, multiple studies cite a rate of 0%.\textsuperscript{4,53} Bleeding complications following angioplasty at later time points are very unlikely given the retroperitoneal location and postoperative scarring.

Another rare, albeit feared, complication is stent migration, which can occur secondary to respiratory (and cardiac) motion, or due to the complex and dynamic anatomy of the hepatic venous anastomoses. In one retrospective study involving 152 pediatric liver transplant patients, 18 of whom required intervention for HVOO, no stent placements were complicated by stent migration.\textsuperscript{62} In two additional retrospective studies, stent migration occurred in only one

Fig. 5 A 35-year-old man with piggyback technique liver transplant 10 years prior developed new enlarged abdominal wall collaterals. (A) Coronal image from the venous phase of a computed tomographic scan of the abdomen demonstrates a high-grade stenosis (arrow) of the suprahepatic inferior vena cava (IVC). There is hepatic congestion evidenced by heterogeneous enhancement of the liver. (B) Digital subtraction venogram with 5 French pigtail catheter positioned in the infrahepatic IVC from right internal jugular venous access demonstrates a 90% stenosis involving the suprahepatic IVC (arrowheads) with a trans-stenotic gradient of 14 mm Hg. Contrast refluxes into the hepatic veins (asterisk) and multiple collateral varices (arrow) are opacified. (C) Serial venoplasty is performed, first with a 14 mm balloon, demonstrating a waist (arrowheads) at the stenosis. (D) Prolonged venoplasty with an 18 mm balloon demonstrates resolution of the waist. (E) Post venoplasty digital subtraction venogram demonstrates improved luminal gain with a residual stenosis of < 50%, and an improved trans-stenotic pressure gradient of 1 mm Hg. After venoplasty, abdominal wall collaterals resolved.
patient per study—in one case, the stent migrated slightly into the IVC requiring no further intervention, and in the second case, migration occurred into the right atrium, requiring retrieval over the wire with balloon assistance. At the authors’ institution, general anesthesia is often used to limit respiratory motion, as deep inspiration during stent deployment can result in maldeployment necessitating stent retrieval from the IVC or right atrium. Selection of the appropriate stent size is also critical in preventing migration. In the event that a stent migrates or is minimally misplaced into the IVC, the stent can be stabilized by placement of an overlapping stent. However, if a stent migrates or extends too far centrally into the right atrium, the consequences can be severe and life threatening, potentially requiring cardiac surgery for removal if it cannot be retrieved through standard endovascular techniques.

**Inferior Vena Cava**

Caval complications posttransplantation most frequently result from stenosis of the suprahepatic IVC or infrahepatic IVC anastomoses in standard technique liver transplants. Historically, venoplasty has been successful but resulted in recurrence rates near 50%. Small retrospective studies utilizing caval stent placement show high rates of technical and clinical success with primary assisted patency rates of 94% and 100% reported at 1 and 7 years, respectively. Given these rates of success, caval stenting is often considered to be a first-line intervention with stent sizes ranging between 14 and 24 mm. Additionally, Parvinian and Gaba proposed the utilization of a cutting balloon over stepwise sessions to augment caval luminal caliber, reporting successful luminal expansion from 2 to 3 mm to 10 to 11 mm. This technique, akin to addressing biliary strictures, would provide an alternative route when caval stenting is undesirable.

Complication profiles for venoplasty and stenting of IVC stenosis are similar to those seen with hepatic venous stenosis. While there is a theoretical risk of anastomotic rupture after venoplasty, particularly in the early postoperative setting, there are no documented cases of rupture in the literature. Stent migration, while potentially serious, is rare. The open architectural design and high radial force of the Gianturco Z-stent (Cook Medical, Bloomington, IN) make it a desirable choice for use in the IVC. The stent interstices do not obstruct the hepatic outflow when placed across the confluence. This also allows future venoplasty and stenting of the hepatic veins if a concomitant hepatic venous stenosis warrants treatment. Additionally, anchoring barbs are incorporated into the struts, a design feature intended to reduce migration.

**Conclusion**

HVOO is an infrequent complication of liver transplantation that affects graft survival by compromising outflow via transplant hepatic veins or IVC. While conventional OLT creates end-to-end drainage pathways between the native and transplant IVC, PBLT technique involves creation of an anastomotic cuff between the recipient hepatic veins and donor outflow tract. PBLT is commonly used in LDLT, split/reduced graft transplant, and pediatric transplant, and is implicated in higher rates of HVOO due to the complex and variable anatomy encountered in these scenarios. HVOO can occur in the early postoperative phase or in a delayed manner, resulting in clinical signs and symptoms of venous congestion, renal failure, and graft dysfunction or failure. Ultrasound is the best noninvasive screening tool to evaluate the venous anastomoses, and may demonstrate a monophasic hepatic waveform, a visible stenosis, reduced hepatic venous velocities, or reversal of flow within the hepatic and/or portal venous system. Conventional venography is
the gold standard for confirming the diagnosis of HVOO, providing both visual assessment of a stenosis and non-invasive measurement of a significant pressure gradient. Furthermore, it facilitates endovascular treatment of significant lesions with either serial angioplasty or stent placement, both of which demonstrate efficacy and high rates of long-term assisted-patency in adult and pediatric populations.

Disclosure Statement
MP, AL, and MN have nothing to disclose.

Conflict of Interest
None.

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